Hoofd-halstumoren

Inhoudsopgave

behandelfase van patiënten met hoofd-halstumoren

Startpagina - Hoofd-halstumoren

Deze richtlijn valt onder het cluster Hoofd-halstumoren.

Waar gaat deze richtlijn over?

Deze richtlijn richt zich op wat volgens de huidige maatstaven de beste zorg is voor patiënten met hoofd-halstumoren:

- Mondholtecarcinoom
- Orofarynxcarcinoom
- Hypofarynxcarcinoom
- Larynxcarcinoom
- Speekselkliercarcinoom
- Neus en neusbijholte carcinoom
- Nasofarynx carcinoom
- Halskliermetastasen
- Afstandsmetastasen
- Premaligne afwijkingen

Wat is er nieuw in 2023?

- **De indeling van de richtlijn is aangepast** en per tumortype zijn alle relevante modules te vinden. Sommige modules (zoals Systemische therapie bij radiotherapie lokaal gevorderde tumoren) zijn daarom bij zowel Orofarynxcarcinoom, Hypofarynxcarcinoom, als Larynxcarcinoom in de richtlijn te vinden.
- In de meest recente UICC/AJCC classificatie is **lipcarcinoom** niet langer ondergebracht bij mondholte (TNM7) maar bij huid (TNM8). Dit brengt een verandering in stadiëring (volgens TNM8) met zich mee, maar niet in behandeling (volgens TNM7).
- **Nieuwe modules** zijn ontwikkeld over het bepalen van botinvasie, bepalen HPV-status, indicaties voor onderzoek naar afstandsmetastasen en het diagnostisch onderzoek naar afstandsmetastasen, de behandeling van HPV-positieve orofarynxtumoren, dosering cisplatin en systemische therapie bij radiotherapie voor lokaal gevorderde tumoren, Tis/T1 supgraglottisch larynxcarcinoom en fotodynamische therapie bij patiënten met een lokaal recidief.
- Een groot aantal modules zijn **herzien**. Literatuuronderbouwingen, overwegingen en aanbevelingen zijn geupdate.
- Een aantal modules zijn **herbevestigd** en waar nodig tekstueel verbeterd.
- Een aantal modules zijn **vervallen**: Indicaties FDG PET-CT-scan, Behandeling per lokalisatie en T-classificatie, Reconstructieve chirurgie mondholtecarcinoom, Invasieve chirurgie bij orofarynxcarcinoom, Reconstructieve chirurgie orofarynxcarcinoom, T1-T4N+ hypofarynxcarcinoom, Stemkwaliteit als uitkomstmaat na behandeling, T2- en kleine T3 larynxcarcinomen, Niet gemetastaseerde speekselklier tumoren. Deze modules werden door de werkgroep als overbodig beschouwd, of zijn samengevoegd in een (nieuwe) module.

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bestemd voor alle zorgverleners in de tweede en derde lijn die betrokken zijn bij de zorg voor volwassen patiënten met hoofd-halstumoren.

Voor patiënten

Hoofd-halstumoren zijn kwaadaardige gezwellen in het hoofd-halsgebied. De tumoren kunnen voorkomen in de neus, neusbijholte, neuskeelholte, mondholte, mondkeelholte, keelholte, strottenhoofd en speekselklier. De hoofd-halstumoren vormen gezamenlijk bijna 5 procent van het totale aantal kwaadaardige gezwellen. Daarmee behoort deze groep tot de tien meest voorkomende soorten kanker in Nederland.
Meer informatie over hoofd-halstumoren is te vinden op kanker.nl: https://www.kanker.nl/bibliotheek/hoofd-halskanker/wat-is/6758-hoofd-halskanker

Hoe is de richtlijn tot stand gekomen?

Het initiatief voor deze richtlijn is afkomstig van de Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied (NVKNO). De richtlijn is opgesteld door een multidisciplinaire werkgroep met vertegenwoordigers vanuit KNO-artsen, mond- kaak- en aangezichtschirurgen, hoofd-halschirurgen radiotherapeuten, medisch oncologen, radiologen, nucleair geneeskundigen, pathologen, plastisch chirurgen en verpleegkundig specialisten. Daarnaast nam een afgevaardigde van patiëntenvereniging HOOFD-HALS (PVHH) deel aan de werkgroep.

Geldigheid van de richtlijn

De richtlijnmodules zijn anno 2023 als actueel beoordeeld.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Diagnostiek

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Diagnostiek mondholtecarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Bepaling invasiediepte

Uitgangsvraag

Hoe zou de invasiediepte van mondholtecarcinomen bepaald dienen te worden?

Aanbeveling

Bepaal de invasiediepte met een beeldvormingstechniek, bij voorkeur MRI, met als alternatief intraorale echografie.

Overwegingen

De gevonden resultaten met betrekking tot invasiediepte zijn samengevat in Tabel 1, welke is te vinden in de samenvatting van de literatuur (onder het tabblad 'onderbouwing'). Voor de overeenkomst op T-stadium met behulp van invasiedieptemetingen ten opzichte van histopathologie werd er geen data gevonden voor het gebruik van CT en PET-CT. Voor de overeenkomst, gecategoriseerd door een afkapwaarde, in invasiedieptemetingen werd er geen data gevonden die CT of PET-CT vergeleek met histopathologie. Voor de overeenstemming van invasiedieptemetingen op een continue schaal, in millimeters, werden ten slotte geen data gevonden voor CT, PET-CT en ultrageluid.

De bewijskracht werd met een aangepaste versie van GRADE beoordeeld (Mokkink, 2018). Voor de overeenstemming op T-stadium waarbij invasiedieptemetingen werden gebruikt was het vertrouwen, volgens de GRADE, in een klinische beoordeling (met onduidelijke procedures) laag. Goel (2016) rapporteerde een overeenstemming van k = 0,47 tussen een klinische beoordeling (met onduidelijke procedures) en histopathologie. Het vertrouwen in de gerapporteerde uitkomsten van MRI voor de overeenstemming op T-stadium was redelijk. Hier rapporteerden drie studies (Goel, 2016; Verma, 2019; Vidiri, 2019) hun uitkomsten. Verma (2019) en Vidiri (2019) gebruikten in de studies de 8e editie van de TNM-classificering (Verma (2019) gebruikte óók de 7e editie). Er werden kappa-waarden van 0.69 (95%BHI: niet gerapporteerd), 0.65 (95%BHI: niet berekend), 0.74 (ervaren beoordelaar, 95%BHI: 0.56 tot 0.92) en 0.60 (onervaren beoordelaar, 95%BHI: 0.40 tot 0.80) door de studie-auteurs gerapporteerd (Goel, 2016; Verma, 2019; Vidiri, 2019). De gevonden resultaten liggen rond de vooraf gedefinieerde grens van besluitvorming (dat wil zeggen dat K ≥ 0.70 als voldoende overeenstemming werd gezien).

Twee studies werden geïncludeerd voor invasiedieptemetingen die gecategoriseerd werden aan de hand van een afkappunt (Alsaffar, 2016; Iida, 2018). De enige afkapwaarde die werd gebruikt was 5 millimeter waardoor er twee categorieën ontstonden (dat wil zeggen een invasiediepte van < 5 millimeter of ≥ 5 millimeter). Het vertrouwen in de gerapporteerde uitkomsten waren volgens GRADE zeer laag voor een klinische beoordeling, MRI en ultrageluid. De zeer lage GRADE-beoordeling ontstond vooral vanwege het risico op vertekening van de resultaten en de beperkte omvang van de steekproeven. In beide studies was de periode tussen het preoperatieve assessment en het histopathologische assessment onduidelijk.

Ten slotte werd er voor de overeenstemming van invasiedieptemetingen op een continue schaal (in millimeters) tussen modaliteiten en histopathologie alleen data gevonden voor MRI (Mao, 2019; Vidiri, 2019). Beide studies rapporteerden de tijdsperiode tussen het preoperatieve assessment en het histopathologisch

assessment deels. Mao (2019) beschreef dat de preoperatieve meting met MRI binnen 1 week vóór resectie werd uitgevoerd, terwijl dit 3 tot 4 weken was voor Vidiri (2019). De werkgroep had a priori vastgesteld dat een meting tot maximaal 4 weken vóór de chirurgische resectie als adequaat werd gezien. Voor het meten van de invasiediepte op continue schaal (in millimeters) met MRI is er, volgens GRADE, een redelijk vertrouwen in de gevonden resultaten voor MRI uit de twee studies. In de gerapporteerde data werd gezien dat 95% van de MRI metingen (n=150) tussen een onderschatting van 0,97 millimeter en een overschatting van 5,61 millimeter lag in één van de studies (Mao, 2019). In de andere studie (n=53) lagen 95% van de metingen tussen 5,5 millimeter onderschatting en 4,9 millimeter overschatting door een ervaren radioloog en tussen 6,6 millimeter onderschatting en 5,8 millimeter overschatting door een onervaren radioloog (Vidiri, 2019).

De gevonden resultaten met betrekking tot tumordikte zijn samengevat in Tabel 2 en is te vinden in de samenvatting van de literatuur (onder het tabblad 'onderbouwing'). Voor de overeenkomst op T-stadium met behulp van tumor diktemetingen werd geen data gevonden voor het gebruik van CT, PET-CT, MRI en ultrageluid. Voor de overeenkomst, gecategoriseerd door een afkapwaarde, in tumor diktemetingen werd er voor geen enkele modaliteit van interesse data gevonden (dat wil zeggen klinisch onderzoek, CT, PET-CT, MRI en ultrageluid). Voor de overeenstemming van invasiedieptemetingen op een continue schaal, in millimeters, werden ten slotte enkel voor klinisch onderzoek geen data gevonden.

Voor de overeenstemming op T-stadium met behulp van tumor diktemetingen werd er één studie geïncludeerd (Choi, 2017). Deze studie beschreef een work-up (bestaande uit een endoscopisch beoordeling, palpatie en beeldvorming door CT of MRI) ten opzichte van een histopathologische beoordeling. Er werd een kappa-waarde van 0.80 gerapporteerd, maar het 95%BHI werd niet vermeld en het vertrouwen in deze uitkomst was laag (volgens GRADE).

Er werden geen studies geïncludeerd die de overeenstemming voor tumordikte categoriseerden met behulp van specifieke afkapwaarden. Hierdoor is er voor geen enkele modaliteit van interesse data voor deze specifieke situatie beschikbaar.

Wanneer de overeenstemming op een continue schaal (in millimeters) werd onderzocht was het vertrouwen in de gerapporteerde resultaten, volgens GRADE, in CT zeer laag, in MRI laag en in ultrageluid redelijk. Het vertrouwen in de gerapporteerde uitkomsten van MRI werd verlaagd vanwege de beperkte steekproefomvang en het risico op vertekening van de resultaten. De tijdsperiode tussen het preoperatieve assessment en het histopathologische assessment was onduidelijk in beide studies. Bij het gebruik van MRI lagen 95% van de metingen tussen een onderschatting van 5,3 millimeter en een overschatting van 5,4 millimeter bij 83 participanten (Brouwer de Koning, 2019) en tussen een onderschatting van 4,6 en een overschatting van 4,99 millimeter bij 150 patiënten (Nair, 2018) ten opzichte van histopathologie. Er was een redelijk vertrouwen in de gerapporteerde uitkomsten van ultrageluid. Klein Nulent (2018) combineerde data van 10 studies waardoor de gepresenteerde Bland-Altman plots data van 240 patiënten bevatte. Er werd gerapporteerd dat 95% van de metingen met ultrageluid tussen een onderschatting van 5,5 millimeter en een overschatting van 6,5 millimeter lagen ten opzichte van histopathologie (Klein Nulent, 2018).

Een onderschatting van de invasiediepte of tumordikte geeft een verhoogd risico op inadequate snijranden,

terwijl een overschatting een verhoogd risico op te ruime resectieranden geeft. Als de resectieranden inadequaat zijn is er (vaak in combinatie met andere negatieve histopathologische bevindingen) een indicatie voor adjuvante therapie in de vorm van een heroperatie of radiotherapie met of zonder chemotherapie. Door inadequate resectieranden kan de overleving verminderd zijn. Als gevolg van adjuvante behandeling of te ruime resectieranden kunnen mondfuncties zijn aangedaan en kwaliteit van leven verminderd zijn. In het algemeen wordt onderschatting ernstiger gevonden dan overschatting.

De werkgroep werd na de zoekdatum voor literatuur op de hoogte gesteld van een aantal relevante publicaties. Deze publicaties werden daarom niet in de literatuuranalyse opgenomen, maar zullen kort besproken worden ter overweging. Deze korte bespreking geeft wellicht geen compleet literatuuroverzicht van de periode na de systematische zoekopdracht in deze richtlijnmodule en bevat geen GRADE-beoordelingen.

Noorlag (2020) onderzocht met retrospectieve data de tumordiepte gemeten met MRI of intra-orale echografie ten opzichte van een postoperatief histopathologisch assessment. De auteurs rapporteerden een Pearson's correlatiecoëfficiënt van 0.792 (p<0,001) voor MRI ten opzichte van histopathologie. Er werd ook bekeken welke beeldvorming een groter verschil ten opzichte van histopathologie had bij tumoren met een kleine invasiediepte (≤ 1 centimeter) en een grote invasiediepte (> 1 centimeter). De auteurs concludeerden dat intra-orale echografie voor tumoren met een kleine invasiediepte accurater zou zijn dan MRI, maar dat echografie bij dikkere tumoren de invasiediepte zou onderschatten.

Baba (2020) onderzocht aan de hand van retrospectieve data wat de correlatie tussen MRI en histopathologie was bij het meten van invasiediepte in het buccale slijmvlies. Er werd een correlatie gerapporteerd tussen coronale T2-gewogen MRI en histopathologie (Spearman's r=0.67, p=0.012) en tussen coronale T1-gewogen MRI met contrast en vetsupressie (CET1) en histopathologie (Spearman's r=0.68, p<0.001). De auteurs concludeerden dat MRI-metingen behulpzaam zouden kunnen zijn bij het schatten van de histopathologische invasiediepte.

Chin (2020) rapporteerde de overeenkomst tussen contrast CT en histopathologie voor het meten van invasiediepte bij patiënten met plaveiselcelcarcinomen op de tong. Voor de overeenstemming tussen axiale contrast CT en histopathologie werd een ICC (ICC=0.96, 95%BHI: 0.89-0.98, p=<0.001) en een Bland-Altman plot (gemiddeld verschil: -0.72 millimeter,95% limieten van overeenstemming: 3.34 tot -4.78 millimeter) gerapporteerd. Voor een coronale contrast CT was de ICC 0.957 (95%BHI: 0.86-0.99, p<0.001) en het gemiddelde verschil -1.11 millimeter (95% limieten van overeenstemming: 2.73 tot -4.93 millimeter). De auteurs concludeerden dat er een excellente overeenstemming was tussen contrast CT en histopathologie.

Cocker (2020) gebruikte retrospectieve data om de overeenstemming tussen histopathologie en verschillende modaliteiten voor het meten van invasiediepte bij patiënten met mondholtecarcinomen. Er werd data voor echografie (exacte overeenstemming: 9 metingen, binnen 3 millimeter: 52 metingen, buiten 3 millimeter: 17 metingen), MRI (exacte overeenstemming: 1 meting, binnen 3 millimeter: 58 metingen, buiten 3 millimeter: 45 metingen) en CT (exacte overeenstemming: 1 metingen, binnen 3 millimeter: 11 metingen,

buiten 3 millimeter: 9 metingen) gerapporteerd. De auteurs concludeerden dat, van de drie modaliteiten, echografie de meest betrouwbare modaliteit was en dat de huidige beeldvormende modaliteiten wellicht geen robuuste en accurate metingen geven.

Filauro (2020) rapporteerde de correlatie van MRI of echografie met histopathologie voor metingen van invasiediepte bij patiënten met mondholtecarcinomen. Er werd een correlatie gevonden tussen metingen met MRI en histopathologie (Spearman's r=0.83, p<0.000) en tussen echografie en histopathologie (Spearman's r=0.76, p<0.0001). De overeenstemming op T-stadium werd tevens vermeld voor MRI en histopathologie (gewogen kappa=0.53, 95%BHI: 0.32-0.74, p<0.0001) en voor echografie en histopathologie (gewogen kappa=0.36, 95%BHI: 0.14-0.58). De auteurs concludeerden dat beide modaliteiten valide manieren zijn om preoperatief invasiediepte te bepalen, hetzij met andere kosten-effectiviteitsprofielen en indicaties.

Waech (2020) onderzocht de correlatie tussen MRI of contrast CT en histopathologie voor het meten van invasiediepte bij patiënten met mondholtecarcinomen. De Spearman's r werd gerapporteerd voor de correlatie van T1-gewogen MRI (r=0.635, p<0.0001), T2-gewogen MRI (r=0.679, p<0.0001) of contrast CT (r=0.718, p<0.0001) met histopathologie. De auteurs concludeerden dat preoperatieve metingen met MRI of CT tot een overschatting van de histologische invasiediepte leiden, vooral in tumoren met een invasiediepte kleiner dan vijf millimeter.

Wanneer invasiediepte gebruikt wordt voor T-stadiering kan door over- of onderschatting het klinische T-stadium veranderen. Aangezien het T-stadium op basis van invasiediepte meestal niet het primaire behandelplan beïnvloedt, lijkt dit minder belangrijk voor T-stadiering dan het bepalen van de resectie. Indien het beleid ten aanzien van het electief behandelen van de lymfeklieren in de hals gebaseerd is op invasiediepte (in plaats van schildwachtklierprocedure of beeldvormend onderzoek van de hals) kan onder- of overschatting wel het beleid van de hals beïnvloeden.

Voordeel van een MRI is dat deze meestal al gemaakt wordt om de uitbreiding van de primaire tumor en lymfeklieren in de hals te onderzoeken. Ook kunnen later de invasiediepte en tumordikte nog bepaald worden. Er kunnen contra-indicaties zijn voor het gebruik van een MRI. Dit betreffen de gebruikelijke contra-indicaties voor MRI. Patiënten dienen, zoals gangbaar is, gescreend te worden op deze contra-indicaties. Patiënten zouden eventueel een andere beeldvorming kunnen prefereren wegens claustrofobische klachten die bij het afnemen van een MRI zouden kunnen optreden. Echografie is doorgaans meer afhankelijk van de ervaring van de verrichter en metingen kunnen alleen real-time verricht worden. Daarbij moet de tumor voldoende bereikbaar zijn voor de intraorale probe. Hoewel met de zogenaamde hockey-stick probes tumoren ook achter in de mond beter bereikbaar zijn geworden, kunnen factoren als de (veranderde) lokale anatomie, dentitie, trismus en tumorgrootte een goede meting verhinderen. Voor het gebruik van intra-orale echografie zijn er geen directe contra-indicaties, behalve wanneer de tumor niet te bereiken is. Hierbij is, bijvoorbeeld, te denken aan pijnklachten, trismus en/of de tumorlocatie die het bereiken van de tumor met de probe niet mogelijk maken. Deze echografie kan gemakkelijk tegelijk met een eventuele echografie van de lymfeklieren in de hals plaatsvinden. Hiervoor dient dan alleen de probe gewisseld te worden.

In de diagnostische work-up worden er al vaak een MRI en/of echografie uitgevoerd voor andere doeleinden.

Deze beelden zijn echter ook te gebruiken voor het bepalen van de invasiediepte (en/of tumordikte), zonder dat er nieuwe beeldvorming plaats hoeft te vinden. Daardoor zullen er weinig extra kosten worden verwacht bij het gebruik van MRI of intra-orale echografie. Wanneer met verwacht dat een oppervlakkige tumor niet zichtbaar is op een MRI kan echografie overwogen worden indien de locatie bereikbaar is. De lokalisatie van de tumor kan leidend zijn voor de keuze tussen MRI of echografie. Vooral voor tumoren op de tong is er data over het gebruik van echografie bekend, maar minder voor andere tumorlocaties. Voor het gebruik van de intra-orale echografie kan, specifiek bij moeilijk bereikbare tumorlocaties, een hockey-stick probe worden gebruikt. De werkgroep beseft zich dat deze probe niet overal beschikbaar is en dat aanschaf van een dergelijke probe extra kosten met zich meebrengt. Ook de extra tijd die echografie in beslag neemt en training van personeel kunnen kosten met zich meebrengen. Zowel MRI als echografie zijn geaccepteerde beeldvormingstechnieken in de diagnostische work-up van patiënten met hoofd-halstumoren, waardoor er geen problemen worden verwacht in de aanvaardbaarheid, haalbaarheid en implementatie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Beeldvormingstechnieken, zoals MRI en intra-orale echografie, die voor andere doeleinden worden ingezet bij patiënten met hoofd-halstumoren kunnen worden gebruikt om de invasiediepte te meten zonder grote bijkomende kosten. MRI en intra-orale echografie lijken de voorkeur te hebben boven de mogelijke alternatieven, zoals palpatie of CT. Doordat er weinig informatie beschikbaar is en er weinig zekerheid bestaat over het gebruik van palpatie, acht de werkgroep het van belang om in elk geval een beeldvormingstechniek te gebruiken voor het meten van de invasiediepte.

Onderbouwing

Achtergrond

Invasiediepte van de primaire tumor is een prognostische factor. In de nieuwe TNM-classificatie is de invasiediepte opgenomen als belangrijke parameter voor het stadiëren van mondholtecarcinomen. Ook is bij mondholtecarcinomen de invasiediepte een voorspeller voor de aanwezigheid van lymfkliermetastasen. De invasiediepte is de afstand van de (gereconstrueerde) mucosa tot het diepste punt van de tumor in het weefsel. Dit is niet gelijk aan de tumordikte. Bij ulceratieve tumoren is de tumordikte kleiner dan de invasiediepte, bij exofytisch groeiende tumoren is het omgekeerde het geval. Er worden diverse technieken gebruikt om preoperatief de invasiediepte te bepalen, maar het is nog onduidelijk wat de beste modaliteit is om mondholte carcinomen preoperatief te stadiëren.

Samenvatting literatuur

Description of studies included for the agreement on depth of invasion
Alsaffar (2016) assessed the agreement between palpation or MR images and histopathology for the depth of invasion. The study recruited patients with newly diagnosed oral squamous cell carcinoma (n=53) of which there were 34 males. The mean age was 64 (SD or range not reported). Various T-stages (T1: n=22, T2: n=22, T3: n=7, T4: n=2) and N-stages (N0: n=32, N1: n=7, N2: n=11) were in the sample. It was unclear which staging system was used, however it is likely the AJCC TNM-staging system (presumably the 7th edition) was used. The palpation was performed by the treating surgeon, prior to the radiological assessment. Preoperative MRI was performed and the depth of invasion was measured from the adjacent mucosa to the

deepest tumor invasion. The time period between the preoperative assessments and the histopathological assessment (on formalin fixed specimens) was unclear. Tumor invasion was categorized in two categories: < 5 millimeters and ≥ 5 millimeters. A Cohen's kappa was calculated to assess the agreement.

Goel (2016) recruited patients (n=61) to assess the agreement between clinical examination or MRI and histopathology for the depth of invasion (categorized in T-stages) in patients with biopsy proven squamous cell carcinomas of the tongue or gingiva-buccal area. Forty-five of the included patients were male and various T-stages were in the sample (T1: n=4, T2: n=16, T3: n=13, T4: n=28). A TNM staging system was used (unclear edition). No procedures were described for the clinical examination or histopathological assessment. However, the tissue was probably fixed with formalin. MRI was performed with a 1.5T scanner (used sequence: axial and coronal T2WI, postcontrast T1WI). The time period between the preoperative assessments and histopathological assessment was unclear. Agreement between the clinical examination or MR imaging and histopathology on the T-stage was calculated with a Cohen's kappa.

Iida (2018) assessed the agreement on depth of invasion between ultrasound and histopathology in patients with an early oral tongue squamous cell carcinoma between June 2008 and December 2015. Fifty-six patients were included, with a mean age of 59 years (range: 25 to 90) and of which 34 were male. All participants had their carcinoma located on the lateral ledge of the tongue. Tumor stage was not reported for the participants. It was unclear if and which edition of a staging system was used. The ultrasound assessment was performed in an outpatient clinic, using a 16-MHz scanner and a T-shaped ultrasonographic probe, where the patient extended their tongues during the preoperative ultrasound measurement. Histopathological assessment was performed with a micrometer in the tumor specimen, which was formalin-fixed and paraffin-embedded. The time period between preoperative ultrasound and postoperative histopathology was unclear. The depth of invasion was categorized by a threshold, resulting in two categories: < 5 millimeters and ≥ 5 millimeters. A Cohen's kappa was calculated for the agreement.

Mao (2019) investigated the agreement between MR imaging and histopathology in patients first diagnosed with squamous cell carcinoma of the tongue (n=150). The mean age of patients was 58 years (SD: 12.1). There were 80 males and 70 females in the sample, with various tumor locations: ventral side of the tongue (n=35), border of the tongue (n=89), dorsal side of the tongue (n=19), and the base of the tongue (n=7). Several tumor morphologies were identified: ulcer type (n=41), invasive type (n=94), and exogeneous type (n=15). Participants had a T-stage of T1 (n=43), T2 (n=71), or T3 (n=36) and an N-stage of N1 (n=16), N2b (n=17), or N2c (n=2). The 7th edition of the AJCC staging system was used. A 1.5T MR scanner was used 1 week preoperatively to measure the depth of invasion with a section thickness of 1 millimeter (used sequences: T1 axial, coronal and sagittal sequences, T2 axial and coronal sequences with fat suppression, T1-weighted axial, coronal and sagittal sequences with fat suppression and contrast media). Surgical tumor specimens were preserved in formalin. Pathological sections and staining were performed to measure the tumor invasion. Agreement was quantified in Bland-Altman plots for all participants, per T-stage, and per tumor morphology.

Verma (2019) assessed the agreement between MR imaging and histopathology for tumor thickness (per T-stage) in patients with biopsy proven squamous cell carcinoma of the tongue (n=50). The sample consisted of 38 males and 12 females with mean age of the sample was 49 (SD not reported). Various T-stages were prevalent in the sample: T1 (n=24), T2 (n=18), and T3 (n=8). The 7th and 8th edition of the AJCC staging

system were used for the study. No other characteristics were reported. Tumor thickness was preoperatively assessed with MR imaging (4 millimeter slices, used sequences: T1W1 axial and coronal, T2WI axial, coronal and saggital, coronal STIR, and postcontrast axial T1W). Tumor dimensions (anteroposteriorly, mediolaterally, superoinferiorly) were measured. Tumor thickness was measured in three dimensions with histopathology (presumably on formalin fixed material), however no further procedures were reported. The time period between the preoperative MR imaging and the histopathological assessment was unclear. A Cohen's kappa was not calculated by the authors, but could be calculated from the presented 3-by-3 table showing the T-classifications of MR imaging and histopathology.

Vidiri (2019) assessed the depth of invasion as well as tumor thickness (per T-stage) in patients diagnosed with oral tongue squamous cell carcinoma between 2013 and 2018. The median age for the patients (n=43, 18 males and 25 females) was 65 with a range from 31 to 81. Various T-stages were prevalent: T1 (n=10), T2 (n=12), and T3 (n=21). The 8th edition of the AJCC staging system was used. Preoperative MR imaging was performed with a 1.5T scanner 3 to 4 weeks preoperatively (used sequences: coronal T2W, axial FSE T2W, pre-contrast axial T1WI, DWI through single-shot spin-echo and echo-planar imaging). Two radiologists, one experienced and one inexperienced, assessed the images independently from each other. Agreement between histopathology (on formalin fixed material) and the results of both radiologists were reported separately. Resected tissue was fixed in formalin. Embedding, sectioning, and staining (with hematoxylin and eosin) was performed for histopathological analyses. Bland-Altman plots were reported for the depth of invasion and Cohen's kappa was reported for agreement on T-stage as tumor thickness.

Studies included for the agreement on tumor thickness
Brouwer de Koning (2019) investigated the agreement between ultrasound or MR imaging and histopathology for tumor thickness in clinically stages T1-2 oral cavity carcinomas. MR images were acquired between 2011 and 2016. A total of 83 patients were included in the analyses with a mean age of 61 years (range: 31 to 88). Forty-five patients were male. Several tumor locations were included in the study: tongue (n=58), floor of the mouth (n=24), palate (n=2), and the lip (n=1). The 7th and 8th editions of the AJCC staging system were used. Tumor thickness was measured with ultrasound in 46 patients and with MR imaging in 76 patients. For ultrasound, the probe (13 to 7 MHz transducer) was placed directly on the lesion. MR imaging was performed and tumor dimensions were measured in 3D (used sequences: T1W, TSE, TRA, TR, TE 538/10ms, flip angle 90, matrix 288/248, slice thickness of 4mm, STIR TSE COR, TR/TE 2500/60ms, matrix 216/170, T1 3D Thrive fat-saturation, intravenous injection of 15cc gadoterate meglumine, TR/TE 9.86/4.59ms, flip angle 10, matrix 200/179, slice thickness 1mm). Radiologists reported the MRI outcome and suggested a T-stage. The pathologist reported the tumor dimension in the pathological report. Further pathological procedures were not described and it was unclear how specimens were fixed. The time period between the preoperative assessments and the histopathological assessment was unclear.

Choi (2017) assessed the agreement between clinical examination and histopathology for the tumor thickness (categorized in T-stages) in n=252 patients with biopsy proven squamous cell carcinomas of the oral cavity. Patients had a median age of 55 years (range: 47 to 65) and had tumors on the tongue (n=195), floor of mouth (n=34), or on the buccal mucosa (n=23). Various T-stages were included in the sample: pT1 (n=109), pT2 (n=80), pT3 (n=25), pT4a (n=37), and pT4b (n=1). The 7th edition of the AJCC staging system was used. Clinical examination consisted of a physician performing preoperative endoscopic assessment, palpation and

imaging with either CT or MRI. Surgical specimens of the primary tumor were assessed microscopically, however it remained unclear how specimens were fixed. Agreement between the T-stages as assessed with the preoperative clinical examination and postoperative histopathology was quantified with a Cohen's kappa. The time period between both assessments was unclear.

Klein Nulent (2018) performed a systematic review with a search up to the 6th of July 2016 in PubMed (Medline), EMBASE, and the Cochrane databases for studies comparing intraoral ultrasound tumor thickness measurements with postoperative pathological assessment. Included studies had to contain patients with oral squamous cell carcinoma and the ultrasound measurements had to be performed preoperatively or intraoperatively. Included patients had tongue tumors, buccal mucosa tumors, tumors on the floor of the mouth, lip tumours, or alveolar mucosa tumors. Data was extracted according to the 7th edition of the AJCC staging system. Ten out of the twelve included studies (n=240) were used for the assessment of the agreement between intraoral ultrasound and postoperative histopathology in a Bland-Altman plot. For one of the included studies the authors estimated the individual patient data from a figure. The QUADAS-2 tool was used to assess the risk of bias of the included studies. Time between preoperative measurement and postoperative histology was not assessed. The tissue fixation method for histopathological analyses were not reported for the individual studies included in the systematic review.

Nair (2018) recruited patients with biopsy proven T1N0 (n=18) or T2N0 (n=6) primary squamous cell carcinomas of the tongue to assess the agreement between ultrasound and histopathology for tumor thickness. A total of 25 patient were recruited with a median age of 55 years (range: 22 to 76). Sixteen of the recruited patients were male. The 6th edition of the AJCC staging system was used. Preoperative ultrasound assessments using a 17 or 9 MHz conventional linear probe were performed with patients extending their tongue. The probe was placed directly upon the lesion. The surgical tumor specimens were placed in saline and immediately send to the pathology department for assessment (specimens were not fixed in formalin), where the specimens were cut into 2 to 3 millimeter thick transverse slices. The time period between the preoperative ultrasound assessment and the histopathological assessment was unclear.

Shintani (2001) assessed the agreement between CT or MRI and histopathology for the measurement of tumor thickness in 38 patients with oral cancer. Furthermore, ultrasound (7.5-Mhz intracavitarytransducers) was assessed and this data was included in the systematic review of Klein Nulent (2018). The patients had a mean age of 58.2 years (SD: not reported, range: 36 to 91) and had tumors on the tongue (n=26), buccal mucosa (n=8), and floor of mouth (n=4). The 5th edition of the UICC TNM staging system was used. Tumor thickness was measured with a contrast-enhanced 5-mm axial CT in 38 participants and with 4-mm axial and coronal T1/T2-weighted MR imaging in 26 patients. Histological sections (presumably from formalin fixed tissue) were assessed with a micrometer. The authors state that tumors smaller than 5 millimeters were difficult to differentiate with CT or MRI. Tumors were not detected by CT in 19 patients and by MRI in 11 patients. These patients were therefore not included in the analyses. Furthermore, the time period between the preoperative assessment and the histopathologic assessment was unclear.

Results

Depth of invasion

Results concerning the instrument agreement for depth of invasion are summarized in Table 1.

Categorical (T-stage)
Clinical examination

Goel (2016) reported the agreement between a clinical examination and histopathology in T-stages in 63 patients. It was unclear what the procedures for clinical examination were. Clinical assessment for T-stage showed an agreement of Cohen's kappa = 0.47 (95%CI: not reported) with histopathology.

CT

No studies were included that reported the T-stage agreement between CT and histopathology while measuring depth of invasion.

PET-CT

No studies were included that reported the T-stage agreement between PET-CT and histopathology while measuring depth of invasion.

MRI

Goel (2016) reported the agreement between MRI and histopathology in T-stages in 63 patients. A Cohen's kappa of 0.69 (95%CI: not reported) was found.

Verma (2019) reported the T-stage classifications of MRI and histopathology in a three-by-thee table (T1-3) from 50 included patients. A Cohen's kappa was not reported but could be calculated from the table. Here, a kappa of 0.65 was calculated (95%CI: not calculated).

Vidiri (2019) reported the T-stage agreement of an experienced and an inexperienced radiologist interpreting MR imaging with the histopathology results. The experienced radiologist showed a Cohen's kappa of 0.74 (95%CI: 0.56 to 0.92) for the agreement of T-stage between MRI and histopathology. For the inexperienced radiologist the Cohen's kappa was 0.60 (95%CI: 0.40 to 0.80).

Ultrasound

No studies were included that reported the T-stage agreement between ultrasound and histopathology while measuring depth of invasion.

Categorical (at a threshold)
Clinical examination

Alsaffar (2016) categorized the depth of invasion, which resulted in two categories: < 5 millimeters depth of invasion and ≥ 5 millimeters depth of invasion. The treating surgeon performed a palpation to assess the depth of invasion. The agreement between the treating surgeon's preoperative palpation and the postoperative histopathology was quantified with a Cohen's kappa (n=53). A kappa of 0.61 (95%CI: 0.36 to 0.87) was reported.

CT

No studies were included that reported the agreement at a specified threshold between CT and histopathology while measuring depth of invasion.

PET-CT

No studies were included that reported the agreement at a specified threshold between PET-CT and histopathology while measuring depth of invasion.

MRI

Alsaffar (2016) assessed the agreement between MRI and histopathology for measuring depth of invasion and used two categories: < 5 millimeters and ≥ 5 millimeters. A Cohen's kappa of 0.80 (95%CI: 0.59 to 1.00) was reported (n=43).

Ultrasound

Iida (2018) assessed the agreement between ultrasound and histopathology for the depth of invasion in 53 participants. Depth of invasion was categorized in: < 5 millimeters and ≥ 5 millimeters. A Cohen's kappa of 0.65 (95%CI: 0.43 to 0.87) was reported.

<u>Continuous (in millimeters)</u>

Clinical examination

No studies were included that reported the agreement on a continuous scale between clinical examination (palpation) and histopathology while measuring depth of invasion.

CT

No studies were included that reported the agreement on a continuous scale between CT and histopathology while measuring depth of invasion.

PET-CT

No studies were included that reported the agreement on a continuous scale between PET-CT and histopathology while measuring depth of invasion.

MRI

Mao (2019) constructed Bland-Altman plots for the agreement between MRI and histopathology measuring the depth of invasion. Several plots were constructed for different tumor stages and types. Overall, MRI showed a mean overestimation of 2.32 millimeters when compared to the histopathologic results (n=150). In 95% of the measurements, MRI measured between an underestimation of 0.97 millimeters (-0.97 millimeters) and an overestimation of 5.61 millimeters. Furthermore, agreement per tumor stage was assessed: T1 (mean difference: 1.46 millimeters, 95% limits of agreement: -0.67 to 3.63 millimeters, n=43), T2 (mean difference: 2.08 millimeters, 95% limits of agreement: -0.45 to 4.62 millimeters, n=71), and T3 (mean difference: 3.79 millimeters, 95% limits of agreement: -0.13 to 7.7 millimeters, n=36). Finally, agreement per tumor type was assessed: ulcer type (mean difference: 3.72 millimeters, 95% limits of agreement: -0.16 to 7.6 millimeters, n=41), invasive type (mean difference: 1.83 millimeters, 95% limits of agreement: -0.59 to 4.25 millimeters, n=91), and exogenous type (mean difference: 1.53 millimeters, 95% limits of agreement: 0.01 to 3.06 millimeters, n15).

Vidiri (2019) constructed Bland-Altman plots for the agreement between an experienced or inexperienced

radiologist using MRI and histopathology for the depth of invasion in 43 patients. The MRI measurements by an experienced radiologist had a mean underestimation of 0.3 millimeters (-0.3 millimeters), where 95% of the measurements lay between an underestimation of 5.5 millimeters (-5.5 millimeters) and an overestimation of 4.9 millimeters. For the inexperienced radiologist the MRI measurements had a mean underestimation of 0.4 millimeters (-0.4 millimeters), while 95% of the MRI measurements lay between an underestimation of 6.6 millimeters (-6.6 millimeters) and 5.8 millimeters overestimation.

Ultrasound
No studies were included that reported the agreement on a continuous scale between ultrasound and histopathology while measuring depth of invasion.

Table 1 Study results for depth of invasion per measurement level per instrument

Variable	Measurement level	Measurement instrument	Threshold	Author	Result	Risk of Bias (COSMIN, unless stated otherwise)
Depth of invasion	**Categorical (T-stage)**	Clinical examination (unclear procedures)	T-stage	Goel 2016	Kappa for the agreement of T-stage, n=61 (clinical examination versus pathological data): K=0.47 (95%CI: not reported)	Doubtful
		CT	No studies were included that reported the T-stage agreement between CT and histopathology while measuring depth of invasion.			
		PET-CT	No studies were included that reported the T-stage agreement between PET-CT and histopathology while measuring depth of invasion.			
		MRI	T-stage	Goel 2016	Kappa for the agreement of T-stage, n=61 (MRI versus pathological data): K=0.69 (95%CI: not reported)	Doubtful
			T-stage	Verma 2019	Kappa for the agreement of tumour thickness (T-stage) as measured by MRI and histopathology was not reported. However, the 3x3 table was reported from which a kappa could be calculated in n= 50: Kappa = 0.65	Doubtful

			T-stage	Vidiri 2019	Kappa for the agreement of T-stage, n=43 (MRI experienced radiologist versus pathological data): K=0.74 (95%CI: 0.56-0.92) Kappa for the agreement of T-stage, n=43 (MRI inexperienced radiologist versus pathological data): K=0.60 (95%CI: 0.40-0.80)	Adequate
		Ultrasound	T-stage	No studies were included that reported the T-stage agreement between ultrasound and histopathology while measuring depth of invasion.		
Categorical (at a threshold)	Clinical examination (palpation)	5 mm	Alsaffar 2016	Kappa at a threshold of 5 millimetres, n=53: K=0.61 (95%CI: 0.36-0.87)		Doubtful
	CT	No studies were included that reported the agreement at a specified threshold between CT and histopathology while measuring depth of invasion.				
	PET-CT	No studies were included that reported the agreement at a specified threshold between PET-CT and histopathology while measuring depth of invasion.				
	MRI	5 mm	Alsaffar 2016	Kappa at a threshold of 5 millimetres, n=53: K=0.80 (95%CI: 0.59-1.00)		Doubtful
	Ultrasound	5 mm	Iida 2018	Kappa at a threshold of 5 millimetres, n=59: K=0.651 (95%CI: 0.43-0.87)		Doubtful
Continuous	Clinical examination	No studies were included that reported the agreement on a continuous scale between clinical examination (palpation) and histopathology while measuring depth of invasion.				
	CT	No studies were included that reported the agreement on a continuous scale between CT and histopathology while measuring depth of invasion.				
	PET-CT	No studies were included that reported the agreement on a continuous scale between PET-CT and histopathology while measuring depth of invasion.				
	MRI	NA	Mao 2019	Bland-Altman plot overall n=150 (MRI-histopathology), mm: Mean difference: 2.32. 95% upper limit: 5.61 95% lower limit: -0.97 Bland-Altman plot tumour T1-stage	Adequate

n=43 (MRI-histopathology), mm:
Mean difference: 1.48.
95% upper limit: 3.63
95% lower limit: -0.67

Bland-Altman plot tumour T2-stage
n=71 (MRI-histopathology), mm:
Mean difference: 2.08.
95% upper limit: 4.62
95% lower limit: -0.45

Bland-Altman plot tumour T3-stage
n=36 (MRI-histopathology), mm:
Mean difference: 3.79.
95% upper limit: 7.70
95% lower limit: -0.13

Bland-Altman plot ulcer type tumour
n=41 (MRI-histopathology), mm:
Mean difference: 3.72.
95% upper limit: 7.60
95% lower limit: -0.16

Bland-Altman plot invasive type
tumour n=91 (MRI-histopathology),
mm:
Mean difference: 1.83.
95% upper limit: 4.25
95% lower limit: -0.59

Bland-Altman plot exogenous type
tumour n=15 (MRI-histopathology),
mm:
Mean difference: 1.53.
95% upper limit: 3.06
95% lower limit: 0.01

		NA	Vidiri 2019	Bland-Altman plot n=43 (MRI experienced radiologist-histopathology), mm: Mean difference: -0.3 95% upper limit: 4.9 95% lower limit: -5.5 Bland-Altman plot n=43 (MRI inexperienced radiologist-histopathology), mm: Mean difference: -0.4 95% upper limit: 5.8 95% lower limit: -6.6	Adequate
		Ultrasound		No studies were included that reported the agreement on a continuous scale between ultrasound and histopathology while measuring depth of invasion.	
NA: Not Applicable					

Tumor thickness
Results concerning the instrument agreement for tumor thickness are summarized in Table 2.

Categorical (T-stage)
Clinical examination
Choi (2017) reported a Cohen's kappa = 0.81 (95%CI not reported) for the agreement of T-stages between a preoperative clinical assessment and a histopathologic assessment in 252 participants. The clinical examination consisted of an endoscopic assessment, a palpation, and either CT or MR imaging.

CT
No studies were included that reported the T-stage agreement between CT and histopathology while measuring tumor thickness.

PET-CT
No studies were included that reported the T-stage agreement between PET-CT and histopathology while measuring tumor thickness.

MRI
No studies were included that reported the T-stage agreement between MRI and histopathology while measuring tumor thickness.

Ultrasound
No studies were included that reported the T-stage agreement between ultrasound and histopathology while measuring tumor thickness.

Categorical (at a threshold)

Clinical examination

No studies were included that reported the agreement at a specified threshold between clinical examination and histopathology while measuring tumor thickness.

CT

No studies were included that reported the agreement at a specified threshold between CT and histopathology while measuring tumor thickness.

PET-CT

No studies were included that reported the agreement at a specified threshold between PET-CT and histopathology while measuring tumor thickness.

MRI

No studies were included that reported the agreement at a specified threshold between MRI and histopathology while measuring tumor thickness.

Ultrasound

No studies were included that reported the agreement at a specified threshold between ultrasound and histopathology while measuring tumor thickness.

Continuous (in millimeters)

Clinical examination

No studies were included that reported the agreement on a continuous scale between clinical examination (palpation) and histopathology while measuring tumor thickness.

CT

Shintani (2001) did not report agreement parameters. However, the agreement could be calculated from the reported individual patient data (n=19). CT had a mean overestimation of 5.93 millimeters. When the 95% limits of agreement were calculated, 95% of the CT measurements lay between an underestimation of 5.66 millimeters (-5.66 millimeters) and an overestimation of 17.53 millimeters compared to histopathology.

PET-CT

No studies were included that reported the agreement on a continuous scale between PET-CT and histopathology while measuring tumor thickness.

MRI

Brouwer de Koning (2019) constructed a Bland-Altman plot where the mean overestimation of MRI was 1.3 millimeters in 83 patients. Ninety-five percent of the MRI measurements fell between an underestimation of 6.1 millimeters (-6.1 mm) and an overestimation of 8.6 millimeters compared to histopathology.

Shintani (2001) did not report agreement parameters. Nonetheless, the agreement between MRI and

histopathology could be calculated (n=13). The mean difference was an overestimation of 8.55 millimeters by MRI. When the 95% limits of agreement were calculated, 95% of the MRI measurements lay between an underestimation of 5.94 millimeters (-5.94 millimeters) and an overestimation of 23.05 millimeters compared to histopathology.

Ultrasound
Brouwer de Koning (2019) reported a mean overestimation of 0.05 millimeters by ultrasound when compared to histopathological results in 83 patients. The ultrasound measurements were in 95% of the cases between an underestimation of 5.3 millimeters (-5.3 millimeters) and an overestimation of 5.4 millimeters when compared to histopathologic results.

Klein Nulent (2018) performed a systematic review and used individual patient data from 240 patients to construct a Bland-Altman plot. Ultrasound had a mean overestimation of 0.5 millimeters compared to histopathology. In 95% of the measurements the ultrasound resulted in measurements between -5.5 millimeters (5.5 millimeters underestimation) and 6.5 millimeters (6.5 millimeters overestimation) when compared to histopathology results.

Nair (2018) recruited 24 patients for the agreement between ultrasound and histopathology measuring tumor thickness. A Bland-Altman plot showed a mean difference between ultrasound an histoplathology where ultrasound underestimated the tumor thickness by 0.15 millimeters (-0.15 millimeters). The limits of agreement were not reported but could be approximated from the reported figure. Here, 95% of the ultrasound measurements were between 4.6 millimeters underestimation (-4.6 millimeters) and 4.99 millimeters overestimation compared to histopathologic results.

Table 2 Study results for tumor thickness per measurement level per instrument

Variable	Measurement level	Measurement instrument	Threshold	Author	Result	COSMIN Risk of Bias
Tumor thickness	**Categorical (T-stage)**	Clinical examination (endoscopic + palpation + CT or MRI)	T-stage	Choi 2017	Kappa for the agreement of T-stage n=252 (clinical examination versus pathological data): K=0.81 (95%CI: not reported)	Doubtful
		CT	No studies were included that reported the T-stage agreement between CT and histopathology while measuring tumor thickness.			
		PET-CT	No studies were included that reported the T-stage agreement between PET-CT and histopathology while measuring tumor thickness.			
		MRI	No studies were included that reported the T-stage agreement between MRI and histopathology while measuring tumor thickness.			

		Ultrasound	No studies were included that reported the T-stage agreement between ultrasound and histopathology while measuring tumor thickness.		
	Categorical (at a threshold)	Clinical examination	No studies were included that reported the agreement at a specified threshold between clinical examination and histopathology while measuring tumor thickness.		
		CT	No studies were included that reported the agreement at a specified threshold between CT and histopathology while measuring tumor thickness.		
		PET-CT	No studies were included that reported the agreement at a specified threshold between PET-CT and histopathology while measuring tumor thickness.		
		MRI	No studies were included that reported the agreement at a specified threshold between MRI and histopathology while measuring tumor thickness.		
		Ultrasound	No studies were included that reported the agreement at a specified threshold between ultrasound and histopathology while measuring tumor thickness.		
	Continuous	Clinical examination	No studies were included that reported the agreement on a continuous scale between clinical examination (palpation) and histopathology while measuring tumor thickness.		
		CT	NA	Shintani 2001	Bland-Altman parameters calculated from presented data n=19 (CT-histopathology), mm: Mean difference: 5.93. 95% upper limit: 17.53 95% lower limit: -5.66	Doubtful
		PET-CT	NA	No studies were included that reported the agreement on a continuous scale between PET-CT and histopathology while measuring tumor thickness.		

MRI	NA	Brouwer de Koning 2019	Bland-Altman plot n=83 (MRI-histopathology), mm: Mean difference: 1.3. 95% upper limit: 8.6 95% lower limit: -6.1	Doubtful
	NA	Shintani 2001	Bland-Altman parameters calculated from presented data n=13 (MRI-histopathology), mm: Mean difference: 8.55. 95% upper limit: 23.05 95% lower limit: -5.94	Doubtful
Ultrasound	NA	Brouwer de Koning 2019	Bland-Altman plot n=83 (US-histopathology), mm: Mean difference: 0.05. 95% upper limit: 5.4 95% lower limit: -5.3	Doubtful

| | | | NA | Klein Nulent 2018 | Bland-Altman plot n=240 (ultrasound-histopathology), mm: Mean difference: 0.5. 95% upper limit: 6.5 95% lower limit: -5.5 | Klein Nulent 2018 assessed the risk of bias with the QUADAS-2 tool. For flow and timing: 4 low risk / 1 high risk / 7 unclear |
| | | | NA | Nair 2018 | Bland-Altman plot overall n=150 (US-histopathology), mm: Mean difference: -0.15 95% upper limit: 4.99 95% lower limit: -4.6 Limits of agreement were approximated from the provided Bland-Altman plot: | Doubtful |

NA: Not applicable

Level of evidence of the literature
Depth of invasion
Categorical (T-stage)
Clinical examination
The level of evidence regarding clinical examination for the outcome measure 'categorical agreement (T-stage)' was downgraded by 3 levels because of study limitations (2 level for risk of bias: there is only one study of doubtful quality), and the number of included patients (1 level for imprecision: sample size was less than 100, but more than 50); publication bias was not assessed.

CT
GRADE could not be applied because none of the included studies reported data about the categorical agreement on T-stage between CT and histopathology when measuring depth of invasion.

PET-CT

GRADE could not be applied because none of the included studies reported data about the categorical agreement on T-stage between PET-CT and histopathology when measuring depth of invasion.

MRI
The level of evidence regarding MRI for the outcome measure 'categorical agreement (T-stage)' was downgraded by 1 level because of study limitations (1 level for risk of bias: multiple studies of doubtful quality and one study of adequate quality); publication bias was not assessed.

Ultrasound
GRADE could not be applied because none of the included studies reported data about the categorical agreement on T-stage between ultrasound and histopathology when measuring depth of invasion.

<u>Categorical (at a threshold)</u>
Clinical examination
The level of evidence regarding clinical examination (palpation) for the outcome measure 'categorical agreement (at a threshold)' was downgraded by 3 levels because of study limitations (2 levels for risk of bias: there is only one study of doubtful quality) and the number of included patients (1 level for imprecision: sample size was less than 100, but more than 50); publication bias was not assessed.

CT
GRADE could not be applied because none of the included studies reported data about the categorical agreement for depth of invasion at a threshold between CT and histopathology.

PET-CT
GRADE could not be applied because none of the included studies reported data about the categorical agreement for depth of invasion at a threshold between PET-CT and histopathology.

MRI
The level of evidence regarding MRI for the outcome measure 'categorical agreement (at a threshold)' was downgraded by 3 levels because of study limitations (2 levels for risk of bias: there is only one study of doubtful quality) and the number of included patients (1 level for imprecision: sample size was less than 100, but more than 50); publication bias was not assessed.

Ultrasound
The level of evidence regarding ultrasound for the outcome measure 'categorical agreement (at a threshold)' was downgraded by 3 levels because of study limitations (2 levels for risk of bias: there is only one study of doubtful quality) and the number of included patients (1 level for imprecision: sample size was less than 100, but more than 50); publication bias was not assessed.

<u>Continuous (in millimeters)</u>
Clinical examination
GRADE could not be applied because none of the included studies reported data about the agreement on a continuous scale for depth of invasion between a clinical examination and histopathology.

CT

GRADE could not be applied because none of the included studies reported data about the agreement on a continuous scale for depth of invasion between CT and histopathology.

PET-CT

GRADE could not be applied because none of the included studies reported data about the agreement on a continuous scale for depth of invasion between PET-CT and histopathology.

MRI

The level of evidence regarding MRI for the outcome measure 'continuous agreement (in millimeters)' was downgraded by 1 level because of conflicting results (1 level for inconsistency: Mao (2019) reports a mean overestimation of 2.32 millimeters, while Vidiri (2019) reports a mean underestimation of 0.3 millimeters. Furthermore, Vidiri (2019) reports wider 95% lower limits of agreement when compared to Mao (2019): an underestimation of 5.5 millimeters (Vidiri, 2019) versus an underestimation of 0.97 millimeters (Mao, 2019)); publication bias was not assessed.

Ultrasound

GRADE could not be applied because none of the included studies reported data about the agreement on a continuous scale for depth of invasion between ultrasound and histopathology.

Tumor thickness
<u>*Categorical (T-stage)*</u>
Clinical examination
The level of evidence regarding a clinical examination (consisting of an endoscopic examination, palpation, and either CT or MR imaging) for the outcome measure 'categorical agreement (T-stage)' was downgraded by two levels because of study limitations (2 levels for risk of bias: there is only one study of doubtful quality); publication bias was not assessed.

CT

GRADE was not applied because none of the included studies reported data about the categorical agreement on T-stage between CT and histopathology when measuring tumor thickness.

PET-CT

GRADE was not applied because none of the included studies reported data about the categorical agreement on T-stage between PET-CT and histopathology when measuring tumor thickness.

MRI

GRADE was not applied because none of the included studies reported data about the categorical agreement on T-stage between MRI and histopathology when measuring tumor thickness.

Ultrasound

GRADE was not applied because none of the included studies reported data about the categorical agreement on T-stage between ultrasound and histopathology when measuring tumor thickness.

Categorical (at a threshold)
Clinical examination
GRADE was not applied because none of the included studies reported data about the categorical agreement for tumor thickness at a threshold between a clinical examination and histopathology.

CT
GRADE was not applied because none of the included studies reported data about the categorical agreement for tumor thickness at a threshold between CT and histopathology.

PET-CT
GRADE was not applied because none of the included studies reported data about the categorical agreement for tumor thickness at a threshold between PET-CT and histopathology.

MRI
GRADE was not applied because none of the included studies reported data about the categorical agreement for tumor thickness at a threshold between MRI and histopathology.

Ultrasound
GRADE was not applied because none of the included studies reported data about the categorical agreement for tumor thickness at a threshold between ultrasound and histopathology.

Continuous (in millimeters)
Clinical examination
GRADE was not applied because none of the included studies reported data about the agreement on a continuous scale for tumor thickness between a clinical examination and histopathology.

CT
The level of evidence regarding CT for the outcome measure 'agreement on a continuous measurement level (in millimeters)' was downgraded by 4 levels because of study limitations (2 levels for risk of bias: there is only one study of doubtful quality) and the number of included patients (2 levels for imprecision: the sample size was less than 50); publication bias was not assessed.

PET-CT
GRADE was not applied because none of the included studies reported data about the agreement on a continuous scale for tumor thickness between PET-CT and histopathology.

MRI
The level of evidence regarding MRI for the outcome measure 'agreement on a continuous measurement level (in millimeters)' was downgraded by 2 levels because of study limitations (1 level for risk of bias: there were multiple studies of doubtful quality) and the number of included patients (1 level for imprecision: the

sample size was less than 100, but more than 50); publication bias was not assessed.

Ultrasound
The level of evidence regarding ultrasound for the outcome measure 'agreement on a continuous measurement level (in millimeters)' was downgraded by 1 level because of study limitations (1 level for risk of bias: there were multiple studies of doubtful quality. Klein Nulent 2018 assessed the risk of bias with the QUADAS-2 and scored 4 studies with low risk / 1 study with high risk / 7 studies with unclear risk on the 'flow and timing' item); publication bias was not assessed.

Conclusions
Depth of invasion
The agreement estimates of modalities measuring depth of invasion and their certainty (following GRADE) are summarized in Table 3.

Table 3 Summarized results for the agreement and GRADE certainty of clinical examination, CT, PET-CT, MRI, or intraoral ultrasound measuring depth of invasion

Modality	Agreement on a categorical level per T-Stage (GRADE certainty)	Agreement on a categorical level using a threshold (GRADE certainty)	Agreement on a continuous level (GRADE certainty)
Clinical examination	K = 0.47 (unclear procedures) (VERY LOW)	K = 0.61 (95%CI: 0.36-0.87) at a 5-millimeter threshold (palpation) (VERY LOW)	NA
	References: Goel 2016	*References: Alsaffar 2016*	*NA*
CT	NA	NA	NA
PET-CT	NA	NA	NA
MRI	Range: K = 0.60-0.74 (MODERATE)	K = 0.80 (95%CI: 0.59-1.00) at a 5-millimeter threshold (VERY LOW)	Range upper 95% LoA: 4.9-5.8* Range mean difference: -0.4–2.32* Range lower 95% LoA: -0.97– -6.6* (MODERATE)
	References: Goel 2016; Verma 2019; Vidiri 2019	*References: Alsaffar 2016*	*References: Mao 2019; Vidiri 2019*
Ultrasound	NA	K = 0.65 (95%CI: 0.43-0.87) at a 5-millimeter threshold (VERY LOW)	NA
	NA	*References: Iida 2018*	*NA*
*Sub-analyses in Mao 2019 were not included in the range **CI: Confidence Interval** **LoA: Limit of Agreement** **NA: Not Available**			

Tumor thickness
The agreement estimates of modalities measuring tumor thickness and their certainty (following GRADE) are summarized in Table 4.

Table 4 Summarized results for the agreement and GRADE certainty of clinical examination, CT, PET-CT, MRI, or intraoral ultrasound measuring tumor thickness

Modality	Agreement on a categorical level per T-Stage (GRADE certainty)	Agreement on a categorical level using a threshold (GRADE certainty)	Agreement on a continuous level (GRADE certainty)
Clinical examination	K = 0.81 (endoscopic examination, palpation, and either CT or MR imaging) (LOW)	NA	NA
	References: *Choi 2017*	*NA*	*NA*
CT	NA	NA	Upper 95% LoA: 17.53 Mean difference: 5.93 Lower 95% LoA: -5.66 (VERY LOW)
	NA	NA	*References:* Shintani 2001
PET-CT	NA	NA	NA
MRI		NA	Range upper 95% LoA: 8.6-23.05 Range mean difference: 1.3-8.55 Range lower 95% LoA: -5.94– -6.1 (LOW)
	NA	*NA*	*References:* *Brouwer de Koning 2019;* *Shintani 2001*

Ultrasound	NA	NA	Range upper 95% LoA: 4.99-6.5
			Range mean difference: -0.15-0.5
			Range lower 95% LoA: -4.6– -5.5 (MODERATE)
	NA	*NA*	*References: Brouwer de Koning 2019; Klein Nulent 2018; Nair 2018*

CI: Confidence Interval
LoA: Limit of Agreement
NA: Not Available

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What is the agreement between preoperative clinical examination (by palpation), computed tomography (CT), positron emission tomography/computed tomography (PET-CT), magnetic resonance imaging (MRI) or intraoral ultrasound, and postoperative histopathologic results for measuring the depth of the invasion (or tumor thickness) by a tumor in patients with an oral cavity carcinoma?

P: patients with an oral cavity carcinoma;
I: preoperative determination of the depth of invasion (or tumor thickness) with palpation, CT, PET-CT, MRI, or intraoral ultrasound;
C: comparisons between palpation, CT, PET-CT, MRI, or intraoral ultrasound with postoperative pathological assessment as a reference standard;
O: agreement parameters on a continuous (depth in millimeters) or categorical (at a threshold, or for T-stage) measurement level.

Relevant outcome measures
The guideline development group considered agreement parameters regarding the final T-staging of the tumor and agreement on a continuous measurement level as a critical outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined an underestimation and overestimation of >2 millimeter compared to the postoperative pathological assessment as a clinically important disagreement. This is acknowledged to be an arbitrary choice, since evidence regarding the clinical importance of the 2-millimeter border is lacking. A

Cohen's kappa (k) was considered sufficient when the K was greater or equal to 0.70 (Terwee, 2007; Prinssen, 2016).

The working group defined the time between preoperative assessment and the surgical resection shorter than or equal to 4 weeks as adequate. This is acknowledged to be an arbitrary interval, however it was presumed that this period would usually not allow a change in the construct to be measured.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 12th of November 2019 for systematic reviews and primary diagnostic studies. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 311 hits. Studies were selected based on the following criteria: patients had an oral cavity carcinoma, agreement between preoperative assessment of the depth of invasion or tumor thickness with palpation (clinical examination) /CT/PET-CT/MRI/intraoral ultrasound and a postoperative pathological assessment was reported, reported parameters were for absolute agreement or these could be calculated. Initially 35 studies were selected after the screening of title and abstract. The working group checked the methods of the full-text studies to determine whether 'depth of invasion' or 'tumor thickness' was measured. After reading the full text, 24 studies were excluded (see the table with reasons for exclusion under the tab Evidence tables). Ten primary studies and one systematic review were included.

<u>Results</u>

Six primary studies were included in the analyses of literature for depth of invasion. One systematic review (10 studies provided information) and four primary studies were included for tumor thickness. Important study characteristics and results were extracted in the evidence tables. Results are summarized in Table 1 (depth of invasion) and Table 2 (tumor thickness) under the 'summary of literature'. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab Evidence tables).

Risk of bias was assessed with the *Consensus-based Standards for the selection of health Measurement INstruments* (COSMIN) risk of bias checklist (Mokkink, 2010). The boxes concerning reliability and measurement error were used for the risk of bias assessment, since the clinical question concerned inter-instrument reliability and/or inter-instrument agreement. The conclusive risk of bias outcome is the lowest score on the COSMIN 4-point risk of bias tool (i.e. the lowest-score-counts principle). The study design and procedures for each assessed instrument was assessed. For example, when a study assessed both CT and MRI measurements (separately) versus histopathological measurements, both the design and procedures of CT versus histopathology and MRI versus histopathology are assessed individually for potential risk of bias. A preoperative assessment with an interval of 4 weeks or shorter before surgery was deemed appropriate.

The adapted GRADE assessment was conducted in accordance with the described procedure by Mokkink (2018). The adapted GRADE procedure entailed that three levels could be downgraded in the risk of bias domain: one level for a serious risk (multiple studies of doubtful quality or one study of adequate quality), two levels for a very serious risk (multiple studies of inadequate quality or one study of doubtful quality), or three levels for an extremely serious risk (only one study of inadequate quality). The inconsistency domain could be downgraded by one or two levels when there was unexplained heterogeneity between the reported

outcomes. A maximum of two levels could be downgraded for imprecision: one level (body of evidence contains n=50 to n=100), or two levels (body of evidence contains less than n=50). When the included study did not completely match the PICO as defined in this guideline module, one or two levels could be downgraded for indirectness. Publication bias is not assessed in the adjusted GRADE procedure.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Bepaling botinvasie

Uitgangsvraag

Hoe dient botinvasie van de mandibula preoperatief bepaald te worden?

Aanbeveling

Gebruik voor het detecteren van botinvasie de beeldvormende technieken (CT en/of MRI) die standaard gebruikt worden voor het bepalen van de uitbreiding van de primaire tumor.

Overweeg bij een onzekere CT of MRI uitslag een cone beam-CT (CBCT) te maken bij alle mondholtecarcinomen die tegen de mandibula aangelegen zijn om botinvasie te diagnosticeren.

Overweeg het gebruik van SPECT-CT alleen in geselecteerde gevallen waar de uitslagen van CT/MRI/CBCT onzeker zijn en het uitsluiten van botinvasie van invloed is op het chirurgisch behandelplan.

Overwegingen

Er is een redelijk vertrouwen in de gevonden sensitiviteit van SPECT (0,97; 95% betrouwbaarheidsinterval(BHI) 0,92 tot 0,99) bij de diagnostisering van mandibulaire botinvasie. De zekerheid over de gevonden sensitiviteit was laag voor CBCT (0,90; 95%BHI 0,85 to 0,93), CT (0,73; 95%BHI 0,66 tot 0,80), MRI (0,88; 95%BHI 0,78 tot 0,94) en OPG (0,75; 95%BHI 0,67 tot 0,82) bij de diagnostisering van botinvasie en zeeg laag voor CT (0,85; 95%BHI 0,43 tot 0,98), PET-CT (0,90; 95%BHI: 0,58 tot 0.98) en MRI (0,93; 95%BHI 0,81 tot 0,98) bij de diagnostisering van beenmerginvasie door een tumor. Er werden geen data gerapporteerd voor dual energy-CT (DECT).

Voor de specificiteit van beeldvormende modaliteiten is er een redelijk vertrouwen in CT (0,91; 95%BHI 0,88 tot 0,94) en OPG (0,83; 95%BHI 0,79 tot 0,86) bij de diagnostisering van botinvasie. De zekerheid van de gevonden specificiteit van SPECT (0,69; 95%BHI 0,52 tot 0,82), CBCT (0,85; 95%BHI 0,62 tot 0,95), en MRI (0,90; 95%BHI 0,80 tot 0,95) was laag bij de diagnostisering van botinvasie en zeer laag voor CT (0,86; 95%BHI 0,73 tot 0,93), PET-CT (0,89; 95%BHI: 0,85 tot 1,00) en MRI (0,84; 95%BHI 0,60 tot 0,95) bij de diagnostisering van beenmerginvasie. Er werden geen data gerapporteerd voor DECT.

Er was tevens een zeer laag vertrouwen in de acht algoritmen uit Van Cann (2008), voornamelijk door het lage aantal deelnemers in de studie. De diagnostische test accuratesse van elk algoritme is te zien in Tabel 5 (tabblad 'Samenvatting literatuur'). De auteurs concludeerden dat het uitvoeren van een CT of MRI gevolgd door een SPECT het aantal mandibulaire resecties aanzienlijk zou verminderen en dat SPECT alleen noodzakelijk is indien de voorafgaande CT of MRI geen mandibulaire invasie laat zien (Van Cann, 2008).

Het zeer lage vertrouwen in beeldvormende modaliteiten voor het diagnosticeren van beenmerginvasie door tumoren wordt met name veroorzaakt door onverklaarbare heterogeniteit tussen studies en/of het lage aantal deelnemers in de studies (Qiao, 2018). Er werden geen data gerapporteerd met betrekking tot de positief en negatief voorspellende waarde in de systematische review van Qiao (2018). Na de zoekdatum van deze richtlijnmodule verscheen er een artikel over de diagnostische accuratesse van DECT voor het detecteren van

beenmergoedeem (Timmer, 2020). Beenmergoedeem kan optreden bij botinvasie, maar ook bij trauma, bloedingen of ontstekingen. DECT (2e of 3e generatie scanners) werd als indextest afgezet tegenover MRI (Short Tau Inversion Recovery (STIR) of T2-weighted MRI met vetonderdrukking). De gemiddelde tijd tussen DECT en MRI was 9 dagen (SD: 11). Er werden 33 patiënten geselecteerd die tussen 2016 en 2018 zowel DECT als MRI ondergingen voor hoofd-hals abnormaliteiten. Indicaties in de steekproef waren hoofd-hals maligniteiten (n=27, waarvan n=15 voor mondholte maligniteiten), infecties (n=3), goedaardige tumor (n=1), en veranderingen na radiotherapie (n=2). Alle beelden werden door twee radiologen onafhankelijk van elkaar beoordeeld en waren geblindeerd voor de indicatie, klinische diagnose en andere patiëntgegevens. De auteurs rapporteerden de sensitiviteit (0,85), specificiteit (0,92), positief voorspellende waarde (0,94) en negatief voorspellende waarde (0,80), maar geen bijgaande 95% betrouwbaarheidsintervallen. De auteurs concludeerden dat, wanneer er contra-indicaties zijn voor het maken van een MRI, DECT de potentie heeft om als alternatief het beenmergoedeem te kunnen detecteren.

Bij een onjuiste diagnose van botinvasie kan onder- of overbehandeling plaatsvinden. Bij een fout-positieve bevinding wordt onterecht een (uitgebreidere) mandibularesectie verricht. Het hierna ontstane defect dient meestal gereconstrueerd te worden en bemoeilijkt dentale rehabilitatie. Bij een fout-negatieve bevinding zal bij de tumorresectie de resectierand positief zijn, waardoor adjuvante behandeling (heroperatie en/of (chemo)radiotherapie) met bijbehorende morbiditeit nodig is en de prognose waarschijnlijk negatief beïnvloed wordt. Er zijn geen aanvullende argumenten vanuit andere groepen of interventies bekend. Het genoemde probleem bij fout-positieve bevinding en op basis hiervan marginale mandibularesectie is een groter probleem bij patiënten met een lage onderkaak. Bij deze patiënten ontstaat eerder een continuïteitsonderbreking, waardoor meestal een uitgebreidere reconstructie nodig is.

Preoperatief is het belangrijk om zo goed mogelijk geïnformeerd te zijn over eventuele botinvasie van een primair mondholtecarcinoom. Deze informatie wordt gebruikt bij het opstellen van het therapieplan, met name of een marginale dan wel segmentale mandibularesectie dient te worden verricht. De uitgebreidheid van de operatie hangt hier dus (gedeeltelijk) vanaf. De meeste van deze beeldvormend onderzoeken kunnen poliklinisch laagdrempelig gemaakt worden (bijvoorbeeld orthopantomogram (OPG) en CBCT) of worden al gemaakt om de uitbreiding in de weke delen te beoordelen (bijvoorbeeld MRI). De sensitiviteit van de CBCT en MRI is hoog bij een acceptabele specificiteit, waardoor het risico op positieve of krappe resectieranden (met indicatie voor adjuvante behandeling en kans op slechtere overleving) laag is en het risico op een te uitgebreide behandeling (met risico op extra morbiditeit) acceptabel is.

Een CT of MRI wordt in de meeste centra standaard vervaardigd om de uitbreiding naar weke delen te bepalen bij mondholtecarcinomen. Deze scans hebben ook een waarde bij de diagnostiek naar botinvasie. Het gebruik van deze, reeds vervaardigde beeldvorming, zal dan geen belasting en geen extra kosten met zich meebrengen voor het detecteren van botinvasie. Een CBCT is vaak gemakkelijk met lage kosten beschikbaar en heeft ook een goede sensitiviteit. Hoewel een SPECT (botscintigrafie) de hoogste sensitiviteit lijkt te hebben, is dit onderzoek duurder en minder gemakkelijk toegankelijk dan de alternatief beschikbare beeldvormende technieken, die laagdrempelig en tegen lagere kosten kunnen worden vervaardigd. Daarnaast is de kwaliteit van beeldvorming voor (vrijwel) alle modaliteiten in de loop der jaren verbeterd. Dit is een ook in de toekomst een continu proces.

Alle onderzochte beeldvormende onderzoeken zijn voor iedereen bereikbaar. SPECT en DECT zijn minder gemakkelijk toegankelijk, terwijl OPG, CBCT, CT en MRI juist gemakkelijk voor iedere patiënt toegankelijk zijn. Een OPG en CBCT worden routinematig zeer frequent op de polikliniek Mondziekten, Kaak-, en Aangezichtschirurgie verricht. CT en MRI zijn standaard onderzoeken bij patiënten met hoofd-halskanker. Niet elke patiënt kan echter een MRI ondergaan door angst, claustrofobie of metalen voorwerpen in het lichaam. Daarnaast kunnen er restricties zijn voor nierpatiënten om een CT met contrastvloeistof te ondergaan. Zie hiervoor ook de algemene contra-indicaties voor MRI en CT. In deze situaties zou een CBCT alleen mogelijk ook voldoende kunnen zijn. Er zijn geen subgroepen van patiënten bekend met andere waarden en voorkeuren.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Een OPG wordt veelal standaard verricht voor focusonderzoek. De sensitiviteit (met name voor invasie van het beenmerg) lijkt te laag te zijn, zodat bij een negatieve uitslag aanvullend onderzoek verricht dient te worden. CT en/of MRI worden veelal standaard voor andere doeleinden gemaakt. De sensitiviteit en specificiteit van deze modaliteiten lijken acceptabel te zijn voor het detecteren van botinvasie, zonder extra kosten. SPECT lijkt het meest sensitief te zijn, maar is minder goed toegankelijk en is duurder. Een CBCT lijkt een hoge sensitiviteit en specificiteit voor het detecteren van botinvasie van de mandibula te hebben. CBCT is een onderzoek dat laagdrempelig en tegen lage kosten vaak poliklinisch kan worden verricht omdat veel MKA poliklinieken CBCT apparatuur beschikbaar hebben.

Onderbouwing

Achtergrond

Mandibulaire botinvasie door een mondholtecarcinoom is geassocieerd met een slechtere lokale controle. Botinvasie zou daarom behandeld dienen te worden met een chirurgische resectie van een deel van de mandibula, wat meer functieverlies voor de patiënt kan veroorzaken. Vanwege de verstrekkende consequenties van een chirurgische resectie is het belangrijk om met beeldvorming vóór de ingreep betrouwbaar te kunnen bepalen of er sprake is van mandibulaire botinvasie.

Conclusies

Algorithms to detect mandibular bone invasion

Very low GRADE	There is a very low certainty about the **sensitivity** of the diagnostic algorithm in Van Cann (2008) for diagnosing mandibular bone invasion by a tumor in patients with an oral cavity carcinoma. *Sources: (Van Cann, 2008)*

Very low GRADE	There is a very low certainty about the **specificity** of the diagnostic algorithm in Van Cann (2008) for diagnosing mandibular bone invasion by a tumor in patients with an oral cavity carcinoma. *Sources: (Van Cann, 2008)*

Very low GRADE	There is a very low certainty about the **positive predictive value** of the diagnostic algorithm in Van Cann (2008) for diagnosing mandibular bone invasion by a tumor in patients with an oral cavity carcinoma. *Sources: (Van Cann, 2008)*

Very low GRADE	There is a very low certainty about the **negative predictive value** of the diagnostic algorithm in Van Cann (2008) for diagnosing mandibular bone invasion by a tumor in patients with an oral cavity carcinoma. *Sources: (Van Cann, 2008)*

Samenvatting literatuur

<u>Description of the systematic review for the diagnostic accuracy of imaging modalities</u>
Qiao (2018) performed a diagnostic test accuracy systematic review of imaging modalities for the diagnosis of mandibular bone invasion. On the first of November 2017 the following databases were searched by Qiao (2018): MEDLINE, CINAHL, Latin American and Caribbean Health Sciences, Chinese Biomedical Literature Databases, China National Knowledge Infrastructure, VIP database, and the Wanfang Database. Grey literature was searched in Science Paper Online, System for Information on Grey Literature in Europe, and the WHO International Clinical Trials Registry Platform. Twenty-one Chinese journals were hand-searched for additional relevant studies (journals were not referenced). Studies were included when designed as a cohort, participants were diagnosed with oral or head and neck cancer with preoperative biopsy and mandibulectomy during surgery, the index test of interest was used (CT, MRI, CBCT, OPG, PET-CT, SPECT, BS, US), pathological diagnosis was used as a reference test, the target condition was mandible invasion by the tumor, and when outcomes of interest were reported (or could be calculated). Their search and selection resulted in the inclusion of 49 unique studies (of which 45 were relevant to the PICRO in this guideline module). All of the included studies recruited patients with oral cavity carcinomas, while less than half the studies also recruited some patients with tumor locations outside the oral cavity. Twenty-six studies exclusively selecting oral cavity carcinomas recruited 1372 patients in total. Twenty-three studies recruiting patients with tumors at oral cavity sites as well as head and neck sites included the following tumor locations: cheek (13 studies), lymph node (1 study), tonsil (6 studies), mandible (2 studies), submandibular trigone (1 study), submandibular glad (1 study), oropharynx (5 studies), and/or pharynx (1 study). Two authors independently assessed the risk of bias of the individual studies with the QUADAS-2 instrument. Results of the studies were pooled (statistical model was not mentioned) and a meta-regression was performed, if possible, to assess the observed heterogeneity between studies. The mean age (when reported) of patients varied from 51.5 to 73.6 years. The number of male patients (when reported) participating in studies varied from 50% to 88.2%. The prevalence of mandibular invasion in the included studies varied from 17.6% to 95.2%. The used tracers for SPECT in the 14 included studies were: [99m]Technetium mythelene diphosphonate (n=7), [99m]Technetium hydroxymethelene di phosphonate (n=4), [99m]Technetium dicarboxy propan (n=1), [99m]Technetium 3,3-disphosphono-1,2-propanedicarboxylic acid (n=1), [201]TI-chloride (n=1), [99m]Technetium-bisphosphonate (n=1, unclear which

specific type), unclear (n=2). Two studies used two different tracers for separate groups in the sample (^{99m}Technetium mythelene diphosponate or ^{99m}Technetium hydroxymethylene diphosponate). One study used a dual isotope protocol (^{99m}Technetium hydroxymethylene diphosphonate and ^{201}TI-chloride).

Description of studies with diagnostic algorithms
Van Cann (2008) described eight different diagnostic algorithms using SPECT, CT, and MRI to diagnose mandibular bone invasion in patients with oral cavity carcinomas. Data from 67 patients (62.7% male) were analyzed. The mean age was 64 years (range: 43-84). Patients had tumours at the following sites: floor of mouth (n=31), retromolar area (n=20), lower alveolar process (n=13), or cheek mucosa (n=3). There were two assessors for each imaging modality. The assessors were blinded from the results of the imaging modalities they did not assess. A positive result for CT was defined as the absence of cortex adjacent to an abnormal tissue mass. A positive result for MRI was defined as the replacement of the hypointense signal of cortical bone by the signal intensity of a tumour on both the SE T2-weighted and SE T1-weighted images, or as a replacement of hyperintense signal of medullary bone by the tumour intensity signal. No criteria were provided for a positive SPECT. The reference test was a histopathological assessment. Cortical bone invasion was defined as the replacement of bone by an advancing tumour front, without invasion to cancellous spaces, the dental canal, or the periodontal ligament. Medullary invasion was defined as the diffuse growth through the cortex into cancellous bone, the dental canal, or the periodontal ligament. The absence of bone invasion was defined as a continuous periosteal layer separating the tumor from bone. Eight algorithms were presented:

Algorithm I: start with SPECT

- Negative SPECT à No invasion.
- Positive SPECT, continue with MRI:
    - Negative MRI, continue with CT:
        - Negative CT à No invasion.
        - Positive CT à Invasion.
    - Positive MRI à Invasion.

Algorithm II: start with SPECT:

- Negative SPECT à No invasion.
- Positive SPECT, continue with CT:
    - Negative CT, continue with MRI:
        - Negative MRI à No invasion.
        - Positive MRI àInvasion.
    - Positive CT à Invasion.

Algorithm III: start with MRI:

- Positive MRI à Invasion.
- Negative MRI, continue with SPECT:

- Positive SPECT, continue with CT:
    - Negative CT à No invasion.
    - Positive CT à Invasion.
- Negative SPECT à No invasion.

Algorithm IV: start with MRI:

- Positive MRI à Invasion.
- Negative MRI, continue with CT:
    - Negative CT, continue with SPECT:
        - Negative SPECT à No invasion.
        - Positive SPECT à Invasion.
    - Positive CTà invasion.

Algorithm V: start with CT:

- Positive CT à Invasion.
- Negative CT, continue with SPECT:
    - Positive SPECT, continue with MRI:
        - Negative MRI à No invasion.
        - Positive MRI à Invasion.
    - Negative SPECT à No invasion.

Algorithm VI: start with CT:

- Positive CT -> Invasion.
- Negative CT, continue with MRI:
    - Negative MRI, continue with SPECT:
        - Negative SPECT à No invasion.
        - Positive SPECT à Invasion.
    - Positive MRI à Invasion.

Algorithm VII: start with MRI:

- Positive MRI à Invasion.
- Negative MRI, continue with SPECT:
    - Positieve SPECT à Invasion
        - Negatieve SPECT à No invasion

Algorithm VIII: start with CT:

- Positive CT à Invasion.

- Negative CT, continue with SPECT:
  - Positive SPECT à Invasion.
  - Negative SPECT à No invasion.

Results

Diagnostic test accuracy of imaging modalities

Orthopantogram (OPG)

Sensitivity

From 15 studies (n=772, as described in the systematic review's characteristics table) data were pooled by Qiao (2018) for the sensitivity of OPG in diagnosing mandibular bone invasion. A pooled sensitivity estimate of 0.75 (95%CI: 0.67 to 0.82, I^2=62%) was reported. For medullary invasion, Qiao (2018) included 1 study (n=29, as described in the study characteristics table) where a sensitivity of 0.63 was found (95%CI not reported).

Specificity

A pooled specificity estimate of 0.83 (95%CI: 0.79 to 0.86, I^2=19%) was calculated by Qiao (2018) for OPG in diagnosing mandibular bone invasion. Data were pooled from 15 studies (n=772, as described in the systematic review's characteristics table). Qiao (2018) included 1 study (n=29, as described in the study characteristics table) for the specificity of OPG in diagnosing medullary invasion. A specificity of 0.90 was presented (95%CI not reported).

Positive predictive value

No studies were included that reported the positive predictive value for OPG.

Negative predictive value

No studies were included that reported the negative predictive value for OPG.

Cone Beam Computed Tomography (CBCT):

Sensitivity

Data from 5 studies were pooled (n=557, as described in the systematic review's characteristics table) for CBCT diagnosing mandibular invasion (Qiao, 2018). The pooled sensitivity was 0.90 (95%CI: 0.85 to 0.93, I^2=0%).

Specificity

Qiao (2018) pooled data from 5 studies (n=557, as described in the systematic review's characteristics table) for the specificity of CBCT in diagnosing mandibular bone invasion. A pooled specificity of 0.85 (95%CI: 0.62 to 0.95, I^2=80%) was reported.

Positive predictive value

No studies were included that reported the positive predictive value for CBCT.

Negative predictive value

No studies were included that reported the negative value for CBCT.

Computed Tomography (CT)
Sensitivity

From 35 studies (n=1908, as described in the systematic review's characteristics table) data was pooled by Qiao (2018) for the sensitivity of CT diagnosing mandibular bone invasion. The pooled sensitivity was 0.73 (95%CI: 0.66 to 0.80, I^2=70%). Qiao (2018) also pooled data from 4 studies (n=145, as described in the study characteristics table) for the sensitivity of CT in diagnosing mandibular medullary invasion. A pooled sensitivity of 0.85 (95%CI: 0.43 to 0.98, I^2=83%) was found.

Specificity

Qiao (2018) calculated a pooled estimate of the specificity of CT diagnosing mandibular bone invasion from 35 studies (n=1908, as described in the systematic review's characteristics table). From these 35 studies, 9 were published before the year 2000 (publication range: 1990 and 1998, n=397 participants) and 26 were published since the year 2000 (publication range: 2000-2014, n=1511 participants). A pooled specificity of 0.91 (95%CI: 0.88 to 0.94, I^2=49%) was reported. The pooled specificity for CT diagnosing medullary invasion was calculated from 5 studies (n=145, as described in the study characteristics table) and was 0.86 (95%CI: 0.73 to 0.93, I^2=32%).

Positive predictive value

No studies were included that reported the positive predictive value for CT.

Negative predictive value

No studies were included that reported the negative predictive value for CT.

Positron Emission Tomography-Computed Tomography (PET-CT)
Sensitivity

Four studies (n=114, as described in the systematic review's characteristics table) were pooled by Qiao (2018) to calculate a summary sensitivity for diagnosing mandibular bone invasion. All of these four studies were published after the year 2000 (range: 2005 and 2011). A pooled sensitivity of 0.90 (95%CI: 0.58 to 0.85, I^2= 64%) was reported. Qiao (2018) also included 2 studies for diagnosing medullary invasion with PET-CT. The reported sensitivity in both studies were 0.78 and 1.00, respectively (95% CI's were not reported).

Specificity

Qiao (2018) pooled 4 studies (n= 114, as described in the systematic review's characteristics table) to calculate a summary specificity. The four studies were published between 2005 and 2011. A summary specificity of 0.89 (95%CI: 0.77 to 0.96) was reported for PET-CT diagnosing mandibular bone invasion. Qiao (2018) also included two studies for diagnosing medullary invasion with PET-CT. The reported specificity in both studies were 0.14 and 0.86, respectively (95% CI's were not reported).

Positive predictive value

No studies were included that reported the positive predictive value for PET-CT.

Negative predictive value
No studies were included that reported the negative predictive value for PET-CT.

Single-Photon Emission Computed Tomography (SPECT)
Sensitivity
Qiao (2018) used data from 13 studies on the diagnostic accuracy of SPECT for diagnosing mandibular bone invasion. There was data from 858 patients (as described in the systematic review's characteristics table of Qiao (2018). Data was pooled and a sensitivity of 0.97 (95%CI: 0.92 to 0.99, I^2=72%) was reported.

Specificity
Qiao (2018) reported a pooled specificity of 0.69 (95%CI: 0.52 to 0.82, I^2=79%) for SPECT diagnosing mandibular bone invasion. Data from 13 studies (n=858, as described in the systematic review's characteristics table) was pooled.

Positive predictive value
No studies were included that reported the positive predictive value for SPECT.

Negative predictive value
No studies were included that reported the negative predictive value for SPECT.

Dual Energy Computed Tomography (DECT):
No studies were included that reported the diagnostic test accuracy of DECT.

Magnetic Resonance Imaging (MRI)
Sensitivity
For the sensitivity of MRI in diagnosing mandibular bone invasion, Qiao (2018) pooled data from 18 studies (n=820, as described in the systematic review's characteristics table). A pooled sensitivity of 0.88 (95%CI: 0.78 to 0.94, I^2=76%) was presented. For diagnosing medullary invasion with MRI, data from 7 studies (n=311, as described in the study characteristics table) were pooled by Qiao (2018). The pooled sensitivity was 0.93 (95%CI: 0.81 to 0.98, I^2=79%).

Specificity
The pooled specificity of MRI for diagnosing mandibular bone invasion was calculated by Qiao (2018) from data in 18 studies (n=820, as described in the systematic review's characteristics table). The pooled specificity was 0.90 (95%CI: 0.80 to 0.95, I^2=81%). Qiao (2018) also pooled data for the specificity of MRI in diagnosing medullary invasion. From 7 studies (n=311, as described in the study characteristics table), a specificity of 0.84 (95%CI: 0.60 to 0.95, I^2=79%) was found.

Positive predictive value
No studies were included that reported the positive predictive value for MRI.

Negative predictive value
No studies were included that reported the positive predictive value for MRI.

Algorithms for bone invasion

Sensitivity

The sensitivity of the algorithms was not reported (Van Cann, 2008). From the reported data about the classifications of the algorithms (i.e. true positives, false positives, false negatives, true negatives) a sensitivity was calculated per algorithm. The sensitivity of the algorithms varied between 0.77 and 1.00. See Table 1 for an overview per algorithm and Figure 1 for a graphical representation.

Specificity

The specificity of the algorithms was not reported (Van Cann, 2008). From the reported data about the classifications of the algorithms (i.e. true positives, false positives, false negatives, true negatives) a specificity was calculated per algorithm. The specificity of the algorithms varied between 0.57 and 1.00. See Table 1 for an overview per algorithm and Figure 1 for a graphical representation.

Positive predictive value

The positive predictive value of the algorithms was not reported (Van Cann, 2008). From the reported data about the classifications of the algorithms (i.e. true positives, false positives, false negatives, true negatives) a positive predictive value was calculated per algorithm. The positive predictive value of the algorithms varied between 0.80 and 1.00. See Table 1 for an overview per algorithm.

Negative predictive value

The negative predictive value of the algorithms was not reported (Van Cann, 2008). From the reported data about the classifications of the algorithms (i.e. true positives, false positives, false negatives, true negatives) a negative predictive value was calculated per algorithm. The negative predictive value of the algorithms varied between 0.69 and 1.00. See Table 1 for an overview per algorithm.

Table 1 An overview of the used modalities and the diagnostic accuracy per algorithm, in Van Cann (2008). The PPV, NPV, sensitivity, and specificity were calculated from the reported (mis)classifications

Algorithm	Sequential tests	Sample size	TP	FP	FN	TN	PPV	NPV	Sensitivity (95%CI)	Specificity (95%CI)
Algorithm I	SPECT-MRI-CT	65	33	1	9	22	0,97	0,71	0.79 (0.63-0.90)	0.96 (0.78-1.00)
Algorithm II	SPECT-CT-MRI	66	33	0	10	22	1,00	0,69	0.77 (0.61-0.88)	1.00 (0.85-1.00)
Algorithm III	MRI-SPECT-CT	65	33	1	9	22	0,97	0,71	0.79 (0.63-0.90)	0.96 (0.78-1.00)
Algorithm IV	MRI-CT-SPECT	66	43	10	0	13	0,81	1.00	1.00 (0.92-1.00)	0.57 (0.34-0.77)
Algorithm V	CT-SPECT-MRI	66	33	1	10	22	0,97	0,69	0.77 (0.61-0.88)	0.96 (0.78-1.00)
Algorithm VI	CT-MRI-SPECT	66	43	10	0	13	0,81	1,00	1.00 (0.92-1.00)	0.57 (0.34-0.77)
Algorithm VII	MRI-SPECT	65	42	10	0	13	0,80	1,00	1.00 (0.92-1.00)	0.57 (0.34-0.77)
Algorithm VIII	CT-SPECT	66	43	10	0	13	0,81	1,00	1.00 (0.92-1.00)	0.57 (0.34-0.77)

TP: True positive
FP: False positive
FN: False negative
TN: True negative
PPV: Positive predictive value
NPV: Negative predictive value
CI: Confidence interval

Figure 1 A graphical representation of the diagnostic accuracy per algorithm, in Van Cann (2008). Sensitivity and specificity were calculated from the reported (mis)classifications

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Algoritme I	33	1	9	22	0.79 [0.63, 0.90]	0.96 [0.78, 1.00]
Algoritme II	33	0	10	22	0.77 [0.61, 0.88]	1.00 [0.85, 1.00]
Algoritme III	33	1	9	22	0.79 [0.63, 0.90]	0.96 [0.78, 1.00]
Algoritme IV	43	10	0	13	1.00 [0.92, 1.00]	0.57 [0.34, 0.77]
Algoritme V	33	1	10	22	0.77 [0.61, 0.88]	0.96 [0.78, 1.00]
Algoritme VI	43	10	0	13	1.00 [0.92, 1.00]	0.57 [0.34, 0.77]
Algoritme VII	42	10	0	13	1.00 [0.92, 1.00]	0.57 [0.34, 0.77]
Algoritme VIII	43	10	0	13	1.00 [0.92, 1.00]	0.57 [0.34, 0.77]
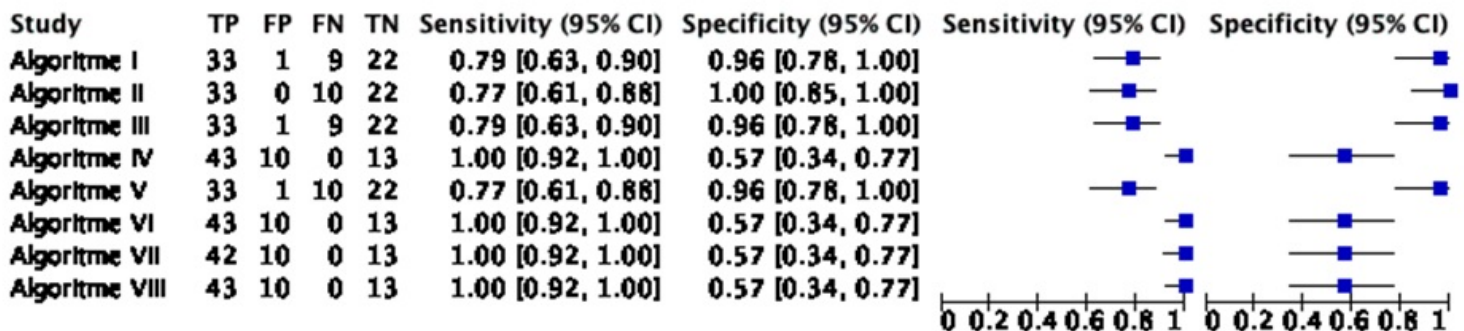
Level of evidence of the literature
Modalities for mandibular bone invasion
OPG

Sensitivity (mandibular bone invasion)
The level of evidence regarding sensitivity (for mandibular bone invasion) was downgraded by 2 levels because of the study limitations (1 level for risk of bias: 72% of the judgements were 'unclear' in the assessment with the QUADAS-2 tool) and the number of included patients (1 level for imprecision: the upper and lower limit of the confidence interval of the pooled accuracy estimate may lead to different conclusions); Publication bias was not assessed.

Specificity (mandibular bone invasion):
The level of evidence regarding specificity (for mandibular bone invasion) was downgraded by 2 levels because of the study limitations (1 level for risk of bias: 72% of the judgements were 'unclear' in the assessment with the QUADAS-2 tool); Publication bias was not assessed.

Positive predictive value:
The positive predictive value was not reported and therefore a GRADE assessment could not be performed.

Negative predictive value:
The negative predictive value was not reported and therefore a GRADE assessment could not be performed.

<u>CBCT</u>
Sensitivity (mandibular bone invasion)
The level of evidence regarding sensitivity (for mandibular bone invasion) was downgraded by 2 levels because of the study limitations (1 level for risk of bias: 4 out of 5 judgements for the selection of participants, 3 out of 5 judgements for the reference test, and 3 out of 5 judgements for the flow and timing were 'unclear' in the assessment with the QUADAS-2 tool) and the number of included patients (1 level for imprecision: the number of included patients is relatively low); Publication bias was not assessed.

Specificity (mandibular bone invasion)
The level of evidence regarding specificity (for mandibular bone invasion) was downgraded by 2 levels because of the study limitations (1 level for risk of bias: 4 out of 5 judgements for the selection of participants, 3 out of 5 judgements for the reference test, and 3 out of 5 judgements for the flow and timing were 'unclear' in the assessment with the QUADAS-2 tool) and conflicting results (1 level for inconsistency: the heterogeneity could not be explained by the variables in the meta-regression for CBCT performed by Qiao (2018), The I^2 was 90%); Publication bias was not assessed.

Positive predictive value:
The positive predictive value was not reported and therefore a GRADE assessment could not be performed.

Negative predictive value:
The negative predictive value was not reported and therefore a GRADE assessment could not be performed.

<u>CT</u>
Sensitivity (mandibular bone invasion)
The level of evidence regarding sensitivity (for mandibular bone invasion) was downgraded by 2 levels

because of the study limitations (1 level for risk of bias: 61% of the judgements were 'unclear' in the assessment with the QUADAS-2 tool) and conflicting results (1 level for inconsistency: the heterogeneity could not be explained by the variables in the meta-regression for CT performed by Qiao (2018), The I^2 was 70%); Publication bias was not assessed.

Specificity (mandibular bone invasion)
The level of evidence regarding specificity (for mandibular bone invasion) was downgraded by 1 level because of the study limitations (1 level for risk of bias: 61% of the judgements were 'unclear' in the assessment with the QUADAS-2 tool); Publication bias was not assessed.

Sensitivity (medullary bone invasion)
The level of evidence regarding sensitivity (for medullary bone invasion) was downgraded by 3 levels because of the study limitations (1 level for risk of bias: 65% of the judgements were 'unclear' in the assessment with the QUADAS-2 tool) and conflicting results (2 levels for inconsistency: the confidence intervals overlap insufficiently while the heterogeneity was unexplained, the I^2 was 83%); Publication bias was not assessed.

Specificity (medullary bone invasion)
The level of evidence regarding specificity (for medullary bone invasion) was downgraded by 3 levels because of the study limitations (1 level for risk of bias: 65% of the judgements were 'unclear' in the assessment with the QUADAS-2 tool) and the number of included patients (2 levels for imprecision: the number of patients was low); Publication bias was not assessed.

Positive predictive value
The positive predictive value was not reported and therefore a GRADE assessment could not be performed.

Negative predictive value
The negative predictive value was not reported and therefore a GRADE assessment could not be performed.

<u>PET-CT</u>
Sensitivity (mandibular bone invasion)
The level of evidence regarding sensitivity was downgraded by 3 levels because of the study limitations (1 level for risk of bias: Three of the four included studies had an unclear risk in the 'patient selection' and 'reference test' domains of the QUADAS-2 tool) and the number of included patients (2 levels for imprecision: the number of patients was low); Publication bias was not assessed.

Specificity (mandibular bone invasion)
The level of evidence regarding specificity was downgraded by 3 levels because of the study limitations (1 level for risk of bias: Three of the four included studies had an unclear risk in the 'patient selection' and 'reference test' domains of the QUADAS-2 tool) and the number of included patients (2 levels for imprecision: the number of patients was low); Publication bias was not assessed.

Positive predictive value
The positive predictive value was not reported and therefore a GRADE assessment could not be performed.

Negative predictive value
The negative predictive value was not reported and therefore a GRADE assessment could not be performed.

SPECT
Sensitivity (mandibular bone invasion)
The level of evidence regarding the sensitivity (for mandibular bone invasion) was downgraded by 1 level because of the study limitations (1 level for risk of bias: 57% of the risk of bias judgements were 'unclear' in the assessment with the QUADAS-2 tool); publication bias was not assessed.

Specificity (mandibular bone invasion)
The level of evidence regarding specificity (for mandibular bone invasion) was downgraded by 2 levels because of the study limitations (1 level for risk of bias: 57% of the risk of bias judgements were 'unclear' in the assessment with the QUADAS-2 tool) and conflicting results (1 level for inconsistency: the heterogeneity could not be explained by the variables in the meta-regression for SPECT performed by Qiao (2018)); Publication bias was not assessed.

Positive predictive value
The positive predictive value was not reported and therefore a GRADE assessment could not be performed.

Negative predictive value
The negative predictive value was not reported and therefore a GRADE assessment could not be performed.

Algorithms for mandibular bone invasion
Algorithms in Van Cann (2008)
Sensitivity
The level of evidence regarding sensitivity was downgraded by 3 levels because of the study limitations (1 level for risk of bias: judgements were largely 'unclear' in the risk of bias assessment) and the number of included patients (2 levels for imprecision: the number of included patients is very low); Publication bias was not assessed.

Specificity
The level of evidence regarding specificity was downgraded by 3 levels because of the study limitations (1 level for risk of bias: judgements were largely 'unclear' in the risk of bias assessment) and the number of included patients (2 levels for imprecision: the number of included patients is very low and the upper and lower limit of the confidence interval of the pooled accuracy estimate may lead to different conclusions); Publication bias was not assessed.

Positive predictive value
The level of evidence regarding positive predictive value was downgraded by 3 levels because of the study limitations (1 level for risk of bias: judgements were largely 'unclear' in the risk of bias assessment) and the number of included patients (2 levels for imprecision: the number of included patients is very low); Publication bias was not assessed.

Negative predictive value
The level of evidence regarding negative predictive value was downgraded by 3 levels because of the study limitations (1 level for risk of bias: judgements were largely 'unclear' in the risk of bias assessment) and the number of included patients (2 levels for imprecision: the number of included patients is very low); Publication bias was not assessed.

Conclusions
Imaging modalities (mandibular bone invasion)
The pooled accuracy estimates of imaging modalities and their certainty (following GRADE) for detecting mandibular bone invasion are presented in Table 2. Positive and negative predictive values were not reported.

Table 2 Pooled accuracy estimates and GRADE certainty for imaging modalities detecting mandibular bone invasion

Imaging modality	Sensitivity (95%CI) (GRADE certainty)	Specificity (95%CI) (GRADE certainty)	Positive / negative predictive values (95%CI) (GRADE certainty)	Reference
OPG	0.75 (0.67-0.82) (LOW)	0.83 (0.79-0.86) (MODERATE)	NA	*Qiao 2018*
CBCT	0.90 (0.85-0.93) (LOW)	0.85 (0.62-0.95) (LOW)	NA	*Qiao 2018*
CT	0.73 (0.66-0.80) (LOW)	0.91 (0.88-0.94) (MODERATE)	NA	*Qiao 2018*
PET-CT	0.90 (0.58-0.85) (VERY LOW)	0.89 (0.77-0.96) (VERY LOW)	NA	*Qiao 2018*
SPECT	0.97 (0.92-0.99) (MODERATE)	0.69 (0.52-0.82) (LOW)	NA	*Qiao 2018*
DECT	NA	NA	NA	*NA*
MRI	0.88 (0.78-0.94) (LOW)	0.90 (0.80-0.95) (LOW)	NA	*Qiao 2018*

Imaging modalities (medullary bone invasion)
The pooled accuracy estimates of imaging modalities and their certainty (following GRADE) for detecting medullary bone invasion are presented in Table 3. Positive and negative predictive values were not reported. The working-group decided not to present the test performance in a hypothetical cohort based on an arbitrarily chosen pretest probability.

Table 3 Pooled accuracy estimates and GRADE certainty for imaging modalities detecting medullary bone invasion

Imaging modality	Sensitivity (95%CI) (GRADE certainty)	Specificity (95%CI) (GRADE certainty)	Positive/negative predictive values (95%CI) (GRADE certainty)	Reference
OPG	NA	NA	NA	*NA*
CBCT	NA	NA	NA	*NA*
CT	0.85 (0.43-0.98) (VERY LOW)	0.86 (0.73-0.93) (VERY LOW)	NA	*Qiao 2018*
PET-CT	NA	NA	NA	*NA*
SPECT	NA	NA	NA	*NA*
DECT	NA	NA	NA	*NA*
MRI	0.93 (0.81-0.98) (VERY LOW)	0.84 (0.60-0.95) (VERY LOW)	NA	*Qiao 2018*

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What is the diagnostic accuracy of an orthopantogram (OPG), Cone Beam Computed Tomography (CBCT), Computed Tomography (CT), Positron Emission Tomography-Computed Tomography (PET-CT), Single-Photon Emission Computed Tomography (SPECT), Dual Energy Computed Tomography (DECT), Magnetic Resonance Imaging (MRI), or diagnostic algorithms with a pathological assessment as reference to diagnose mandibular bone invasion of a tumor preoperatively in patients with oral cancer?

P: patients with an oral cavity carcinoma at risk for mandibular bone invasion;
I: preoperative diagnosis of mandibular invasion with OPG, CBCT, CT, PET-CT, SPECT, DECT, MRI, or with a diagnostic algorithm;
C: comparison of modalities;
R: postoperative pathological assessment;
O: sensitivity, specificity, positive predictive value, negative predictive value.

A priori, the working group did not define cortical/medullary bone invasion but used the definitions used in the studies.

<u>Relevant outcome measures</u>
The guideline development group considered sensitivity and negative predictive value as a critical outcome measure for decision making; and specificity and positive predictive value as an important outcome measure for decision making.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via embase.com) were searched with relevant terms for primary diagnostic studies of diagnostic algorithms until 18th of November 2019. The systematic literature search resulted in 56 hits. Studies reporting diagnostic algorithms were selected on the following criteria: the population were patients with oral cavity carcinomas, the patients were suspected of mandibular bone

invasion, the mandibular invasion was preoperatively diagnosed by using a diagnostic algorithm, the diagnostic accuracy was reported, the reference standard was a postoperative pathological assessment. Studies reporting an algorithm were excluded when the (imaging) data were collected before the year 2000. Based on title and abstract, nineteen studies were initially selected. Eighteen studies were excluded after reading the full-text (see the table with reasons for exclusion under the tab Evidence tables). One study reporting diagnostic algorithms was included.

A second search was performed. The databases Medline (via OVID) and Embase (via embase.com) were searched with relevant terms for diagnostic test accuracy systematic reviews of imaging modalities until 20th of November 2019. The systematic literature search resulted in 22 hits. Studies reporting the diagnostic test accuracy of imaging modalities were selected based on the following criteria: the population were patients with oral cavity carcinomas, the patients were suspected of mandibular bone invasion, the mandibular invasion was preoperatively diagnosed with OPG/CBCT/CT/PET-CT/SPECT/DECT/MRI, the diagnostic accuracy was reported, the reference standard was a postoperative pathological assessment. Based on title and abstract, eleven systematic reviews were initially selected. Ten systematic reviews were excluded after reading the full-text (see the table with reasons for exclusion under the tab Evidence tables). One systematic review reporting the diagnostic accuracy of imaging modalities was included.

The details of both search strategies are depicted under the tab Methods.

Results

Two studies were included in the analysis of the literature (one study for diagnostic algorithms and one diagnostic test accuracy systematic review). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab Evidence tables).

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Qiao X, Liu W, Cao Y, Miao C, Yang W, Su N, Ye L, Li L, Li C. Performance of different imaging techniques in the diagnosis of head and neck cancer mandibular invasion: A systematic review and meta-analysis. Oral Oncol. 2018 Nov;86:150-164. doi: 10.1016/j.oraloncology.2018.09.024. Epub 2018 Sep 25. PubMed PMID: 30409295.
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Diagnostiek orofarynxcarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Bepaling HPV-status

Uitgangsvraag

Hoe moet de HPV-status bepaald worden?

De uitgangsvraag omvat de volgende deelvragen:

1. Hoe moet de HPV-status op histologisch materiaal bepaald worden bij patiënten met een gediagnosticeerd orofarynx carcinoom?
2. Hoe moet de HPV-status bepaald worden bij patiënten met een lymfekliermetastase in de hals van een onbekende primaire tumor?

Aanbeveling

Aanbeveling-1
Onafhankelijkheid
Voer een HPV-test onafhankelijk van kennis over het anamnestische rookgedrag van de patiënt uit.

Aanbeveling-2
Bij (klinische verdenking op) nieuwe orofarynxcarcinomen

- Voer een hoog risico (HR)-HPV test uit op alle nieuw gediagnosticeerde plaveiselcelcarcinomen van de orofarynx, onafhankelijk van het histologische subtype.
- Voer de HR-HPV test uit op de primaire tumor of op een metastase indien deze metastase klinisch afkomstig is van het orofarynxcarcinoom.
- Voer p16 immunohistochemie uit op histologisch materiaal van een orofarynxcarcinoom als HR-HPV test. Overweeg een additionele specifieke test als bevestiging.
- Voer HR-HPV testen uit op cytologisch materiaal van een lymfklierpunctaat indien er geen histologisch materiaal aanwezig is en histologisch materiaal niet te verkrijgen is bij patiënten met een orofarynxcarcinoom dat nog niet eerder getest is of bij patiënten met een klinische verdenking op een orofarynxcarcinoom.

Aanbeveling-3
Bij metastasen van onbekende primaire tumor

- Voer routinematig een HR-HPV test uit op materiaal van patiënten met een plaveiselcelcarcinoommetastase van onbekende primaire tumor bij metastasen in Level II of III van de hals.
- Voer p16 immunohistochemie uit op histologisch materiaal uit een level II of III lymfekliermetastase met onbekende primaire tumor.
- Voer p16 immunohistochemie uit op histologisch materiaal van lymfekliermetastase buiten level II of III met onbekende primaire tumor in geval van niet-keratiniserende morfologie. Overweeg een additionele specifieke test als bevestiging.

- Voer HR-HPV testen uit op cytologisch materiaal van een lymfklierpunctaat indien er geen histologisch materiaal aanwezig is en dit materiaal niet te verkrijgen is bij patiënten met een onbekende primaire tumor.

NB: er wordt geen aanbeveling gegeven over de te gebruiken test op cytologisch materiaal.

Aanbeveling-4
Niet routinematig onderzoek

- Voer niet routinematig HR-HPV testen uit voor niet-plaveiselcelcarcinomen.
- Voer niet routinematig HR-HPV testen uit op andere primaire hoofd-hals carcinomen dan orofarynx.
- Overweeg geen HR-HPV testen uit te voeren bij patiënten met een residu of recidiverende tumor waarvan de HPV status initieel al was vastgesteld. Overweeg bij twijfel of het een recidiverende eerste tumor is om wél een HR-HPV test uit te voeren.
- Voer niet routinematig laag risico HPV testen uit op plaveiselcelcarcinomen van het hoofd-halsgebied.

Aanbeveling-5
Rapportage

- Rapporteer p16-positiviteit in het histologisch materiaal bij ten minste matige tot sterke aankleuring van 70% van de cellen als surrogaat voor HR-HPV.
- Rapporteer p16 immunohistochemie-positieve of HR-HPV-positieve primaire orofarynxcarcinomen als p16-positief of HPV-positief.
- Gradeer de HPV/p16-positieve orofarynxcarcinomen niet.

Overwegingen

Prigge (2017) vond een hoge sensitiviteit (0,93; 95%BHI: 0,87 to 0,97; ^{2}: 23,4%) en een hoge specificiteit (0,96; 95%BHI: 0,89 to 1,00; I^2: 68,4%) voor het gecombineerde gebruik van p16^{INK4a} met een HPV DNA PCR op histologisch materiaal van mensen met een plaveiselcarcinoom van de orofarynx. Er werden geen positief en negatief voorspellende waarden gerapporteerd. De zekerheid in deze diagnostische accuratesse werd echter als zeer laag beoordeeld, gezien het onduidelijk was of de geïncludeerde studies onwenselijke exclusies vermeden, er enige zorgen waren over de toepasbaarheid met betrekking tot te patiënten in de steekproeven en vanwege de kleine informatie grootte door het lage deelnemersaantal (imprecisie).

Er werden veel verschillende methoden en procedures gevonden voor testen op cytologisch materiaal van patiënten met een plaveiselcelcarcinoom metastase in een hals lymfklier. Zo werd er, bijvoorbeeld, getest met verschillende indextesten, verschillende referentietesten, verschillende afkapwaarden voor positieve uitslagen, verschillend materiaal voor referentietesten en/of verschillende fixatiemiddelen. Door deze heterogeniteit werd geacht dat de data uit deze studies niet samen te voegen waren tot gepoolde schatters voor sensitiviteit en specificiteit. Hierdoor varieerden de geobserveerde sensitiviteit (range: 0,00 tot 1,00), de specificiteit (range: 0,16 tot 1,00), de positief voorspellende waarde (range: 0,00 tot 1,00) en de negatief

voorspellende waarde (range: 0,00 tot 1,00), afhankelijk van de tests en procedures. De zekerheid in het gevonden bewijs was zeer laag door risico's op vertekening van uitkomsten, door enige zorgen over de toepasbaarheid en door de zeer kleine informatie grootte in elke afzonderlijke vergelijking (imprecisie).

The College of American Pathologists (CAP) ontwikkelde een richtlijn over HPV diagnostiek bij hoofd-hals carcinomen (Lewis, 2018). De CAP-richtlijn werd multidisciplinair ontwikkeld, met medische expertise, expertise op het gebied van hoofd, hals en moleculaire pathologie, en chirurgische, medische en radiatie oncologie (Lewis, 2018). Ook werd er een methodoloog aan de multidisciplinaire werkgroep toegevoegd en werd er een adviesgroep opgericht. De adviesgroep bestond uit patiëntvertegenwoordigers, pathologen, een medisch oncoloog en moleculair epidemioloog, een radiotherapeut-oncoloog en een methodoloog. Eventuele financiële belangen van de werkgroep werden in kaart gebracht. Twee (van de elf) deelnemers hadden potentiële belangen, maar specifieke acties hierop werden niet gerapporteerd. De ontwikkelmethodologie van de richtlijn werd in een supplement gerapporteerd (Lewis, 2018). Uitgangsvragen werden opgesteld en een systematisch zoekopdracht en literatuurselectie werden uitgevoerd. De in- en exclusiecriteria zijn vermeld, maar kunnen wellicht niet voor elke uitgangsvraag volledig reproduceerbaar zijn. Data werd vervolgens uit de geselecteerde studies geëxtraheerd en de studies werden op kwaliteit beoordeeld. Systematische reviews werden met de AMSTAR-tool beoordeeld en observationele studies met de Newcastle-Ottawa quality assessment scale. (Her)analyses van RCT's werden niet met een specifiek kwaliteitsinstrument beoordeeld. De richtlijnwerkgroep moest vier specifieke overwegingen maken op tot aanbevelingen te komen. De overwegingen betroffen significante bevindingen, de algehele sterkte van het bewijs, de sterkte van de te maken aanbeveling, en de balans tussen schade en voordelen. Er werd geen formeel framework gebruikt om deze beslissingen expliciet en/of transparant te maken. De CAP voorzag de werkgroep van geld voor de projectadministratie en er werden geen gelden uit de industrie gebruik. Werkgroepleden van de CAP-richtlijn werden niet gecompenseerd voor hun betrokkenheid en investeerden kosteloos hun tijd.

De CAP-richtlijn rapporteert een algoritme voor de work-up van patiënt monster (Lewis, 2018). Het algoritme start met een monster door biopsie of resectie van een gediagnosticeerd plaveiselcarcinoom en vertakt afhankelijk van de tumorlocatie (i.e. multi-site met een betrokken oropharynx, cervicale lymfklier, non-orofaryngeale primaire tumor, en orofaryngeale tumor). In het algoritme is de eerste test uit de work-up p16 immunohistochemie wanneer een HPV test geïndiceerd is. Hierin wordt ≥ 70% kleuring van de nuclei en cytoplasma als een positief resultaat gezien. Alleen wanneer het carcinoom keratinizerend is, de metastase zich niet in level II of level III van de hals bevindt, en/of wanneer de betrokken lymfklier niet bepaald kan worden stellen de CAP-richtlijn auteurs dat een HR HPV-specifieke test noodzakelijk is om een positieve p16 immunohistochemische test te bevestigen (Lewis, 2018). De diagnostische accuratesse van het voorgestelde algoritme werd niet onderzocht. Figuur 1 in de CAP-richtlijn laat het gehele voorgestelde algoritme zien van de diagnostische work-up (Lewis, 2018). De richtlijn werd als een open access artikel gepubliceerd (zie de URLs in de bijlagen van deze module).

De CAP-richtlijn vermeldde, als aanbeveling, dat op materiaal van patiënten met een cervicale plaveiselcelcarcinoom metastase van een onbekend primair carcinoom routinematig HR HPV testen zou moeten worden gedaan (Lewis, 2018). Deze vermelding als aanbeveling betekent dat er enkele limitaties aan de kwaliteit van het bewijs, balans tussen schade en voordelen, waarden of kosten zitten. Verder werd er een

expert consensus uitspraak gedaan over HR HPV tests op materiaal afgenomen via een fijne naald aspiraat bij patiënten met een plaveiselcarcinoom metastase van een onbekende primaire tumor. De consensus onder de experts in de CAP-richtlijnwerkgroep was dat HR HPV tests bij alle patiënten met plaveiselcelcarcinoom metastasen van een onbekende primaire tumor zouden moeten worden uitgevoerd (Lewis, 2018). Een expert consensus uitspraak in de CAP-richtlijn betekent dat de werkgroep van de CAP het noodzakelijk achtte om over het onderwerp een uitspraak te doen, maar dat er ernstige limitaties zijn aan de kwaliteit van het bewijs, balans tussen schade en voordelen, waarden of kosten. De CAP-richtlijn vermeldde verder dat er geen specifieke aanbevelingen gegeven konden worden over de test methodologie en dat testen op weefsel (wanneer beschikbaar) uitgevoerd zouden moeten worden indien de HR HPV test op het cytologische materiaal negatief was (Lewis, 2018). Verder merkt de CAP-richtlijnwerkgroep op dat pathologen de afkapwaarden (voor positieve/negatieve uitslagen) zouden moeten valideren wanneer men p16 immunohistochemie op cytologisch materiaal gebruikt (Lewis, 2018).

Uit het literatuuronderzoek zijn geen eenduidige aanbevelingen te destilleren met betrekking tot de "beste" test of combinatie van testen om HR-HPV aan te tonen. Ook het literatuuronderzoek dat verricht is voor het schrijven van de CAP richtlijn heeft dit niet kunnen aantonen. Derhalve sluit de werkgroep zich aan bij de aanbevelingen uit de CAP richtlijn die wel beschrijven in welke situaties er wel en niet getest moet worden voor HPV door de patholoog, maar niet expliciet voorschrijven welke test daarvoor gebruikt moet worden (Lewis, 2018). De makkelijke beschikbaar, relatieve eenvoud en brede beschikbaarheid van p16 immunohistochemie geldt daarbij wel als minimum basis wat elk laboratorium moet kunnen uitvoeren.

Het doel van de PA diagnose is om met het beschikbare materiaal de beste diagnose voor de patiënt te stellen. Voor patiënten is het van belang dat de tumor juist wordt geclassificeerd voor de best mogelijke behandeling. Hierbij is het bepalen van de HPV-status van belang, omdat deze tumor een aparte classificatie heeft gekregen in de TNM 8^e editie. Eventueel kan de hoog-risico HPV nog nader getypeerd worden.

P16 immunohistochemie is een relatief simpele en snel uit te voeren test die elk PA laboratorium in Nederland standaard in zijn pakket heeft. Voor de overige (moleculaire) technieken zijn er verschillen welke test ter beschikking is. Alle PA laboratoria in Nederland zijn ISO15189 geaccrediteerd en voeren dus geregeld kwaliteitscontroles en interlaboratorium vergelijkingen uit voor al hun beschikbare testen, zodat onafhankelijk van het platform de kwaliteit van de uitslag geborgd is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Aanbeveling-1
De aanbevelingen zijn met enige aanpassingen voor de Nederlandse situatie overgenomen uit de richtlijn van de College of American Pathologists (Lewis, 2018). Kennis van het rookgedrag van de patiënt mag het uitvoeren van de HPV-test niet beïnvloeden.

Aanbeveling-2
De aanbevelingen zijn met enige aanpassingen voor de Nederlandse situatie overgenomen uit de richtlijn van de College of American Pathologists (Lewis, 2018). Het is belangrijk om, daar waar mogelijk, op histologisch materiaal te testen. Voor het gebruik van p16 immunohistochemie als eerste test op histologisch materiaal werd gekozen omdat deze test makkelijk beschikbaar en relatieve eenvoudig uit te voeren is. Indien er geen

histologisch materiaal beschikbaar is of beschikbaar komt, is het testen op cytologisch materiaal van een lymfklierpunctaat een alternatief. Het is onduidelijk vanuit de literatuur welke test op cytologisch materiaal gebruikt zou moeten worden.

Aanbeveling-3

De aanbevelingen zijn met enige aanpassingen voor de Nederlandse situatie overgenomen uit de richtlijn van de College of American Pathologists (Lewis, 2018). Indien er histologisch materiaal beschikbaar is uit een Level II of III lymfekliermetastase werd er voor p16 als eerste test gekozen omdat deze test makkelijk beschikbaar en relatieve eenvoudig uit te voeren is. Omdat er in deze situatie niet altijd histologisch materiaal beschikbaar is, worden testen op cytologisch materiaal uit een lymfklierpunctaat als alternatief gezien. Het is onduidelijk vanuit de literatuur met welke test er op cytologisch materiaal gebruikt zou moeten worden.

Aanbeveling-4

De aanbevelingen zijn met enige aanpassingen voor de Nederlandse situatie overgenomen uit de richtlijn van de College of American Pathologists (Lewis, 2018). Routinematige HR-HPV testen voor niet-plaveiselcelcarcinomen, andere primaire hoofd-halscarcinomen, en residu van of recidiverende eerste tumoren (waarvan de HPV status al initieel bepaald werd) worden niet aangeraden. Voor plaveiselcelcarcinomen van het hoofd-halsgebied werd routinematige laag risico HPV (LR-HPV) testen niet aanbevolen.

Aanbeveling-5

De aanbevelingen zijn met enige aanpassingen voor de Nederlandse situatie overgenomen uit de richtlijn van de College of American Pathologists (Lewis, 2018).

Onderbouwing

Achtergrond

De Humaan Papillomavirus (HPV) status van orofarynx carcinomen kan bepaald worden met verschillende testen. Op dit moment is het onduidelijk welke op histopathologie gebaseerde teststrategie de beste diagnostische accuratesse voor het bepalen van de HPV-status van gediagnosticeerde orofarynx carcinomen heeft. In sommige omstandigheden is histopathologisch materiaal niet beschikbaar, bijvoorbeeld wanneer de primaire tumor onbekend is. De HPV-status zou dan wellicht op basis van cytologische tests kunnen worden vastgesteld op cytologisch materiaal dat met een lymfklierpunctaat is verkregen bij patiënten met een onbekende primaire tumor en een gediagnosticeerde halsmetastase. Echter is het op dit moment nog onduidelijk wat de diagnostische accuratesse van HPV-testen op cytologisch materiaal van een positieve lymfeklier uit de hals is.

Conclusies

Very low GRADE	There is a very low confidence in the sensitivity (0.93, 95%CI: 0.87 to 0.97) and specificity (0.96, 95%CI: 0.89 to 1.00) of p16^{INK4a} combined with an HPV DNA PCR on histological material as a test strategy. *Sources: (Prigge, 2017)*

- **GRADE**	Positive and negative predictive values were not reported for p16^{INK4a} combined with an HPV DNA PCR on histological material as a test strategy. *Sources: (Prigge, 2017)*

Very low **GRADE**	There is a very low confidence in the sensitivity (range: 0.00 to 1.00) and specificity (range: 0.16 to 1.00) of the tests performed on cytologic material. *Sources: (Baldassari, 2015; Begum, 2007; Bishop, 2012; Buonocore, 2019; Chute, 2014; Hou, 2016; Jalaly, 2015; Jannapureddy, 2010; Sivars, 2017; Smith, 2014; Takes, 2016; Xu, 2016)*

Very low **GRADE**	There is a very low confidence in the positive predictive value (range: 0.00 to 1.00) and negative predictive value (range: 0.16 to 1.00) of the tests performed on cytologic material. *Sources: (Baldassari, 2015; Begum, 2007; Bishop, 2012; Buonocore, 2019; Chute, 2014; Hou, 2016; Jalaly, 2015; Jannapureddy, 2010; Sivars, 2017; Smith, 2014; Takes, 2016; Xu, 2016)*

Samenvatting literatuur

<u>Description of studies</u>
Diagnostic algorithms on histological material to determine the HPV-status in patients with a confirmed oropharyngeal carcinoma (PICO 1)
Prigge (2017) conducted a systematic review where the diagnostic accuracy of a strategy was assessed where p16^{INK4a} immunohistochemistry and an HPV DNA PCR was combined for HPV-testing in oropharyngeal squamous cell carcinomas. MEDLINE was searched through PubMed on the 8th of January 2016. Studies were included when persons in the sample were diagnosed with oropharyngeal squamous cell carcinoma, p16^{INK4a} was the index test, a reference test was used that detected E6 and/or E7 mRNA and when the study design was prospective or retrospective. Studies were excluded when the authors of the original studies did not respond to inquiries about the presented data, when the sample size was smaller than 10, and when the study did not report primary data. Eleven of the included studies reported the use of p16^{INK4a} and HPV DNA PCR as a combined test for diagnostic test accuracy evaluation against a reference standard that detected E6 and/or E7 mRNA. The eleven studies comprised of a sample of 509 persons (as reported in the study characteristics table in the systematic review). A case was defined as positive when both the p16INK4a and the HPV DNA PCR returned positive results. When one of both or both tests returned a negative result, the case was defined as negative. Studies were assessed with the QUADAS-2 tool for risk of bias and applicability. Most of the 11 studies scored 'unclear' in the patient selection domain, where it was mostly unclear whether studies avoided inappropriate exclusions. The applicability regarding the patient selection was generally judged as having moderate concerns. The cut-off for defining positive/negative cases by using p16^{INK4a} varied among the included studies and was tested on whole tissue section FFPE material (with one exception, where tissue microarray was used on FFPE material). Five studies used the G175-405 antibody clone for p16^{INK4a}, while the

other six studies used E6H4. Variation in procedures was also observed in the HPV DNA PCR methods. Here, GP5+/6+ (reverse line blot genotyping or bead-based genotyping), HPV 16 primers, HPV 16 E6/E7 primers, MY09/MY11/HMB01 (dot blot hybridization genotyping), BSGP5+/6+ (bead-based genotyping) were the described methods. Reference tests also had variation in their procedures. Transcript types used were E6, E6*I, E7, or combinations thereof. Reference tests also showed variation in the detected HPV types. HPV 16 was sought for detection in all studies, however some studies added HPV 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68b, 70, 73, and/or 82 for detection as well. Four of the eleven studies used whole tissue section FFPE material for the reference test, while the remaining seven studies used fresh frozen material.

Tests on cytological material in patients with positive neck nodes and CUP (PICO 2)
Baldassari (2015) used a cobas HPV assay on fine needle aspirates and compared it to a combined test of p16 and HPV ISH on paraffin-embedded formalin-fixed surgical tissue of the primary and/or metastatic tumor. Specimens were collected prospectively, but it remained unclear whether this was consecutively. Inclusion and exclusion criteria were not described. Air-dried and alcohol fixed smears were prepared and stained. A slide was prepared after centrifugation and the cobas HPV assay was performed according to the manufacturer's protocol. Fourteen HPV types were targeted for amplification (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Both p16 IHC and HPV ISH were performed on deparaffinized 5-micrometer sections. For p16, sections were incubated with a mouse monoclonal antibody (E6H4). Sections for HPV ISH were incubated with the INFORM HPV III Family 16 probe, detecting HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66. The cut-off points for a positive/negative case in the cobas HPV assay, p16, and HPV ISH were unclear. Thirty-seven participants were recruited and forty-two fine needle aspirates were taken. Participants had a mean age of 60.4 (SD: 11.6) years. Seventeen participants had a history of head and neck squamous cell carcinomas. Fine needle sample sites were the neck mass (n=36), the mediastinal lymph node (n=5), or a left parapharyngeal mass (n=1).

Begum (2007) searched a database and selected cases when the processing of the initial fine needle aspirate included the preparation of a cellblock by spinning the cell block in a cellular pellet. The index test was p16 on cell blocks, where 5-micron sections were deparaffinized. Sections were then incubated with a mouse monoclonal antibody. Observing any staining in the squamous cells was considered to be positive for HPV. Material from fine needle aspirates were also tested with HPV16 ISH (considered as a reference test). HPV16 ISH was performed on cell blocks for signal amplification and on resections of the primary tumor. Signals visualized as dots in nuclei of the squamous cells were considered positive for HPV. Nineteen participants with oropharyngeal tumors and ten participants with an unknown primary were selected. No other patient characteristics were described.

Bishop (2012) consecutively recruited participants to assess the accuracy of the Hybrid Capture 2 assay (HC2), although inclusion and exclusion criteria were not reported. Metastatic tumors were aspirated using a 12 gauge needle and multiple passes. HC2 detected HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Specimen DNA was denatured into single stranded DNA. RNA/DNA hybrids were then immobilized onto a microplate surface. Light is emitted and measured in relative light units. A case with ≥ 3 RLU/CO was considered positive for HPV, 0.85-3 RLU/CO was considered equivocal, and < 0.85 RLU/CO was considered negative. HPV ISH was used as the reference test. Hybridization was performed using the HPV III Family 16

probe (HPV16, 18, 33, 35, 45, 51, 52, 56, 66) on 5-micron section from the tissue microarray was assessed. HPV ISH was considered positive when signals localized to tumor cell nuclei. Participant recruitment resulted in 24 participants (27 cytologic preparations), of which 12 had a lymph node sample site. From these 12 participants, the tumor site was the skin (n=2), larynx (n=2, floor of mouth (n=1), tongue (n=1), base of tongue (n=1), tonsil (n=4), and unknown (n-1).

Buonocore (2019) recruited 25 participants consecutively (n=24 were positive for HPV by HPV ISH, n=1 was non-contributory). Participants were included when they had previous or unknown oropharyngeal head and neck squamous cell carcinoma (or this was determined at the time of the procedure) and an unknown p16 status. Exclusion criteria were not reported. Fine needle aspirates were performed with a 25 gauge needle. Diff-Quik-stained and ethanol fixed smears were prepared. Passes were allowed to clot before fixed in formalin. From this material both a CytoLyt-fixed and a formalin-fixed cell block were made. Both the CytoLyt-fixed and formalin-fixed cell blocks were tested with p16 (indextest) against HPV ISH (reference test). Mouse monoclonal antibodies (E6H4) were used for p16. A cut-off of ÷70% staining in nuclei and cytoplasm was used to define a HPV-positive case. It was unclear on which material the HPV ISH was performed and it was unclear how an HPV-positive case was defined. HPV ISH targeted HPV 16, 18, 26, 31, 33, 35, 39, 41, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and E6/E7 mRNA. Participants (22 male; 3 female) had a mean age of 60 (range: 47 to 76) years and a variety in smoking history (never smoked: n=14, smoking history: n=11 (range: 0.5-40 pack years)). Similarly, a variety of alcohol use was observed: never (n=1), abstinent (n=1), occasional (n=2), social (n=15), daily (n=3), heavy (n=3).

Chute (2014) recruited 95 participants (resulting in 96 fine needle aspirates) prospectively. Participants were eligible when a fine needle aspirate from a head and neck-site was interpreted as being a squamous cell carcinoma, atypical, or suspicious for squamous cell carcinoma. Exclusion criteria were not reported. A cell block was made in an automated system according to its manufacturer's directions. However, methylene blue was replaced by eosin. HC2 and CISH were performed on cytological material. HC2 was performed according to the manufacturer's instructions, targeting HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. A RLU/CO ≥ 1 was defined as a HPV-positive case. For, CISH, the HPV III Family 16 probe was used (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58). A discrete blue dot-like staining in the tumor nuclei was defines as an HPV-positive case. CISH combined with p16 was performed on a surgical biopsy. An HPV-positive case for p16 was defined as > 75% strong and diffuse cytoplasmic and nuclear staining. For the CISH and p16 combined test, an HPV-positive case was defined as having a positive test result from both CISH and p16. Formalin-fixed paraffin-embedded tissue of the excised primary tumor or neck metastasis were used for testing in the CISH and p16 combined test. Participants (72 male; 21 female) had a median age of 60 (range: 17-93) years. The primary tumor location was oropharyngeal (n=32), non-oropharyngeal (n=32), non-head and neck (n=18), or unknown (n=13).

Hou (2016) searched a database to select cases with metastatic head and neck squamous cell carcinomas in cervical lymph nodes, diagnosed by a fine needle aspirate. HPV ISH and p16 had to be performed on fine needle aspirate material to be selected from the database. No exclusion criteria were reported. Both p16 (index test) and HPV ISH (reference test) were performed on cytologic material. Fine needle aspirates were centrifuged and the specimen was clot dried. The specimen was then placed in a CellSafe mesh capsule and fixated in formalin (10% neutral-buffered). For p16, monoclonal antibodies (E6H4) were used. An HPV-positive

case by p16 was defined as ≥ 70% diffuse or strong nuclear or cytoplasmic staining. HPV ISH was performed according to the manufacturer's protocol on 4-micrometer sections of the cell block. HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, and Y1443 were targeted. Presence of staining in the nuclei defined an HPV-positive case for HPV ISH. Participants (80 male; 7 female) had a mean age of 59 (range: 38 to 86) years. The primary site of the tumor was the base of the tongue (n=32), tonsil (n=19), other oropharyngeal sites (not specified, n=4), non-oropharyngeal (not specified, n=25), or unknown (n=7).

Jalaly (2015) searched a database to select cases that had a metastatic cervical lymph node (proven by fine needle aspirates) with a corresponding surgical specimen (either biopsy or resection). P16 and HPV ISH were performed on the cell blocks created from the fine needle aspirate. Fine needle aspirate material was centrifuged for 2 minutes. The specimen clot was allowed to dry on tissue paper. Thereafter, it was placed in a CellSafe capsule and fixed in formalin (10% neutral-buffered). For p16, a monoclonal antibody (E6H4) was used and an HPV-positive case for p16 was defined as >70% nuclear and cytoplasmic staining of the tumor cells. HPV ISH detected E6/E7 mRNA and was performed according to the manufacturer's instruction and 4-millimeter formalin-fixed paraffin-embedded cell block sections were prepared. Red punctate dots in the nucleus and/or cytoplasm signals higher than the signal on a DapB-negative control slide was defined as a HPV-positive case. Forty-eight participants were recruited (44 male; 4 female). The fine needle aspirate sample site was the neck (n=41), subcarinal (n=2), mediastinal (n=1), submandibular (n=2), chest wall (n=1), or supraclavicular (n=1). The specimen was either resected (n=32) or a biopsy was made (n=16). The tumor site of the primary tumor was at the base of the tongue (n=14), tonsil (n=15), other oropharyngeal (not specified, n=8), oral cavity (n=6), larynx (n=1), maxilla (n=1), or unknown (n=3).

Janapureddy (2010) searched a database to select participants that had a cell block cytologic diagnosis of metastatic squamous cell carcinoma in a cervical lymph node. Participants with inadequate cell block material were excluded. Cytologic material was tested with p16^{INK4a} and ProExC as index tests and compared to HPV ISH on cell block sections. Material from fine needle aspirates were fixed in formalin (10% neutral-buffered). After centrifugation the supernatant was discarded and the resulting content was assessed. Cell block tissue was created (5-micrometer) from the formalin-fixed paraffin-embedded tissue. Incubation was performed with E6H4 monoclonal p16^{INK4a} at room temperature. An HPV-positive case for p16 was defined as the presence of nuclear and cytoplasmic staining. ProExC also had in incubation period at room temperature. Presence of nuclear staining defined an HPV-positive case for ProExC. HPV ISH detected HPV 16, 18, 31, 33, and 51. Cell block tissue was deparaffinized and rehydrated. Slides were air dried, sections were denatured and hybridized. HPV-positive cases by HPV ISH were defined as the presence of punctate or dot-like nuclear staining. Participants (36 male; 4 female) had a mean age of 58.2 (reange 25 to 87) years. The primary tumor site was oropharyngeal (not specified, n=11), nasopharyngeal (n=2), other (not specified, n=5), or was not determined (n=9).

Sivars (2017) prospectively obtained fine needle aspirate material. Participants were recruited when they were suspected of head and neck carcinoma or had a neck mass suspicious for metastasis, and when there was not enough material left for HPV testing after cytological diagnosis. The HPV-status was tested on cytological material from fine needle aspirates and/or formalin-fixed paraffin-embedded material (either resection or biopsy). For cytologic testing, DNA was extracted from fine needle aspirates. The DNA multiplex assay was performed by using GP5+/GP6+ primers and additionally E6 (HPV 16, 33) was amplified. DNA detection was

performed on a bead-based multiplex using mean fluorescent intensity. An HPV-positive case for the multiplex assay was defined as a mean fluorescent intensity above the background * 1.5 + 15. Furthermore, a Real-Time PCR was used in the clinic to detect seven common high-risk HPV genotypes. Is was unclear how a positive/negative case was defined vor the Real-Time PCR in the clinic. Sixty-six patients (35 male; 31 female) participated. Fine needle aspirate sample sites were the primary tumor (n=2) or neck masses (n=64). The mean age was 61 year for persons with an oropharyngeal tumor (n=20), 71.5 years for persons with other malignancies (n=17), and 53 years for persons with benign conditions (n=29).

Smith (2014) recruited participants prospectively when a cervical lymph node was swollen to one centimeter or larger (exclusion criteria were not reported). A modified HC2 HPV assay detected HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 in cytologic material. Fine needle biopsies of cervical metastases were performed with a 25 gauge needle. The aspirate was placed on a slide and was air-dried and stained. A final pass was made with a fresh needle in to the lymph node, which was stored until used for HC2. DNA was denatured and incubated for 45 minutes. Samples were applied to hybrid-specific antibodiy coated microplate wells. Signal amplification was performed with Detection Reagent II and light emission was used to detect HPV DNA. An HPV-positive case for HC2 was defined as ≥ 2.5 RLO/CO, an equivocal case as 0.85 to 2.5 RLU/CO, and a negative case as < 0.85 RLU/CO. HPV ISH was performed on tissue specimen from resected participants. Five-micron formalin-fixed paraffin-embedded tissue sections from either tumors or biopsies were used for HPV ISH. The HPV III Family 16 probe set was used to detect HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66). Punctate signals in the nuclei defined a positive HPV case for HPV ISH. The mean age and sex distribution were not reported for the participants, however 25 persons were recruited. The tumor location was on the palatine tonsil (n=6), base of the tongue (n=8), hypopharynx (n=1), skin of the auricle (n=1), or unknown (n=2).

Takes (2016) searched a database for cases where formalin-fixed paraffin-embedded histological material was available and was tested positive or negative for both HPV and p16. Cases were excluded when there was a secondary tumor in the head and neck region, when there was not enough cytological material, or when there was previous exposure to radiotherapy. A HPV PCR was performed on fine needle aspirates material scraped from archival slides. The DNA was purified, diluted and stored until tested by HPV PCR. A broad-spectrum DNA amplification was performed in the HPV PCR. Probes were used in a micro titer hybridization assay. Cases positive in the micro titer hybridization assay were tested with line-specific probes (LiPA25) for detection of HPV 1, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68/73, 70, and 74. LiPA strips were visually inspected and interpreted. Interpretation was performed following the standardized reference guide. It was unclear how an HPV-positive case was defined. Both the same HPV PCR and p16 were performed. The HPV PCR was performed on DNA isolated from formalin-fixed paraffin-embedded tissue sections of 4-micrometer. The p16 procedures were not reported. It was unclear, for both the HPV PCR and p16, how a HPV-positive case was defined. Participants (33 male; 14 female) had a mean age of 58 (range: 28.9 to 77.2) years. Their N-stage was N0 (n=6), N1 (n=7), or N2 (n=38). The primary tumor site was on the tonsils (n=19), the base of the tongue (n=12), other oropharyngeal (not specified, n=10), or unknown (n=6). Formalin-fixed paraffin-embedded material originated from the tonsils (n=21), base of the tongue (n=9), neck dissection (n=7), other oropharyngeal (not specified, n=10).

Xu (2016) searched a database and selected cases with cervical metastatic squamous cell carcinomas

diagnosed with fine needle aspirates. For the selection, cases had to have p16 performed on both the cytological material and corresponding surgical material. Cases were excluded when tumors originated from outside the head and neck region. Cytologic material was prepared from fine needle aspirates for cell blocks and ThinPrep in CytoLyt solution. The p16 index test was performed on cell bock, smear or ThinPrep with pre-defined thresholds of 1%, 5%, 10%, 15%, and 70% nuclear and cytoplasmic staining to define an HPV-positive case. HPV CISH was performed on cytologic material using high risk HPV probes for detecting HPV 16, 18, 31, 33, and 51. An HPV-positive case for CISH was defined as discrete dot-like stippled nuclear labelling. How HPV-negative and equivocal cases were defined was not reported.

Results
Diagnostic algorithms on histological material to determine the HPV-status in patients with a confirmed oropharyngeal carcinoma (PICO 1)
Sensitivity
Prigge (2017) calculated a summary estimate for the sensitivity of p16^{INK4a} combined with HPV DNA PCR from 11 studies (n=509). There was variation in underlying procedures (for example cut-offs for p16 positivity, materials, reference standards). Prigge (2017) found a pooled sensitivity 0.93 (95%CI: 0.87 to 0.97). Statistical heterogeneity (I^2) was 23.39%.

Specificity
Prigge (2017) pooled the specificity of a p16^{INK4a} and HPV DNA PCR combined test from 11 studies (n=509). Underlying procedures showed variation in procedures (for example cut-offs for p16 positivity, materials, reference standards). A summary estimate was calculated and Prigge (2017) reported a specificity of 0.96 (0.89 to 1.00). Statistical heterogeneity (I^2) was 68.4%.

Positive predictive value
Positive predictive values were not reported.

Negative predictive value
Negative predictive values were not reported.

Tests on cytological material in patients with positive neck nodes and CUP (PICO 2)
Sensitivity
A variety of index tests on cytologic material were found. Tests were evaluated using several different methods and procedures: p16 (on CUP only, on oropharyngeal carcinoma only, on CytoLyt or formalin fixed cytologic material, at several thresholds, reference test on cytological or histological material), HC2 (various reference tests, reference test on cytological or histological material), PCR or RT-PCR (various reference tests, reference test on cytological or histological material), ProExC, HPV CISH, and cobas 4800. Data could not be pooled due to heterogeneity in the study procedures. Sensitivity ranged from 0.00 to 1.00. An overview of the sensitivities (including 95% confidence intervals) are found in Figure 1. Sensitivity and/or 95% confidence intervals were calculated when not reported in the original study. Cases were excluded in most analyses (described in the evidence table, for example due to invalid or equivocal test results, no reference test performed, or inadequate specimens).
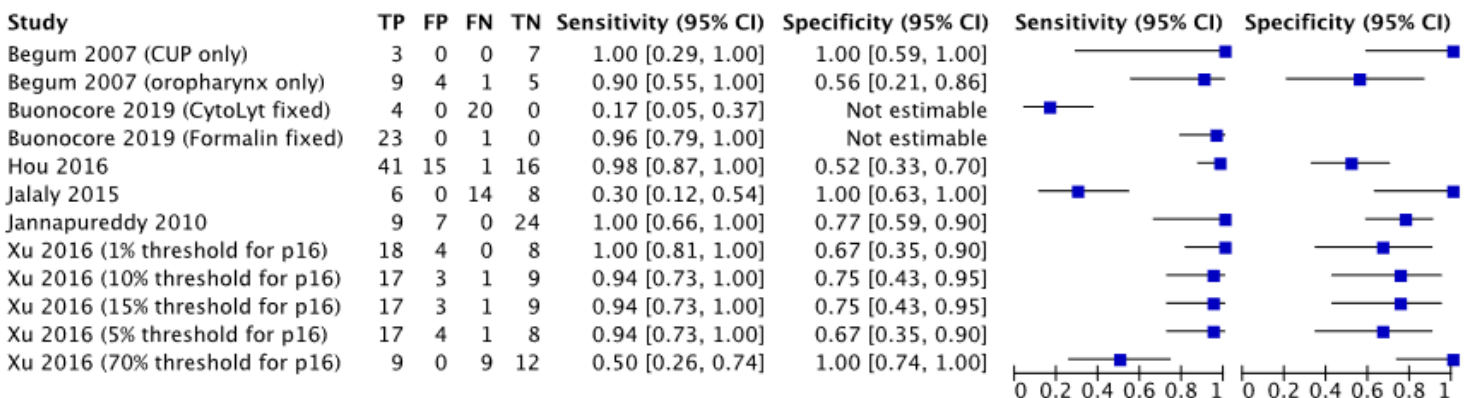
Specificity
A variety of index tests on cytologic material were found. A variety of index tests on cytological material were found, identical to as described under the sensitivity results. Data could not be pooled due to heterogeneity in the study procedures and tests. Specificity and/or 95% confidence intervals were calculated when not reported in the original study. Specificity ranged from 0.16 to 1.00. An overview of the specificities (including 95% confidence intervals) are found in Figure 1 Cases were excluded in most analyses (described in the evidence table, for example due to invalid or equivocal test results, no reference test performed, or inadequate specimens).

Positive and negative predictive value
Most studies did not report the positive and/or negative predictive values. When not reported, positive and negative predictive values were calculated from the extracted data. Positive and negative predictive values ranged from 0.00 to 1.00. Cases were excluded in most analyses (described in the evidence table, for example due to invalid or equivocal test results, no reference test performed, or inadequate specimens).

Figure 1 An overview of the sensitivity and specificity of the tests reported in the included references by index test, reference test and testing material. Category titles show the used index test (type of material) versus reference test (type of material)

p16 (cytology) vs HPV ISH (cytology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Begum 2007 (CUP only)	3	0	0	7	1.00 [0.29, 1.00]	1.00 [0.59, 1.00]
Begum 2007 (oropharynx only)	9	4	1	5	0.90 [0.55, 1.00]	0.56 [0.21, 0.86]
Buonocore 2019 (CytoLyt fixed)	4	0	20	0	0.17 [0.05, 0.37]	Not estimable
Buonocore 2019 (Formalin fixed)	23	0	1	0	0.96 [0.79, 1.00]	Not estimable
Hou 2016	41	15	1	16	0.98 [0.87, 1.00]	0.52 [0.33, 0.70]
Jalaly 2015	6	0	14	8	0.30 [0.12, 0.54]	1.00 [0.63, 1.00]
Jannapureddy 2010	9	7	0	24	1.00 [0.66, 1.00]	0.77 [0.59, 0.90]
Xu 2016 (1% threshold for p16)	18	4	0	8	1.00 [0.81, 1.00]	0.67 [0.35, 0.90]
Xu 2016 (10% threshold for p16)	17	3	1	9	0.94 [0.73, 1.00]	0.75 [0.43, 0.95]
Xu 2016 (15% threshold for p16)	17	3	1	9	0.94 [0.73, 1.00]	0.75 [0.43, 0.95]
Xu 2016 (5% threshold for p16)	17	4	1	8	0.94 [0.73, 1.00]	0.67 [0.35, 0.90]
Xu 2016 (70% threshold for p16)	9	0	9	12	0.50 [0.26, 0.74]	1.00 [0.74, 1.00]

p16 (cytology) vs HPV ISH (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Begum 2007 (oropharynx only)	0	4	2	4	0.00 [0.00, 0.84]	0.50 [0.16, 0.84]

HC2 (cytology) vs HPV ISH (cytology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bishop 2012	5	0	0	7	1.00 [0.48, 1.00]	1.00 [0.59, 1.00]
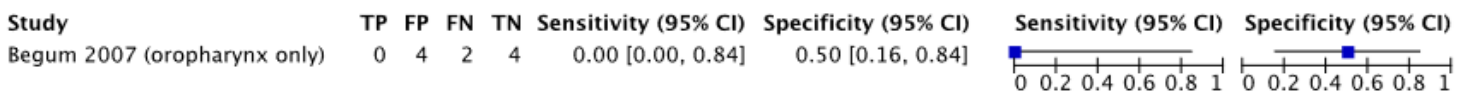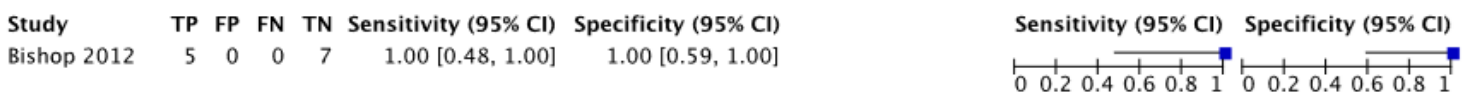
HC2 (cytology) vs HPV CISH (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Smith 2014	7	0	3	5	0.70 [0.35, 0.93]	1.00 [0.48, 1.00]

HC2 (cytology) vs HPV CISH + p16 (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chute 2014	21	0	8	48	0.72 [0.53, 0.87]	1.00 [0.93, 1.00]
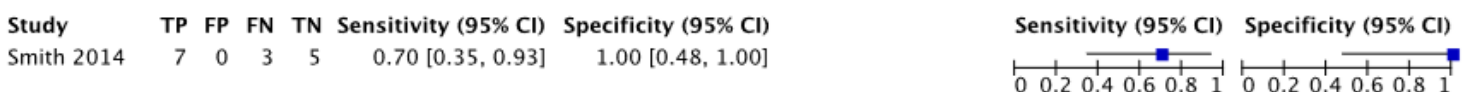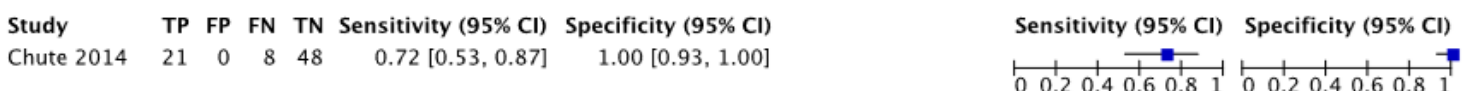
PCR (cytology) vs PCR + p16 (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Takes 2016	24	0	1	22	0.96 [0.80, 1.00]	1.00 [0.85, 1.00]

RT–PCR (cytology) vs Multiplex assay (cytology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sivars 2007	15	0	0	25	1.00 [0.78, 1.00]	1.00 [0.86, 1.00]

RT–PCR (cytology) vs Multiplex assay (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sivars 2007	8	0	0	1	1.00 [0.63, 1.00]	1.00 [0.03, 1.00]

Multiplex assay (cytology) vs Multiplex assay (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sivars 2007	9	0	0	1	1.00 [0.66, 1.00]	1.00 [0.03, 1.00]

ProExC (cytology) HPV ISH (cytology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jannapureddy 2010	9	26	0	5	1.00 [0.66, 1.00]	0.16 [0.05, 0.34]

HPV CISH (cytology) vs HPV CISH + p16 (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chute 2014	11	7	7	27	0.61 [0.36, 0.83]	0.79 [0.62, 0.91]

Cobas 4800 (cytology) vs HPV ISH + p16 (histology)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baldassari 2015	15	16	0	3	1.00 [0.78, 1.00]	0.16 [0.03, 0.40]
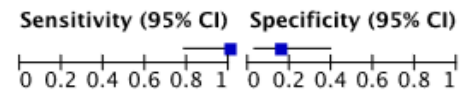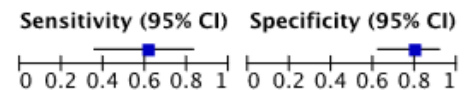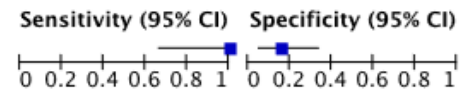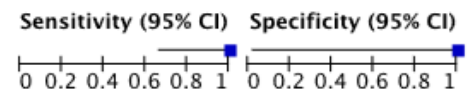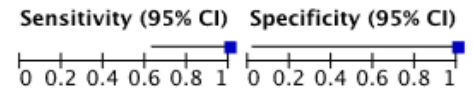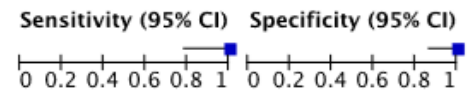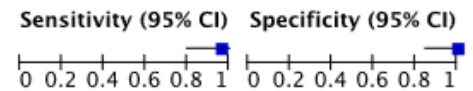
Table 1 Overview of the positive and negative predictive values of the tests on cytologic material by index test, reference test and testing material

Author, year (condition)	TP	FP	FN	TN	PPV	NPV
P16 (cytology) versusHPV ISH (cytology)						
Begum 2007 (CUP only)	3	0	0	7	1.00*	1.00*
Begum 2007 (oropharynx only)	9	4	1	5	0.69	0.833
Buonocore 2019 (CytoLyt fixed)	4	0	20	0	1.00*	0.00*
Buonocore 2019 (Formalin fixed)	23	0	1	0	1.00*	0.00*
Hou 2016	41	15	1	16	0.73	0.94
Jalaly 2015	6	0	14	8	1.00*	0.36
Jannapureddy 2010	9	7	0	24	0.56	1.00*
Xu 2016 (1% threshold for p16)	18	4	0	8	0.82	1.00*
Xu 2016 (10% threshold for p16)	17	3	1	9	0.85	0.90
Xu 2016 (15% threshold for p16)	17	3	1	9	0.85	0.90
Xu 2016 (5% threshold for p16)	17	4	1	8	0.81	0.89

Xu 2016 (70% threshold for p16)	9	0	9	12	1.00*	0.57

P16 (cytology) versus HPV ISH (histology)

Begum 2007 (oropharynx only)	0	4	2	4	0.00*	0.67

HC2 (cytology) versus HPV ISH (cytology)

Bishop 2012	5	0	0	7	1.00*	1.00*

HC2 (cytology) versus HPV CISH (histology)

Smith 2014	7	0	3	5	1.00*	0.63

HC2 (cytology) versus HPV CISH = p16 (histology)

Chute 2014	21	0	8	48	1.00*	0.86

PCR (cytology) versus PCR + p16 (histology)

Takes 2016	24	0	1	22	1.00*	0.96

RT-PCR (cytology) versus Multiplex assay (cytology)

Sivars 2007	15	0	0	25	1.00*	1.00*

RT-PCR (cytology) versus Multiplex assay (histology)

Sivars 2007	8	0	0	1	1.00*	1.00*

Multiplex assay (cytology) versus Multiplex assay (histology)

Sivars 2007	9	0	0	1	1.00*	1.00*

ProExC (cytology) versus HPV ISH (cytology)

Jannapureddy 2010	9	26	0	5	0.26	1.00*

Cobas 4800 (cytology) versus HPV ISH + p16 (histology)

Baldassari 2015	15	16	0	3	0.48	1.00*

HPV ISH (cytology) versus HPV ISH (histology)

Begum 2007 (oropharynx only)	1	0	1	8	1.00*	0.89

*Calculation contained a cell value of zero

Level of evidence of the literature

Diagnostic algorithms on histological material to determine the HPV-status in patients with a confirmed oropharyngeal carcinoma (PICO 1)

The level of evidence regarding the outcome measure sensitivity (for p16^{INK4a} + HPV DNA PCR) was downgraded by 3 levels because of study limitations (1 level for risk of bias: most of the relevant studies were appraised by the authors as unclear regarding inappropriate exclusions); applicability (1 level for bias due to indirectness: most of the relevant studies were appraised by the authors as having moderate applicability concerns regarding patient selection); number of included patients (1 level for imprecision: n=509 according to the general characteristics table); publication bias was not assessed.

The level of evidence regarding the outcome measure specificity (for p16^{INK4a} + HPV DNA PCR) was downgraded by 3 levels because of study limitations (1 level for risk of bias: most of the relevant studies were

appraised by the authors as unclear regarding inappropriate exclusions); applicability (1 level for bias due to indirectness: most of the relevant studies were appraised by the authors as having moderate applicability concerns regarding patient selection); number of included patients (1 level for imprecision: n=509 according to the general characteristics table); publication bias was not assessed.

The positive and negative predictive value was not reported and therefore GRADE was not performed.

Tests on cytological material in patients with positive neck nodes and CUP (PICO 2)
The level of evidence regarding the outcome measure sensitivity was downgraded by 4 levels because of study limitations (1 levels for risk of bias: 27.1% judgements in the QUADAS-2 were high risk of bias (predominantly in patient selection and flow/timing), 41.7% judgements were unclear risk (predominantly in index test and reference standard)); not downgraded for conflicting results (inconsistency: observed heterogeneity might possibly be explained by differences in procedures and thresholds); applicability (1 level for bias due to indirectness: mostly unclear whether the included patients matched the review question); number of included patients (2 levels for imprecision: very low number of participants per comparison); publication bias was not assessed.

The level of evidence regarding the outcome measure specificity was downgraded by 4 levels because of study limitations (1 levels for risk of bias: 27.1% judgements in the QUADAS-2 were high risk of bias (predominantly in patient selection and flow/timing), 41.7% judgements were unclear risk (predominantly in index test and reference standard)); not downgraded for conflicting results (inconsistency: observed heterogeneity might possibly be explained by differences in procedures and thresholds); applicability (1 level for bias due to indirectness: mostly unclear whether the included patients matched the review question); number of included patients (2 levels for imprecision: very low number of participants per comparison); publication bias was not assessed.

The level of evidence regarding the outcome measure positive predictive value was downgraded by 4 levels because of study limitations (1 levels for risk of bias: 27.1% judgements in the QUADAS-2 were high risk of bias (predominantly in patient selection and flow/timing), 41.7% judgements were unclear risk (predominantly in index test and reference standard)); not downgraded for conflicting results (inconsistency: observed heterogeneity might possibly be explained by differences in procedures and thresholds); applicability (1 level for bias due to indirectness: mostly unclear whether the included patients matched the review question); number of included patients (2 levels for imprecision: very low number of participants per comparison); publication bias was not assessed.

The level of evidence regarding the outcome measure negative predictive value was downgraded by 4 levels because of study limitations (1 levels for risk of bias: 27.1% judgements in the QUADAS-2 were high risk of bias (predominantly in patient selection and flow/timing), 41.7% judgements were unclear risk (predominantly in index test and reference standard)); not downgraded for conflicting results (inconsistency: observed heterogeneity might possibly be explained by differences in procedures and thresholds); applicability (1 level for bias due to indirectness: mostly unclear whether the included patients matched the review question); number of included patients (2 levels for imprecision: very low number of participants per comparison); publication bias was not assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:

PICO 1
What is the diagnostic accuracy of diagnostic test algorithms to determine the HPV-status on histological material in patients with an oropharyngeal carcinoma?
P: patients with an oropharyngeal carcinoma;
I: diagnostic strategies/algorithms to determine the HPV-status based on histopathologic tests;
C: diagnostic strategies/algorithms compared;
R: a test to detect HPV-DNA and/or E6/E7 mRNA;
O: sensitivity, specificity, positive predictive value, negative predictive value.

PICO 2
What is the diagnostic accuracy of tests on cytologic material to determine the HPV-status in patients with a carcinoma of unknown primary?
P: patients with a carcinoma of unknown primary and a positive neck node;
I: diagnostic tests to determine the HPV-status based on cytologic material;
C: comparison of tests on cytologic material;
R: a test to detect HPV-DNA and/or E6/E7 mRNA;
O: sensitivity, specificity, positive predictive value, negative predictive value.

Relevant outcome measures
The guideline development group considered sensitivity and negative predictive value as a critical outcome measures for decision making; and specificity and positive predictive value as an important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
PICO 1
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2016 until the 10th of April 2020 for PICO 1 (histology). The time limiter was chosen because the guideline "*Human Papillomavirus Testing in Head and Neck Cancers*" from the College of American Pathologists (CAP) had their latest searched performed in 2016 (Lewis, 2018). The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 251 hits. Studies were selected based on the following criteria: patients had an oropharyngeal carcinoma, diagnostic strategies or algorithms were used to determine the HPV-status with histopathological tests, the reference test was a test that detected HPV DNA and/or mRNA, and at least one of the outcomes of interest was reported or it could be calculated manually from the presented data. Conference abstracts and non-systematic reviews were

excluded. A total of 6 studies were initially selected based on title and abstract screening. After reading the full text, 5 studies were excluded (see the table with reasons for exclusion under the tab Evidence tables), and 1 systematic review (which included 24 primary studies) was included.

PICO 2
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 27th of February 2020 for PICO 2 (cytology). The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 448 hits. Studies were selected based on the following criteria: patients had a (suspected) neck metastasis, patients had (suspected) primary head and neck squamous cell carcinoma at the time material was taken for cytologic tests, the reference test was a test that detected HPV DNA and/or mRNA, and at least one of the outcomes of interest were reported or it could be calculated manually from the presented data. Conference abstracts and non-systematic reviews were excluded. A total of 74 studies were initially selected based on title and abstract screening. After reading the full text, 62 studies were excluded (see the table with reasons for exclusion under the tab Evidence tables) and 12 studies were included.

Results
One systematic review (including 24 primary studies) was included in the analysis of the literature for the histopathology-based diagnostic algorithms. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab Evidence tables).

Thirteen studies were included in the analysis of the literature for the cytology-based tests. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables. Data regarding the classification of cases by the index test compared to the reference test were extracted from each of the included studies. Diagnostic accuracy parameters and/or 95% confidence intervals were calculated based on the extracted data when not reported in the original study.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Diagnostiek hypofarynxcarcinoom

Uitgangsvraag

Aan welke eisen dienen beeldvormende techniek en beoordeling van het radiologisch onderzoek bij het hypofarynxcarcinoom te voldoen?

Welke diagnostiek is verder nodig voor de beoordeling van de lokale uitbreiding, c.q. stadiëring bij het hypofarynxcarcinoom?

Aanbeveling

Verricht een MRI en/of CT bij de diagnostiek en stadiëring van hypofarynx tumoren.

Verricht bij voorkeur een MRI om kraakbeeninvasie van hypofarynxtumoren vast te stellen. Verricht een CT indien MRI niet beschikbaar is of indien MRI onvoldoende informatie biedt.

Overwegingen

Voor deze uitgangsvraag werd geen systematische search verricht. De Amerikaanse richtlijn (NCCN) adviseert in het diagnostisch traject van patiënten met een hypofarynxtumor een CT en/of MRI te maken. Voor kraakbeeninvasie wordt aangegeven dat beide modaliteiten complementair zijn.

Echter, een recente systematische review en meta-analyse verricht door Jin Cho (2020) toont aan dat de sensitiviteit voor het aantonen van kraakbeen invasie van een hypofarynx tumor significant hoger is voor MRI dan voor CT. In dit review werden 14 studies geïncludeerd met in totaal 776 patiënten. CT onderzoek had een gepoolde sensitiviteit van 66% (95% BI: 49-80%) voor kraakbeeninvasie. Dit was 88% (95% BI: 70-93%) voor MRI. De sensitiviteit van MRI was hoger dan van CT (p=0.02). De gepoolde specificiteit was 90% (95% BI: 82-94%) van CT en 81% (95% BI: 76-84%) van MRI. Dit verschil was niet significant (p=0.39).

Onderbouwing

Achtergrond

Hypofarynx tumoren zijn agressieve tumoren die vaak in een laat stadium worden ontdekt. De neiging van de tumor om submucosaale te groeien bemoeilijkt de klinische beoordeling van de lokale uitbreiding. Het doel van beeldvorming is om de exacte driedimensionale uitbreiding te bepalen, en daarnaast de aanwezigheid van halskliermetastasen en tweede primaire tumoren.
Het vaststellen van eventuele invasie van kraakbeen van thyroid, cricoid en hyoid is van belang voor de stadiering en daarmee de behandeling van de patiënt.

CT biedt hierbij het voordeel dat het breed beschikbaar is en het onderzoek snel verricht kan worden bij patiënten die soms moeilijk lang stil kunnen liggen. Op CT kan echter moeilijker onderscheid gemaakt worden tussen tumor en oedeem van de weke delen. MRI biedt het voordeel dat weke delen beter

gevisualiseerd kunnen worden en bijvoorbeeld invasie van prevertebrale fascie gezien kan worden. Het nadeel is dat het veel tijd kost en niet bij elke patiënt verricht kan worden door bijvoorbeeld implantaten of pacemakers.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Beeldvormende diagnostiek larynxcarcinoom

Uitgangsvraag

- Aan welke eisen dienen beeldvormende techniek en beoordeling van het radiologisch onderzoek bij larynxcarcinoom te voldoen?
- Welke diagnostiek is verder nodig voor de beoordeling van de lokale uitbreiding, c.q. stadiëring van het larynxcarcinoom?

Aanbeveling

Aan welke eisen dienen beeldvormende techniek en beoordeling van het radiologisch onderzoek bij larynxcarcinoom te voldoen?
Beeldvorming met MRI en/of CT wordt aanbevolen bij de diagnostiek en stadiëring van larynxcarcinoom.

Welke diagnostiek is verder nodig voor de beoordeling van de lokale uitbreiding, c.q. stadiëring van het larynxcarcinoom?
Beeldvorming met MRI en/of CT wordt aanbevolen bij de diagnostiek en stadiëring van larynxcarcinoom, behoudens het T1a glottisch larynxcarcinoom zonder betrokkenheid van de voorste commissuur.

De keuze tussen CT of MRI wordt voornamelijk bepaald door de voorkeur en ervaring van de radioloog en de beschikbaarheid. CT lijkt in ieder geval aanbevolen bij patiënten met een onrustige ademhaling of indien er een contra-indicatie voor MRI bestaat. MRI lijkt in ieder geval geïndiceerd indien kraakbeeninvasie met zekerheid uitgesloten dient te worden, bijvoorbeeld indien een partiële laryngectomie wordt overwogen.

Overwegingen

Bij deze module werden geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Diagnostiek halskliermetastasen

Deze module is in ontwikkeling.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Diagnostiek afstandsmetastasen

Uitgangsvraag

Wanneer is aanvullende diagnostiek naar afstandsmetastasen geïndiceerd en hoe moeten deze worden gediagnosticeerd?

De uitangsvraag omvat de volgende deelvragen:

1. Wat zijn de indicaties voor onderzoek naar afstandsmetastasen ten tijde van de initiële diagnostiek van patiënten met een hoofd-halstumor?
2. Met welke beeldvormende modaliteit(en) moet onderzoek naar afstandsmetastasen verricht worden?

Aanbeveling

Aanbeveling-1
Verricht diagnostiek naar afstandsmetastasen bij patiënten met ten minste één van de volgende kenmerken:

- Aanwezigheid van drie of meer lymfekliermetastasen.
- Aanwezigheid van bilaterale lymfekliermetastasen.
- Aanwezigheid van een lymfekliermetastase groter of gelijk aan zes centimeter.
- Aanwezigheid van een laag-jugulaire lymfkliermetastase.
- Aanwezigheid van een regionaal recidief.
- Aanwezigheid van een tweede primaire tumor.
- Aanwezigheid van een T3-4 tumor.

Aanbeveling-2
Gebruik PET/CT voor de detectie van afstandsmetastasen, waarbij een CT-thorax als alternatief te overwegen is.

Aanbeveling-3
Besluit gezamenlijk met de patiënt over de inzet van diagnostiek naar afstandsmetastasen met in achtneming van de (behandel)prioriteiten van de patiënt en indien relevant:

- De eventueel aanwezige co-morbiditeiten.
- De uitgebreidheid van de eventuele chirurgische behandeling.
- De levensverwachting.

Overwegingen

Specifieke overwegingen voor Deelvraag 1 - indicaties tijdens de initiële work-up
Er werd geen systematisch literatuuronderzoek verricht naar de deelvraag over de indicaties voor onderzoek ten tijde van de initiële diagnostiek van patiënten met een hoofd-hals tumor. In de door de werkgroepgeïdentificeerde literatuur werd de incidentie van afstandsmetastasen beschreven per subsite van de tumor (Pisani, 2020; Xu, 2017), per stadium (Pisani, 2020), of per indicatie (De Bree, 2000).

Pisani (2020) gaf in een congresrapport per tumor-subsite incidenties van afstandsmetastasen op basis van meerdere referenties. De gerapporteerde subsites waren de neusholte (1,90%), paranasale sinussen (3.50%), mondholte (4.50%), larynx (5,00%), orofarynx (5,90%), nasofarynx (11,00%) en hypofarynx (16,00%).

Xu (2017) includeerde vijf prospectieve diagnostische accuratesse studies die patiënten met nasofaryngeale carcinomen includeerden. De mediane incidentie van afstandsmetastasen in deze studies was 14,4%. Er werd door Pisani (2020) op basis van vier studies een figuur gepresenteerd over het risico per T- en N-stadium. Hierbij kan gezien worden dat het risico toeneemt naar mate de T- en N-stadia avanceren. De hier gerapporteerde risico's werden uit het gepresenteerde figuur benaderd: T1 (1 tot 8%), T2 (7 tot 13%), T3 (12 tot 16%), T4 (15 tot 21%) en N0 (3 tot 5%), N1 (11 tot 20%), N2 (18 tot 22%), N3 (25 tot 30%). Twee studies (Garavello, 2006; Liu, 2018) van de vier studies, door Pisani (2020) beschreven in het figuur, rapporteerden gecorrigeerde relatieve maten ten opzichte van een referentiecategorie. Deze twee studies werden niet formeel beoordeeld op het risico op vertekening.

Garavello (2006) rapporteerde voor het T-stadium relatieve risico's voor T2 (RR = 13,4; 95%BHI: 7,8 tot 24,7), T3 (RR = 15,9; 95%BHI: 8,1 tot 28,5) en T4 (RR = 21,3; 95%BHI: 10,8 tot 34,7) ten opzichte van het T1-stadium. Voor het N-stadium werden relatieve risico's voor N1 (RR = 6,8; 95%BHI: 3,7 tot 13,6), N2 (RR = 7,2; 95%BHI: 4,9 tot 17,5) en N3 (RR = 10,7; 95%BHI: 6,5 tot 21,2) ten opzichte van het N0-stadium. Variabelen in het multivariabele model waren leeftijd, tumorlocatie, T-stadium, N-stadium, histologische differentiatie en locoregionale controle.

Liu (2018) rapporteerde odds ratio's voor T2 (OR = 1,53; 95%BHI: 1,37 tot 1,71), T3 (OR = 2,14; 95%BHI: 1,92 tot 2,39) en T4 (OR = 4,08; 95%BHI: 3,68 tot 4,53) ten opzichte van het T1-stadium. De odds ratio's werden ook per N-stadium gerapporteerd, waarbij N1 (OR = 3,11; 95%BHI: 2,77 tot 3,48), N2 (OR = 5,14; 95%BHI: 4,68 tot 5.64) en N3 (OR = 12,28; 95%BHI: 10,82 tot 13,94) werden vergeleken met het N0-stadium. Variabelen in het multivariabele model waren tumorlocatie, leeftijd, etniciteit, hoog-risico HPV-status, tumor differentiatie, T-stadium en N-stadium.

Pisani (2020) beschreef tevens de risico's per tumor-stadium, gebaseerd op drie studies: stadium I (1%), stadium II (14%), stadium III (15%), stadium IVa (20%) en stadium IVb (24%).

De Bree (2000) beschreef de incidentie van afstandsmetastasen bij verschillende klinische indicaties voor het screenen op afstandsmetastasen. In de steekproef zaten patiënten met carcinomen in de mondholte, orofarynx, hypofarynx, cervicale oesofagus, neus en paranasale sinussen, en een patiënt met lymfeklier metastasen met een onbekende primaire tumor. De incidentie werd gerapporteerd voor de volgende indicaties: totale glossectomie (0% in n=11), lymfeklier metastasen van 6 centimeter of groter (10% in n=10), bilaterale lymfeklier metastasen (13% in n=30), locoregionale terugkeer (18% in n=33), 3 of meer lymfeklier metastasen (21% in n=19), tweede primaire tumor (23% in n=13), 4 of meer lymfe klier metastasen (33% in n=9), en laag-jugulaire lymfeklier metastasen (33% in n=12). In de steekproef (n=101) werden 17 patiënten (17%) gevonden met één of meerdere afstandsmetastasen. In de thorax werden 16 metastasen gevonden (12 in de longen, 4 in de mediastinale lymfeklieren). Daarnaast werden er 4 botmetastasen gevonden en 1 levermetastase.

Specifieke overwegingen voor Deelvraag 2 - impact en misclassificaties van strategieën/modaliteiten
Er werden voor de vraag over de impact van verschillende diagnostische strategieën op patiënten geen systematische reviews gevonden die voldeden aan de inclusiecriteria. In de literatuuranalyse kon daarom geen conclusies getrokken worden ten aanzien van de impact van verschillende modaliteiten op de overleving of de keuze van behandeling van patiënten met hoofd-hals tumoren. Echter, in een observationele studie van Rohde (2017) werd in Denemarken onderzocht of het type diagnostiek de keuze van de vervolgbehandeling veranderde bij het detecteren van afstandsmetastasen. In de studie werd FDG-PET/CT (4MBq/kg) vergeleken met een gecombineerde thorax röntgenbeelden en MRI bij 303 patiënten met hoofd-hals tumoren (mediane leeftijd: 54 (range: 22 tot 89), 75% mannelijke deelnemers). Alle patiënten ondergingen beide diagnostische strategieën. In een multidisciplinair overleg werden keuzes gemaakt over de behandeling die door de FDG-PET/CT óf door de gecombineerde thorax röntgen afbeelding en MRI werden geïnformeerd. Drie maanden later werd er in een nieuw multidisciplinair overleg de complementaire diagnostiek (dat wil zeggen FDG-PET/CT in het geval de röntgenbeelden en MRI eerst werden besproken, en vice versa). Er werd een verschil in behandelintentie gerapporteerd van 8% (95% BHI: 4.8-11.5%, p<0.01). Na diagnostiek met FDG-PET/CT werden er meer patiënten behandeld met een palliatieve intentie in plaats van een curatieve intentie ten opzichte van gecombineerde diagnostiek met röntgenbeelden en MRI. Rohde (2017) concludeerde dat beslissingen van een multidisciplinair team omtrent de behandelintentie veranderden door een strategie gebaseerd op PET/CT wanneer vergeleken met een standaard strategie met thorax röntgenbeelden en MRI.

Ten aanzien van de accuratesse van verschillende modaliteiten voor het detecteren van afstandsmetastasen zou FDG-PET/CT wellicht minder vals negatieve classificaties opleveren dan een conventionele work-up bij patiënten met een nasofarynxcarcinoom (Xu, 2017). De testprestatie van FDG-PET ten opzichte van een conventionele work-up werd afgezet in een hypothetisch cohort met een prevalentie van 14.3% (zie Tabel 2). FDG-PET lijkt per 1000 personen één persoon meer als vals positief classificeren dan een conventionele work-up. Echter, FDG-PET lijkt per 1000 personen 63 personen minder te classificeren als vals negatief. Bij de gerapporteerde sensitiviteit en specificiteit in patiënten met nasofarynxcarcinomen (Xu, 2017) bleek dat er voor een conventionele work-up 2,63 personen (afgerond: 3 personen) nodig zijn om bij één persoon de aandoening te detecteren, tegenover 1.22 personen (afgerond: 2 personen) voor één detectie van de aandoening door FDG-PET.

Tabel 2 Test prestaties op basis van de gerapporteerde diagnostische accuratesse in patiënten met een nasofarynxcarcinoom uit Xu (2017)

	Sensitiviteit (95%BHI)	Specificiteit (95%BHI)	Aantal vals positieven in een hypothetisch cohort van n=1000 bij een prevalentie van 14.3%	Aantal vals negatieven in een hypothetisch cohort van n=1000 bij een prevalentie van 14.3%	Aantal benodigd om één keer de ziekte te detecteren (NND)*
Conventioneel	0.40 (95%BHI: 0.32-0.48)	0.98 (95%BHI: 0.97-0.99)	19 (95%BHI: 11-28)	86 (95%BHI: 74-97)	2.63
FDG-PET	0.84 (95%BHI: 0.77-0.89)	0.98 (95%BHI: 0.96-0.99)	20 (95%BHI: 12-30)	23 (95%BHI: 15-33)	1.22
*NND: Number Needed to Detect a disease, uit Linn (2006)					

Uit de literatuuranalyse blijkt dat er waarschijnlijk geen aanvullend risico bestaat op het onterecht detecteren van afstandsmetastasen (dat wil zeggen vals positief) door modaliteiten als röntgen en ultrasound in vergelijking met FDG-PET/CT bij patiënten met nasofarynxcarcinomen. Voor andere tumorlocaties in het hoofd-hals gebied werd er geen literatuur gevonden met betrekking tot de diagnostische accuratesse. Er werden tevens drie systematische reviews gevonden die niet aan de selectiecriteria voldeden (dat wil zeggen zij rapporteerden geen fout-positieven en -negatieven), maar wel (deels) relevant werden geacht (Blatt, 2016; Xu, 2012).

Blatt (2016) voerde een review uit waarin één studie (Fakhry, 2012) werd opgenomen die de diagnostische accuratesse van FDG-PET/PET-CT vergeleek met CT in 37 patiënten voor de detectie van afstandsmetastasen of secundaire tumoren. Tumorlocaties waren de mondholte (n=10), orofarynx (n=12, hypofarynx (n=5), larynx (n=8), nasofarynx (n=1) en de sinus maxillaris (n=1). De diagnostiek werd na een behandeling met (radio)chemotherapie ingezet tijdens de work-up vóór salvage chirurgie. Uitkomsten worden in Tabel 3 gerapporteerd. De auteurs concludeerden dat het gebruik van PET (FDG-PET/PET-CT) niet de eerste optie lijkt te zijn voor het detecteren van afstandsmetastasen of synchrone tumoren.

Tabel 3 Resultaten van Fakhry (2012) (uit Blatt (2016)) voor de detectie van afstandsmetastasen of secundaire tumoren

Type strategie	Sensitiviteit (95%CI)	Specificiteit (95%CI)	Positief voorspellende waarde (95%CI)	Negatief voorspellende waarde (95%CI)
FDG PET/PET-CT	0.92 (NR)	0.87 (NR)	0.74 (NR)	0.97 (NR)
CT	1.00 (NR)	0.94 (NR)	0.86 (NR)	1.00 (NR)
NR: Niet gerapporteerd				

Xu (2012) voerde een meta-analyse uit van acht studies om het verschil in diagnostische accuratesse van 'whole-body' PET/PET-CT en conventionele beeldvorming (inclusief thorax CT, thorax radiologie, abdominale ultrageluid, botscan en abdominale CT) te onderzoeken in 1147 patiënten. De referentietest was histopathologie en/of een klinische of imaging follow-up (veelal na 6 maanden). Enkele steekproefkarakteristieken worden in Tabel 4 weergegeven. De gepoolde diagnostische accuratesse uitkomsten worden in Tabel 5 beschreven. Het aantal vals positieven en negatieven werden niet weergegeven en konden niet berekend worden omdat de prevalentie van afstandsmetastasen in de steekproeven niet werd gerapporteerd. De classificaties van de testen werden daarom in een hypothetisch cohort berekend aan de hand van de gerapporteerde sensitiviteit en specificiteit met 5%, 10%, en 15% prevalentie in het hypothetische cohort (Tabel 6). De auteurs concludeerden dat gebruik van een 'whole-body' PET/PET-CT ondersteund werd door de resultaten van de meta-analyse en dat conventionele beeldvorming een beperkte sensitiviteit had voor het evalueren van afstandsmetastasen.

Tabel 4 Studiekarakteristieken van de geïncludeerde studies in Xu (2012)

Author	Tumor location (n)	Participant age	Number of male/female	Conventional method	Follow-up
Theodoros 2001	Larynx (4) Other, unspecified (8)	53 to 78 years	100% male	Chest CT	24 months
Sigg 2003	Oropharynx (8) Hypopharynx (6) Larynx (5) Oral cavity (9) Other, unspecified (28)	24 to 84 years	66.1% male	Chest CT	Unclear
Chan 2006	Nasopharynx (131)	Unclear	70.2% male	Chest radiography, abdominal ultrasonography, bone scan	≥ 6 months
Liu 2007	Nasopharynx (n=300)	50.5 years	70.0% male	Chest radiography, abdominal ultrasonography, bone scan	≥ 6 months
Ng 2008	Oropharynx (74) Hypopharynx (86)	26 to 87 years	92.5% male	Chest and abdominal CT	≥ 12 months
Krabbe 2009	Oropharynx (40) Hypopharynx (12) Larynx (13) Oral cavity (84)	61 years	68.5% male	Chest CT	Unclear
Ng 2009	Nasopharynx (111)	24 to 83 years	76.7% male	Chest radiography, abdominal ultrasonography, bone scan	12 months
Chua 2009	Nasopharynx (78)	Unclear	83.3% male	Chest radiography, abdominal ultrasonography, bone scan	≥ 12 months

Tabel 5 Gepoolde resultaten uit Xu (2012)

Patients	Type of strategy	Sensitivity (95%CI)	Specificity (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)
All patients, n=1147 (nasopharynx + non-nasopharynx)	Whole body PET/PET-CT	0.83 (0.76–0.88)	0.96 (0.94–0.97)	20.4 (14.5–28.5)	0.17 (0.12–0.25)
	Conventional anatomic imaging, including CT	0.44 (0.29–0.61)	0.96 (0.88–0.98)	9.9 (3.8–25.5)	0.59 (0.44–0.77)
Non-nasopharynx, n=377	Whole body PET/PET-CT	0.85 (0.73-0.93)	0.95 (0.91-0.97)	16.0 (9.8-26.1)	0.15 (0.08-0.30)
	Conventional anatomic imaging, including CT	0.62 (0.43-0.78)	0.93 (0.69-0.99)	8.8 (2.0-40.1)	0.41 (0.27-0.62)

Tabel 6 Classificaties van testen uit Xu (2012) in een hypothetisch cohort met een prevalentie van 5%, 10% en 15%

Test	Test classificatie	Aantal patiënten (95%BHI) in een hypothetisch cohort van n=1000		
		Prevalentie: 5%	Prevalentie: 10%	Prevalentie: 15%
Whole body PET/PET-CT (alle patiënten)	*Terecht Positief*	**42** (38 tot 44)	**83** (76 tot 88)	**124** (114 tot 132)
	Fout negatief	**8** (6 tot 12)	**17** (12 tot 24)	**26** (18 tot 36)
	Terecht negatief	**912** (893 tot 922)	**864** (846 tot 873)	**816** (799 tot 825)
	Fout positief	**38** (28 tot 57)	**36** (27 tot 54)	**34** (25 tot 51)
Conventional anatomic imaging, including CT (alle patiënten)	*Terecht Positief*	**22** (14 tot 31)	**44** (29 tot 61)	**66** (44 tot 92)
	Fout negatief	**28** (19 tot 36)	**56** (39 tot 71)	**84** (58 tot 106)
	Terecht negatief	**912** (836 tot 931)	**864** (792 tot 882)	**816** (748 tot 833)
	Fout positief	**38** (19 tot 114)	**36** (18 tot 108)	**34** (17 tot 102)
Whole body PET/PET-CT (zonder nasofarynx)	*Terecht Positief*	**43** (37 tot 47)	**85** (73 tot 93)	**128** (110 tot 140)
	Fout negatief	**7** (3 tot 13)	**15** (7 tot 27)	**22** (10 tot 40)
	Terecht negatief	**903** (864 tot 922)	**855** (819 tot 873)	**808** (774 tot 825)
	Fout positief	**47** (28 tot 86)	**45** (27 tot 81)	**42** (25 tot 76)
Conventional anatomic imaging, including CT (zonder nasofarynx)	*Terecht Positief*	**31** (22 tot 39)	**62** (43 tot 78)	**93** (65 tot 117)
	Fout negatief	**19** (11 tot 28)	**38** (22 tot 57)	**57** (33 tot 85)
	Terecht negatief	**884** (656 tot 941)	**837** (621 tot 891)	**791** (586 tot 842)
	Fout positief	**66** (9 tot 294)	**63** (9 tot 279)	**59** (8 tot 264)

Overkoepelende overwegingen

In een kwalitatieve studie met focusgroepen bestaande uit patiënten met hoofd-halstumoren (n=21) en hun

zorgverleners (n=19) werd geconcludeerd dat patiënten het belangrijk vinden om informatie te ontvangen over de levensverwachting (Hoesseini, 2020). In een andere cohortstudie (Windon, 2019) konden patiënten met hoofd-halstumoren (n=150) aangeven wat de hoogste behandelprioriteit voor hen had. Uit 12 onderwerpen werden genezing, overleving, en slikfunctie in deze volgorde als hoogste prioriteit gekozen. In deze studie observeerden de auteurs ook dat de prioriteit voor overleving wellicht af kan nemen bij een toenemende leeftijd van de patiënt (Windon, 2019). De levensverwachting is onder andere afhankelijk van de aanwezigheid van afstandsmetastasen. Het lijkt daarom aannemelijk dat patiënten over het algemeen aanvullend onderzoek naar de aanwezigheid van afstandsmetastasen wensen. Een nadeel van aanvullende onderzoeken is het ondergaan van zowel de emotionele belasting als tijdsbelasting voor de patiënt. Daarnaast kan er sprake zijn van fout-negatieve classificatie door de test, waardoor men onterecht wellicht geen passende interventies ontvangt. Ook kan er sprake zijn van een fout-positieve misclassificatie of de detectie van incidentalomen die geen behandeling behoeven, maar mogelijk wel een verdere emotionele belasting veroorzaken. Zorg waarin de patiënt centraal staat is in toenemende mate terrein aan het winnen binnen onze gezondheidszorg. Met de beschikbare prevalentiegetallen van afstandsmetastasen bij verschillende prognostische factoren en met wellicht een afnemende prioriteit van overleving bij patiënten met een toenemende leeftijd (zie Windon, 2019), zou gedeelde besluitvorming met de patiënt hier uitkomst bieden.

Het is te verwachten dat de wachttijden toe kunnen nemen wanneer er voor elke patiënt een FDG-PET/CT scan wordt aangevraagd. Er moet daarom rekening gehouden worden met de beperkte capaciteit en de hogere kosten van een FDG-PET/CT. Een PET-scan kost op dit moment ongeveer €1200,- tegenover ongeveer €200,- voor een CT-scan. Een echo van de hals kost rond de €86,- en een x-thorax ongeveer €45. Op dit moment worden PET/CT-scans routinematig gebruikt, waardoor er geen implementatieproblemen worden verwacht. Wel wordt opgemerkt dat er op dit moment landelijk nog wisselende indicatiestellen zijn voor het aanvragen van de PET/CT. De werkgroep ziet een CT-thorax als geschikt alternatief bij afweging van beschikbaarheid en kosten.

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Aanbeveling-1
Patiënten met één of meer dan de volgende kenmerken hebben, ten tijde van de diagnose, een prevalentie van afstandsmetastase van 10% of meer: ≥ 3 lymfklieren, bilaterale lymfklieren, klier ≥ 6 cm, laag jugulaire lymfklieren, locoregionaal recidief, Tweede primaire tumor. Bij deze groepen patiënten acht de werkgroep het daarom aangewezen om diagnostiek te verrichten naar afstandsmetastasen.

Aanbeveling-2
Hoewel het aanvullende bewijs geen formele kwaliteitsbeoordeling onderging, lijkt PET/CT eventueel een hogere sensitiviteit te hebben dan conventionele diagnostiek in een indirecte vergelijking. Hierdoor zullen er mogelijk minder patiënten fout-negatief geclassificeerd worden. Gezien de indirecte vergelijking in een hypothetisch cohort lijkt de conventionele diagnostiek wellicht gelijkwaardig qua het classificeren van patiënten zonder afstandsmetastasen (dat wil zeggen terecht-negatieven en fout-positieven). De werkgroep is van mening dat een CT-thorax als een alternatief gezien kan worden indien de betere beschikbaarheid en lagere kosten mee worden gewogen.

Aanbeveling-3
Het is belangrijk om samen met de patiënt over de inzet van diagnostiek naar afstandsmetastasen te spreken en te beslissen. Afhankelijk van de (behandel)prioriteiten van de patiënt (bijvoorbeeld genezing, overleving, functiebehoud), de aanwezige co-morbiditeiten, de uitgebreidheid van de eventuele chirurgische behandeling en de eventuele levensverwachting kan er gezamenlijk besloten worden over de inzet van de diagnostiek naar afstandsmetastasen.

Onderbouwing

Achtergrond

Er is praktijkvariatie met betrekking tot het gebruik van diagnostische strategieën/ verschillende modaliteiten.

Conclusies

Clinical sub-question 1 - indications during the initial work-up
Literature conclusions could not be drawn for this clinical sub-question. Systematic searches were not performed and no studies were selected for the literature analyses.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
PICO 1 (impact)

- GRADE	No conclusions could be drawn regarding the impact of different diagnostic strategies on the **one-year survival** and **chosen treatment.** None of the studies met the inclusion criteria.

PICO 2 (diagnostic misclassification)

LOW GRADE	The evidence suggests with low certainty that FDG-PET/CT slightly reduces **the number of false negative detections** of distant metastasis in patients with nasopharyngeal carcinoma compared to conventional work-ups. *Sources: (Xu, 2017)*

- GRADE	No conclusions could be drawn regarding **the number of false negative detections** of distant metastasis in patients with head and neck carcinomas other than nasopharynx carcinomas.

MODERATE GRADE	FDG-PET/CT probably does not reduce **the number of false positive detections** of distant metastasis in patients with nasopharyngeal carcinoma compared to conventional work-ups. Data for other subsites in the head and neck region was not found. *Sources: (Xu, 2017)*

- **GRADE**	No conclusions could be drawn regarding **the number of false positive detections** of distant metastasis in patients with head and neck carcinomas other than nasopharynx carcinomas.

- **GRADE**	No conclusions could be drawn regarding the effect of different diagnostic strategies on **costs**. None of the included studies reported costs.

- **GRADE**	No conclusions could be drawn regarding the effect of different diagnostic strategies on **radiation exposure**. None of the included studies reported radiation exposure outcomes.

Samenvatting literatuur

Description of studies
Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
PICO 1 (impact)
No systematic reviews were included in the literature analysis of PICO 1.

PICO 2 (diagnostic accuracy)
Xu (2017) conducted a meta-analysis of four studies investigating difference in accuracy of F-FDG PET/CT and conventional work-ups (skeletal scintigraphy, chest X-ray examination and liver ultrasound) in a total of 1029 patients with primary nasopharyngeal carcinomas, from which results were compared with biopsy, imaging and clinical follow-up of at least six months. Brief characteristics are shown in Table 1. Xu (2017) searched MEDLINE, EMBASE, the Cochrane Library, and the Chinese database CBMDisc, which was last updated on the 3rd of October 2016. Studies were included when: 18F-FDG PET/CT and conventional work-ups were used to detect whole-body distant in patients with nasopharyngeal carcinomas, per patient statistics were reported (including true positives and negatives, and false positives and negatives), and biopsy, imaging, and/or clinical follow-up were used as a reference standard. The largest study was selected when there were multiple cohorts with overlapping data. Studies were excluded when: patients had residual or recurrent nasopharyngeal carcinoma, the study sample contained a mixture of patients with untreated and residual or recurrent disease (if data of untreated patients could not be obtained), the study enrolled patients with no evidence of distant metastasis by conventional work-up, and when the study was a case report / conference abstract / review. Two authors independently assessed the study quality using the QUADAS-II tool.

Table 1 Charactistics of studies included by Xu (2017)

	Mean age	Number of male/female	Prevalence distant metastasis	Follow-up
Chua 2009	50.00	60/18	7.7%	≥ 6 months
Ng 2009	48.90	84/27	14.4%	≥ 12 months
Zhang 2011	45.00	201/56	15.2%	≥ 36 months
Tang 2013	46.00	474/109	14.8%	≥ 12 months

Results

Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
PICO 1 (impact)
No studies could be included for the literature analysis of PICO 1.

PICO 2 (diagnostic misclassification)
<u>False negatives</u>
Xu (2017) reported the false negatives, sensitivity, and prevalence per study. False negatives per 1000 patients were calculated from the pooled sensitivity for FDG-PET/CT (0.84, 95%CI: 0.77 to 0.89) and CWU (0.40, 95%CI: 0.32 to 0.48) reported by Xu (2017) at a pre-test probability of 14.3%. The number of false negatives for FDG-PET/CT was 63 per 1000 patients less than for CWU. FDG-PET/CT had 23 false negatives (95%CI: 15 to 33) compared to 86 false negatives (95%CI: 74 to 97) for CWU.

<u>False positives</u>
Xu (2017) reported the false positives, specificity, and prevalence per study. False positives per 1000 patients were calculated from the pooled specificity for FDG-PET/CT (0.98, 95%CI: 0.96 to 0.99) and CWU (0.98, 95%CI: 0.97 to 0.99) reported by Xu (2017) at a pre-test probability of 14.3%. The number of false positives for FDG-PET/CT was 1 per 1000 patients more than for CWU. FDG-PET/CT had 20 false positives (95%CI: 12 to 30) compared to 19 false positives (95%CI: 11 to 28) for CWU.

<u>Costs</u>
None of the included studies reported costs.

<u>Radiation exposure</u>
None of the included studies reported radiation exposure.

<u>Level of evidence of the literature</u>
Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities

PICO 1 (impact)
No studies could be included for the literature analysis of PICO 1.

PICO 2 (diagnostic misclassification)
<u>False negatives</u>
Level of evidence for diagnostic studies starts at high level, but was downgraded to low because of risk of bias (one level, see Xu (2017) and risk of bias table: High or unclear risks regarding patient selection, unclear risks regarding reference standard and flow and timing) and imprecision (one level, due to wide confidence intervals of FDG-PET/CT sensitivity). Publication bias was not assessed.

<u>False positives</u>
Level of evidence for diagnostic studies starts at high level, but was downgraded to moderate because of risk of bias (one level, see Xu (2017) and risk of bias table: High or unclear risks regarding patient selection, unclear risks regarding reference standard and flow and timing). Publication bias was not assessed.

<u>Costs</u>
The level of evidence could not be determined as none of the included studies reported costs.

<u>Radiation exposure</u>
The level of evidence could not be determined as none of the included studies reported radiation exposure.

Zoeken en selecteren

Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed for the clinical question concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
Systematic searches were performed for the second underlying clinical sub-question only, concerning the impact and accuracy of diagnostic tests. Two PICOs were used:

PICO 1 (impact)
What are the (un)beneficial effects of a diagnostic strategy (or modality) to detect distant metastases and secondary primary tumors in the initial work-up on the one-year survival and choice of treatment in patients with head and neck carcinomas?

P: patients with a head and neck carcinoma;
I: Diagnostic strategy or modality (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
C: other diagnostic strategy (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
O: one-year survival, chosen treatment (yes/no, type of treatment).

PICO 2 (diagnostic misclassification)

What is the diagnostic accuracy of diagnostic strategies/modalities to detect distance metastasis and second primary tumors in the initial work-up of patients with head and neck carcinomas?

P: patients with a head and neck carcinoma;
I: diagnostic strategy or modality (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
C: other diagnostic strategy (PET-scan, CT-thorax (incl. LODO-CT) or X-thorax) to detect distance metastasis;
R: disease progression regarding distant metastasis after one year as detected with a PET-scan or pathological report;
O: number of false negatives, number of false positives, costs, radiation exposure.

Relevant outcome measures
The guideline development group considered overall survival, number of false negatives and number of false positives as a critical outcome measure for decision making; and chosen treatment, costs, radiation exposure as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a risk difference of 5% regarding one-year survival as a minimal clinically (patient) important difference.

Search and select (Methods)
Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed for the clinical question concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
The databases (Medline (via OVID) and Embase (via Embase.com)) were searched with relevant search terms until November 28th,2019 and December 5th,2019. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 367 (systematic reviews and RCTs) hits.

Studies were selected based on the following criteria:
For PICO 1 (impact)

- Systematic review (including evidence tables, risk of bias assessments) or RCT.
- Patients with head and neck carcinoma; comparing survival and/or disease progression between different modalities.

For PICO 2 (diagnostic accuracy)

- Systematic review (including evidence tables, risk of bias assessments).
- Patients with head and neck carcinoma.

- Comparing diagnostic accuracy, costs and/or radiation exposure between different modalities within the same population.

Twenty-seven studies were initially selected based on title and abstract screening. After reading the full text, 26 studies were excluded (see the table with reasons for exclusion under the tab Methods) and one study was included.

Results

Clinical sub-question 1 - indications during the initial work-up
Systematic searches were not performed. No studies were selected for the literature analyses concerning indications for diagnosis during the initial work-up.

Clinical sub-question 2 - impact and misclassifications of strategies/modalities
For PICO 1 (impact), no systematic reviews were selected for the literature analysis. However, one relevant observational study (Rohde, 2017) is described in the considerations without GRADEing the outcomes.

For PICO 2 (diagnostic accuracy), one systematic review was included in the literature analysis. Important study characteristics and results of GRADEd studies are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Furthermore, three systematic reviews did not report the outcomes of interest and were excluded from the literature analysis (Blatt, 2016; Li, 2020; Xu, 2012). Due to their relevance they were described in the considerations without GRADEing the outcomes

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Aanvraag en verslag

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Wat er minimaal in de aanvraag voor en in het verslag van beeldvormend onderzoek bij hoofd-halstumoren moet staan

Uitgangsvraag

Wat moet er minimaal in de aanvraag voor en in het verslag van beeldvormend onderzoek staan?

Aanbeveling

Aanvraagformulier voor beeldvormend onderzoek
De clinicus vermeldt **altijd** de volgende gegevens:

- indicatie voor het onderzoek;
- relevante (oncologische) voorgeschiedenis;
- behandelingsvoorgeschiedenis (zoals recente operaties, puncties, radiotherapie, chemotherapie);
- bevindingen bij klinisch onderzoek / scopie (zo mogelijk klinisch TN-stadium);
- voor het onderzoek relevante resultaten van eerder beeldvormend onderzoek;
- allergie voor contrastmiddelen;
- nierfunctie (GFR) bij CT met contrast.

De clinicus vermeldt **aanvullend** de volgende gegevens voor PET:

- lengte en gewicht;
- recent verrichtte puncties en/of histologische biopten;
- diabetes mellitus en medicatiegebruik voor diabetes;
- comorbiditeit, zoals inflammatoire ziekten;

corticosteroïd gebruik.

Verslag beeldvormend onderzoek
De verslaggever vermeldt minimaal de volgende **algemene** gegevens:

- naam aanvrager;
- datum;
- patiënt identificatiegegevens;
- (soort) onderzoek;
- klinische informatie/ vraagstelling;
- behandelingsvoorgeschiedenis (onder andere recente operaties, puncties, radiotherapie, chemotherapie.);
- beschrijving onderzoek (uitvoering, bevindingen);
- conclusie (zo nodig een differentiaaldiagnose, beantwoording vraagstelling);
- aanbeveling (zo nodig);
- naam verslaggever.

Het radiologie verslag (CT/MR) bevat daarnaast minimaal de volgende **specifieke** gegevens:

- kwaliteit en beoordeelbaarheid van het onderzoek, waaronder bewegingsartefacten;
- primaire tumor:
  - afmetingen in drie dimensies (cm);
  - weke delen uitbreiding in relatie met de omringende anatomie:
    - craniocaudaal;
    - links-rechts;
    - voor-achterwaarts:
    - met (afhankelijk van de lokalisatie) speciale aandacht voor de relatie tot kritische omliggende structuren, zoals extrinsieke tongspieren bij mondholtecarcinomen, kraakbeen (larynx) of bot (onder andere mandibula, maxilla, schedelbasis), zenuwen en grote vaten.
  - aan- of afwezigheid van (tekenen van) een tweede primaire hoofd-halstumor.
- lymfeklieren:
  - hals links: aan- of afwezigheid van kliervergroting met vermelding Level I t/m VI, korte as diameter (mm), bij metastatische klieren maximale diameter en morfologische maligne kenmerken; m.n. extracapsulaire groei en centrale necrose;
  - hals rechts: aan- of afwezigheid van kliervergroting met vermelding Level I t/m VI, korte as diameter, bij metastatische klieren maximale diameter en morfologische maligne kenmerken; m.n. extracapsulaire groei en centrale necrose;
  - retrofaryngeale loge: aan- of afwezigheid van klieren met korte as diameter (mm).
- conclusie: (zo mogelijk) voorstel radiologische TN-stagering (gebaseerd op UICC TNM Classification of Malignant Tumours, eigth edition).

Het nucleair verslag (PET) bevat daarnaast minimaal de volgende **specifieke** gegevens:

Voorbereidingen:

- nuchter tenminste zes uur voorafgaand aan het onderzoek: ja/nee;
- geen parenterale en intraveneuze vloeistoffen die glucose bevatten tenminste vier uur voorafgaand aan het onderzoek: ja/nee;
- nuchtere plasma glucose spiegel (<7 mmol/l): ja/nee;
- prehydratie (geen glucose bevattende infusie vloeistoffen): ja/nee;
- diabetes mellitus en daarvoor gebruikte medicatie;
- glucocorticosteroïd gebruik.

Onderzoekstechniek:

- radiofarmacon en geïnjecteerde dosis;
- injectieplaats;
- tijd tussen toedienen van radiofarmacon gevolgd door rusten in prikkelarme omgeving en start scan;
- scan traject;

- CT-protocol (low-dose of diagnostisch, al dan niet met contrast toediening).

Resultaten:

- kwaliteit van het PET/CT onderzoek (bewegingsartefacten, FDG opname in spieren of bruin vet);
- mate van pathologische FDG opname in relatie tot het normale weefsel;
- de PET/CT bevindingen dienen in de context van de klinische vraagstelling te worden gerapporteerd en zo mogelijk worden geïnterpreteerd binnen de context van ander beeldvormend onderzoek en eerder verrichtte PET/CT scans;
- de afwijkingen op de PET/CT scan dienen in de conclusie te worden geïnterpreteerd;
- differentiaal diagnose passend bij de afwijkingen.

Aanbevelingen voor follow-up onderzoek

Overwegingen

Over de specifieke inhoud van het radiologisch verslag bij beeldvorming van hoofd- hals-maligniteiten zijn geen literatuurgegevens beschikbaar. Onderstaande tekst is een expert opinion van de werkgroep. Daarnaast is gebruik gemaakt van de Europese richtlijn 'Tumour PET imaging' (Boellaard et al., 2015).

Onderbouwing

Achtergrond

De waarde van de uitslag van beeldvormend onderzoek wordt sterk bepaald door de vooraf verstrekte klinische gegevens. Beeldvorming van hoofd-halstumoren biedt de aanvragend arts een grote hoeveelheid (aanvullende) gegevens over de metabole activiteit en uitbreiding van de primaire tumor, de lymfklierstatus van de hals en eventuele afstandsmetastasen (Som et al., 2000). Het is van belang dat deze informatie door de beeldvormend specialist op een gestructureerde manier wordt verwerkt tot een verslag (Wallis et al., 2011).

Samenvatting literatuur

Niet van toepassing.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Aanvraag en verslag pathologie-onderzoek

Uitgangsvraag

Wat moet er minimaal in de aanvraag voor en in het verslag van pathologie-onderzoek staan?

Aanbeveling

Vermeld op het aanvraagformulier voor algemeen pathologie-onderzoek het volgende:
De clinicus vermeldt **altijd** de volgende gegevens:

- ingreep;
- tumorlokalisatie;
- zijdigheid
- klinische TN classificatie;
- relevante voorgeschiedenis (eerdere behandeling, relevante comorbiditeit).

De clinicus vermeldt bij halsklierdissectie **aanvullend** de volgende gegevens:

- type halsklierdissectie;
- levels van het halsklierdissectiepreparaat;
- markering van levels op preparaat of bijgevoegde tekening.

De clinicus vermeldt bij een schildwachtklierprocedure **aanvullend** de volgende gegevens:

- welke klier(en) volgens de schildwachtklierprocedure bewerkt moeten worden.

Vermeld in het verslag pathologie-onderzoek onderstaande en **gebruik** hierbij bij voorkeur de PALGA protocol module:
De patholoog vermeldt minimaal de volgende algemene gegevens:

- naam aanvrager;
- datum;
- data patiënt;
- klinische gegevens (letterlijk overgenomen van het aanvraagformulier);
- naam patholoog;
- macroscopie;
- microscopie;
- conclusie.

Specifieke gegevens verslag *mucosaal plaveiselcelcarcinoom*
Het verslag van een *biopt* bevat minimaal de volgende gegevens:

- histologisch type;
- differentiatiegraad optioneel;
- bij orofarynxbiopt: HPV bepaling.

Het verslag van een *resectiepreparaat* bevat minimaal de volgende gegevens:

- aard preparaat, zijdigheid;
- plaats tumor;
- histologisch type en differentiatiegraad tumor;
- groeipatroon;
- maximale diameter;
- invasiediepte;
- kleinste afstand carcinoom tot de resectievlakken in mm, zowel mucosale- als weke delen resectievlakken;
- aan- of afwezigheid (lymf)vaat-ingroei;
- aan- of afwezigheid perineurale groei ter plaatse van het invasieve front;
- aan- of afwezigheid (ernstige) dysplasie in de mucosale resectievlakken;
- indien van toepassing:
- aan- of afwezigheid kraakbeen- of botinvasie;
- aan- of afwezigheid doorgroei in de schildklier.
- aan- of afwezigheid humaan papillomavirus (HPV) bij plaveiselcelcarcinomen van de orofarynx.

Specifieke gegevens verslag *speekselkliercarcinomen*
Het verslag van een *resectiepreparaat* bevat minimaal de volgende gegevens:

- aard preparaat, zijdigheid;
- histologisch tumortype en indien relevant (bijvoorbeeld mucoepidermoïd carcinoom) gradering;
- maximale diameter;
- ingroei in omgevende structuren;
- perineurale groei in "named nerves";
- kleinste afstand carcinoom tot de resectievlakken in mm.

Specifieke gegevens verslag *neus- en neusbijholtetumoren*
Het verslag van een *resectiepreparaat* bevat minimaal de volgende gegevens:

- aard preparaat, zijdigheid;
- histologisch tumortype en indien relevant (bijvoorbeeld esthesioneuroblastoom) gradering;
- maximale diameter;
- ingroei in omgevende structuren (bot);
- perineurale groei in "named nerves";
- Kleinste afstand carcinoom tot de resectievlakken in mm, zowel mucosale- als weke delen resectievlakken.

Specifieke gegevens verslag *lymfeklierresectie*

Het verslag van een *lymfeklierresectiepreparaat* van de hals bij een primair hoofd-hals carcinoom of bij een metastase ven onbekende primaire tumor bevat minimaal de volgende gegevens:

- aard preparaat (type halsklierdissectie met vermelding levels);
- per level:
- aantal lymfklieren;
- aantal lymfklieren met metastasen;
- diameter van de grootste metastase;
- aan- of afwezigheid van extranodale groei.

Specifieke gegevens verslag *schildwachtklierprocedure*

Het verslag van een *schildwachtklierprocedure* bevat minimaal de volgende gegevens:

- aantal lymfklieren;
- aan- of afwezigheid van een metastase;
- diameter van de metastase (Isolated Tumor Cells/micro-/macrometastasen);
- aan- of afwezigheid van extranodale groei.

Overwegingen

Algemeen

Het beleid bij de behandeling van hoofd-halstumoren wordt mede bepaald door het type tumor. De meeste in het hoofd-halsgebied voorkomende tumoren betreffen mucosale plaveiselcelcarcinomen. Daarnaast komen andere typen carcinomen voor in de speekselklieren en neus(bijholte). Zowel speekselkliercarcinomen als sino-nasale carcinomen zijn relatief zeldzaam. De meeste literatuur over prognostische tumorkenmerken geldt voor de mucosale plaveiselcelcarcinomen.

Plaveiselcelcarcinoom van het hoofd-halsgebied

Na een biopt of resectie voor een hoofd-halscarcinoom wordt het verdere therapeutische beleid in eerste instantie mede bepaald op basis van de WHO-classificatie en stadiering van de tumor (Barnes, 2005). Derhalve is het cruciaal dat in het PA verslag van de resectie alle componenten van de TN classificatie volledig worden benoemd. Daarnaast zijn er parameters die prognostische waarde hebben, onafhankelijk van de classificatie, die mede bepalend zijn voor het postoperatief beleid. Dit betreft karakteristieken van de tumor en metastasen die uitsluitend middels microscopisch onderzoek kunnen worden vastgesteld (Barnes, 2005; Odell, 1994; Woolgar, 1999, 2005, 2006 en 2009; Pentenero, 2005; Bradley, 2007; Weijers, 2009; Jones, 2009; Huang, 2009; Brandwein-Gensler 2010; Coca-Pelaz, 2012; Jerjes, 2012; Brown, 2012). Om tot een beslissing over het postoperatief beleid bij een patiënt te komen, moeten al deze ingrediënten in het pathologieverslag eenduidig benoemd staan. In het verslag staan zowel alle ingrediënten die nodig zijn voor het vaststellen van de pTN classificatie als de prognostische parameters die het postoperatief beleid mede bepalen. Bij gebruik van de PALGA protocolmodule is de volledigheid en uniformiteit van het verslag gewaarborgd.

Sommige aanvragen van bepalingen zijn vooralsnog niet standaard, maar kunnen wellicht op indicatie aangevraagd worden in specifieke klinische settings. Zo is te denken aan een immunohistochemische bepaling van PD-L1 eiwitten als indicatie voor pembrolizumab, welke aan PD-L1 scores is gekoppeld en wordt uitgedrukt in het zogenoemde 'combined positive score' (CPS).

HPV gerelateerde hoofd-halstumoren

Een deel van de carcinomen in de orofarynx zijn humaan papillomavirus (HPV) gerelateerd (Hobbs, 2006; Smeets, 2007; Lechner, 2013; Holzinger, 2013; Ragin and Taioli, 2007; Westra, 2012; Robinson, 2012). Dikwijls wordt een orofarynxcarcinoom behandeld met (chemo)radiatie. Derhalve is een biopt het enige materiaal dat bij deze tumoren wordt verkregen. Omdat de huidige TNM classificatie (8^e ed) verschillend is voor p16positieve en -negatieve oropharynxcarcinomen, moet in geval van een biopt uit de orofarynx (tonsil, tongbasis, orofarynx nos) standaard een HPV-bepaling verricht worden. P16 immunohistochemie is een goede surrogaatmarker voor "high-risk"HPV typen. Zie voor de overige aanbevelingen met betrekking tot HPV bepaling de richtlijnmodule HPV-statusbepaling.

De onderstaande minimale histologische dataset voor plaveiselcelcarcinoom is een bewerking van de richtlijnen van de Royal College of Pathology, in gebruik binnen de British Society of Head and Neck Oncology.

PA data resectiepreparaten

1. histologisch (sub)type en differentiatiegraad: subtypen van plaveiselcelcarcinomen (bijvoorbeeld basaloid, verruceus, sarcomatoid, papillair (Barnes, 2005) moeten worden vermeld. Differentiatiegraad wordt vermeld volgens WHO (Barnes, 2005; Weijers, 2009). Indien binnen een tumor variatie is in differentiatiegraad, wordt de hoogste graad (slechtste differentiatie) vermeld. Bij aanwezigheid van uitsluitend een premaligne laesie, wordt de hoogste mate van dysplasie vermeldt volgens WHO (Barnes, 2005);
2. groeipatroon: het groeipatroon in het tumorfront heeft prognostische waarde (Odell, 1994; Woolgar, 1999, 2006; Coca-Pelaz, 2012; Jerjes, 2012; Brown, 2012). Hierbij wordt onderscheid gemaakt in expansieve versus sprieterige groei, waarbij ook een (kleine) component van de tumor met een sprieterig groeipatroon moet worden vermeld. In de PPMI worden 5 typen groeipatronen onderscheiden die daarnaast (optioneel in de module) apart vermeld kunnen worden (Heeremam 2015);
3. tumor diameter: de macroscopisch gemeten tumordiameter wordt vermeld tenzij de microscopische uitbreiding groter is dan macroscopisch werd gemeten. De tumordiameter bepaalt het T stadium;
4. invasiediepte: de invasiediepte wordt gemeten vanaf het mucosale oppervlak. In geval van ge-ulcereerde tumoren wordt het gereconstrueerde mucosale oppervlak als referentiepunt genomen. Invasiediepte van orale carcinomen is gerelateerd aan de kans op lymfkliermetastasen (Pentenero, 2005; Huang, 2009);
5. afstand ten opzichte van de chirurgische resectievlakken: vanuit chirurgisch opzicht is > 5 mm radicaal, 1 tot 5 mm krap radicaal en < 1 mm irradicaal (Woolgar, 2005, 2006; Bradley, 2007; Coca-Pelaz, 2012; Jerjes, 2012; Brown, 2012);
6. vasculaire invasie: hierbij is het niet van belang of het bloedvat- of lymfvatinvasie betreft (Jones, 2009; Brandwein-Gensler, 2010; Jerjes, 2012). Dit moet wel onderscheiden worden van retractie-artefacten

rond de tumorvelden;

7. perineurale groei: bij perineurale groei aan het tumorfront is er een grotere kans op lokaal recidief of lymfkliermetastasen (Coca-Pelaz, 2012; Jerjes, 2012);
8. dysplasie in de mucosale resectieranden: gradering volgens WHO (Barnes, 2005);
9. bot/kraakbeeninvasie: hierbij dient een onderscheid te worden gemaakt tussen boterosie waarbij uitsluitend usurering van de cortex aanwezig is en botinvasie waarbij de tumor de cortex volledig doorbreekt. Botinvasie bepaalt de tumorstadiering. In het geval van larynxtumoren bepaalt de invasie van het larynxskelet (kraakbeen) het tumorstadium. Invasie van epiglottis kraakbeen en cart. arythenoidea gelden niet als larynxskelet.

Speekselkliercarcinomen

Speekselkliercarcinomen worden geclassificeerd volgens de WHO (Barnes, 2005). Hierin worden 24 typen maligne tumoren onderscheiden. Voor de prognose is het tumorstadium belangrijker dan het histologisch subtype (Regis De Brito Santos, 2001; Terhaard, 2001; Van der Schroeff, 2010). Er is, qua histologische typering een indeling gemaakt tussen speekselkliercarcinomen van lage en hoge maligniteitsgraad (Speight, 2009) en dit geeft ook een indicatie voor de prognose. Bij sommige speekselkliertumoren wordt gegradeerd, bijvoorbeeld het mucoepidermoïd carcinoom in hoog-, midden- en laaggradig, of het adenoïd cysteus carcinoom qua groeiwijze in cribriform, tubulair, of solide (zie bijlage 1: gradering mucoepidermoid carcinoom) (Barnes,, 2005; Van der Schroeff, 2010; Speight, 2009).

Voor de prognose is radicaliteit van de resectie een criterium (Terhaard, 2001). Postoperatieve radiotherapie is onder andere geïndiceerd bij niet-radicale resecties en uitgebreide perineurale groei in "named nerves" (Barrett, 2009).

Neus, neusbijholte

Sinonasale carcinomen worden geclassificeerd volgens de WHO (Barnes, 2005). Er worden diverse, epitheliale en non-epitheliale maligne tumoren onderscheiden (Barnes, 2005; Ejaz, 2005; Mendenhall, 2006; Renner, 2007; Stelow, 2008; Khademi, 2009; LLorente, 2009; Thompson, 2009; Stelow, 2010; Ansa, 2013; Haerle, 2013; Van Gompel, 2012; Slootweg, 2013). Voor de prognose is het histologisch type en de tumoruitbreiding van belang. In het geval van een adenocarcinoom is het onderscheid tussen intestinaal en non-intestinaal subtype en de differentiatiegraad van prognostische waarde (Llorente, 2009; Thompson, 2009). In het geval van een esthesioneuroblastoom wordt de prognose mede bepaald door Hyam's gradering (zie bijlage 2: gradering esthesioneuroblastoom) (Thompson, 2009; Van Gompel, 2012). Postoperatieve radiotherapie is geïndiceerd bij niet-radicale resecties en uitgebreide perineurale groei in "named nerves".

Lymfklierdissecties
a. Halsklierdissectie
Omdat de identificatie van de klierniveaus na uitname van het operatiepreparaat lastig of zelfs onmogelijk kan zijn, worden de klierniveaus idealiter aan het aangeleverde preparaat gemarkeerd door de chirurg (Ferlito, 2002).

Halsklierdissecties worden per level benoemd in het verslag. Van elk level wordt vermeld:

- aantal lymfklieren;
- aantal lymfklieren met metastasen;
- diameter van de grootste metastase (NB: dit is niet de diameter van de lymfklier); bij de diameter van de metastase wordt onderscheid gemaakt in "Isolated tumor cells" (ITC) bij een metastase ≤ 0,2 mm, micrometastase (> 0,2 mm, < 2 mm) of macrometastase ≥ 2 mm);
- aan- of afwezigheid van extranodale groei.

Extranodale groei is een prognostisch ongunstig kenmerk. Hierbij is het niet van belang of het microscopische of macroscopische kapseldoorbraak betreft. In geval van twijfel wordt de metastase geclassificeerd als hebbende kapseldoorgroei (Snow, 1982; Ferlito., 2002; Puri, 2003; Oosterkamp, 2006; Wan, 2012; Woolgar, 2013). De aanwezigheid van extranodale groei heeft consequenties voor de keuze van de adjuvante behandeling.

b. Schildwachtklierprocedure
Een schilwachtklierprocedure kan worden verricht bij een klinisch negatieve hals (cN0) bij een patiënt met een klein mondholtecarcinoom dat intra-oraal kan worden verwijderd (Gurney, 2012; Sloan, 2009; Alkureishi, 2010; Trivedi, 2010; Broglie, 2011, 2013 Schilling, 2019). De clinicus vermeldt duidelijk op de aanvraag welke klier(en) volgens de schildwachtklierprocedure moeten worden bewerkt.

De aangeleverde schildwachtklier(en) wordt /worden volledig voor histopathologisch onderzoek ingesloten. Klieren > 0,5 cm worden gelamelleerd in plakjes van circa 0,3 cm. Hiervan worden zes niveaus gesneden met een onderlinge afstand van 150 mu. Van elk niveau wordt een HE coupe vervaardigd en een immunohistochemische kleuring met behulp van een monoclonale antistof gericht tegen pankeratine, zoals AE1/3 (Sloan, 2009; Trivedi, 2010; Broglie, 2013).

Bij de diameter van de metastase wordt onderscheid gemaakt in "Isolated tumor cells" (ITC) bij een metastase ≤0,2 mm, micrometastase (> 0,2 mm, < 2 mm) of macrometastase ≥ 2 mm). Zogenaamde "ghostcells" of "mummified cells" (keratine positieve elementen zonder kern) worden niet beschouwd als tumormetastase (Woolgar, 2013).

Onderbouwing

Achtergrond

Het pathologieverslag dient alle informatie te bevatten die noodzakelijk is voor het bepalen van de therapie door de behandelaar, zowel in het geval van een biopt, als in het geval van een resectie. Daarom is het van belang dat deze informatie door de patholoog op een gestructureerde wijze wordt verwerkt in het pathologieverslag.

Samenvatting literatuur

Er is geen systematische literatuursearch uitgevoerd om de uitgangsvraag te kunnen beantwoorden. Tijdens de voorbereiding heeft de werkgroep afgesproken om aan te sluiten bij het relevante PALGA-protocol (Stichting PALGA, 2019). Idealiter zou de werkgroep beschikken over informatie ('evidence') over de (kosten)effectiviteit van het gebruik van het huidige PALGA protocol in de Nederlandse praktijk. Dergelijke

effectiviteitsstudies zijn volgens de werkgroep niet gedaan en het is niet aannemelijk dat de werkgroep dergelijke studies over het hoofd zou hebben gezien. Vanuit het oogpunt van doelmatig gebruik van beschikbare tijd en middelen voor de richtlijnontwikkeling heeft de werkgroep besloten om geen systematische literatuursearch uit te (laten) voeren voor de onderbouwing van de aanbevelingen van deze module.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Behandeling

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Behandeling van premaligne afwijkingen in het hoofd-halsgebied

Uitgangsvraag

Op welke wijze dienen premaligne afwijkingen behandeld te worden?

Aanbeveling

Bij erythroplakie en klinisch 'onrustige leukoplakie' dient een biopt te worden genomen.

Voor de behandeling van leukoplakie met hoge risicofactoren (matige of ernstige dysplasie) en erythroplakie wordt chirurgie of CO_2-laser evaporisatie aanbevolen.

Strikte follow-up is noodzakelijk.

Overwegingen

Bij deze module werden geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Mondholtecarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Behandeling bij mandibulaire botinvasie

Uitgangsvraag

Wat is de behandeling van voorkeur bij patiënten met mondholtecarcinomen met mandibulaire botinvasie?

Aanbeveling

Overweeg een marginale mandibularesectie bij patiënten met een beperkte aantasting van het corticale bot wanneer er voldoende chirurgische botmarge te behalen is.

Overweeg een segmentale resectie bij patiënten met een uitgebreidere aantasting van het bot waarbij er oncologisch onvoldoende chirurgische botmarge te behalen is of onvoldoende mandibulair bot achterblijft voor voldoende stevigheid van de mandibula.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
In totaal zijn er vijf studies die de (on)gunstige effecten van een marginale resectie vergelijken met een segmentale resectie bij patiënten met botinvasie door een mondholtecarcinoom. Dit betrof één systematisch literatuuronderzoek met 15 observationele studies gepubliceerd tot mei 2016 (Gou, 2018) en vier nieuwere observationele studies die na de zoekdatum van het systematische literatuuroverzicht van Gou (2018) werden gepubliceerd. De uitkomsten in van de verschillende studies worden wel weergegeven in één figuur, echter wordt er geen gepoolde effect schatter weergegeven, omdat (1) er niet gecorrigeerd is voor prognostische factoren in de individuele studies en (2) de procedures van het uitvoeren van de chirurgische interventies mogelijk verschillen tussen de studies (aangezien deze informatie niet duidelijk wordt beschreven in de studies).

De conclusies van de samenvatting van de literatuur met betrekking tot de cruciale uitkomstmaten (dat wil zeggen 'tumor-free resection', 'recurrence rate', 'disease-specific survival', 'overall survival rate') geven aan dat het bewijs erg onzeker is over de (on)gunstige effecten van een marginale resectie vergelijken met een segmentale resectie bij patiënten met mandibulaire botinvasie door een mondholtecarcinoom. Dit wordt mede veroorzaakt doordat het betrouwbaarheidsinterval de grens voor klinische relevatie overlapt, de resultaten tussen de studies inconsistent zijn of door het risico op bias in de individuele studies. Geen enkele studie heeft een randomisatieprocedure gehad. Hierdoor bestaat er een risico dat de geïncludeerde patiënten een indicatie hebben gehad voor één van beide behandelingen. De resultaten op de uitkomsten in de groepen zouden, naast de behandeling, (ook) af kunnen hangen van deze indicatie en/of van andere mogelijke (on)gemeten confounders. Zo kan er bijvoorbeeld voor een marginale resectie zijn gekozen bij patiënten met een beperkte botinvasie van de primaire tumor, maar hangt de beperkte botinvasie wellicht ook op zichzelf samen met een betere locoregionale controle of ziekte-specifieke overleving.De vergelijkingen tussen de groepen op dergelijke uitkomstmaten zal daarom met grote voorzichtigheid moeten worden geïnterpreteerd. De bewijskracht voor de literatuur is om deze redenen *zeer laag*. Ditzelfde geldt ook voor de belangrijk uitkomstmaten (dat wil zeggen 'function', 'duration surgery', 'complications'). De algehele bewijskracht voor de samenvatting van de literatuur is *zeer laag.*

Er werd geen enkele RCT gevonden. De kans bestaat dat de resultaten in de opgenomen studies in de literatuuranalyse vertekend zijn. Patiënten in de studies konden door de eventuele aanwezigheid van een indicatie wellicht een specifieke interventie ontvangen (d.w.z. een segmentale of marginale resectie), welke door een randomisatie zou worden weggenomen in en RCT. Daarnaast lijkt er geen correctie te zijn toegepast voor eventuele verschillen tussen groepen op prognostische factoren. Een marginale resectie lijkt minder belastend te zijn voor de patiënt. Daarnaast lijkt een marginale resectie met grote onzekerheid tot betere uitkomsten te leiden in de literatuur ten opzichte van een segmentale resectie, maar dit is niet erg plausibel. Wellicht leidt bij een (sterk) geselecteerde groep patiënten een marginale resectie niet tot een slechtere oncologische uitkomst, maar kan de functionele uitkomst wel beter zijn. Dit zal nog onderzocht moeten worden.

Bij een mondholtetumor met aanwezigheid van (beperkte) aantasting van het bot kan gekozen worden voor een marginale op segmentale mandibularesectie. Het is aannemelijk dat een beperktere chirurgische ingreep met een marginale mandibularesectie zorgt voor minder morbiditeit, een kleiner chirurgisch defect en een kortere operatieduur. Er is echter geen wetenschappelijk bewijs dat deze ingreep resulteert in een beter functioneel resultaat wanneer er vergeleken wordt met een segmentale mandibularesectie.

Er is tevens geen wetenschappelijk bewijs gevonden hoe veel botresectiemarge aangehouden moet worden bij verwijdering van een mondholte tumor met (beperkte) aantasting van het bot. Het effect van een marginale of segmentale mandibularesectie of de disease-specific of overall survival is eveneens onduidelijk.

Wanneer sprake is van een beperkte aantasting van het corticale bot en voldoende chirurgische marge behaald kan worden en voldoende bot achterblijft om voldoende stevigheid van de onderkaak te waarborgen, is een marginale mandibularesectie te overwegen. Een segmentale mandibularesectie lijkt geïndiceerd bij tumoren met uitgebreide corticale of medullaire aantasting van het bot of bij oppervlakkige botinvasie waarbij door anatomische redenen anders geen chirurgische marge behaald kan worden met behoud van voldoende stevigheid van de mandibula. Voorbeelden zijn een geresorbeerde edentate mandibula of wanneer er onvoldoende hoogte van de mandibula overblijft als er een marginale resectie zou worden uitgevoerd.

Het lijkt de werkgroep verstandig beide behandelopties indien technisch mogelijk (marginale en segmentale resectie) en de gevolgen hiervan op de reconstructieve uitgangssituatie met patiënten te bespreken en de waarden en voorkeuren van de patiënt hierbij in acht te nemen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Een goed oncologisch resultaat met een goede functionele uitkomst zijn voor de patiënt belangrijke uitkomstmaten. Een marginale mandibularesectie resulteert in het algemeen in een kortere operatieduur, waarbij er een beperkter chirurgisch defect ontstaat en de kans op complicaties mogelijk kleiner is. Bij een segmentale mandibularesectie is een grotere reconstructie ingreep noodzakelijk en daarmee nemen de operatieduur en de belasting voor de patiënt toe.

Kosten (middelenbeslag)
Het chirurgische defect dat ontstaat bij een segmentale mandibularesectie zal veelal gereconstrueerd moeten

worden met (titanium) reconstructieplaat met of zonder een bot of weke delen transplantaat. Dit is een operatie met een langere duur, langere opname in het ziekenhuis, meer kans op complicaties en derhalve meer kosten.

Aanvaardbaarheid, haalbaarheid en implementatie
Alle hoofdhals centra waar benige reconstructies worden uitgevoerd kunnen zowel een segmentale als een marginale mandibularesectie aanbieden aan de patiënt. Hierbij zou de ervaring van het behandelteam geen rol hoeven te spelen. Bij kwetsbare patiënten, waar de operatieduur en complexiteit van de behandeling van groot belang zijn, zou overwogen kunnen worden om voor de minder invasieve behandeling van de marginale mandibularesectie te kiezen.

Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er is geen bewijs dat een marginale mandibularesectie resulteert in slechter lokale controle, disease-specific of overall survival en het is aannemelijk dat een marginale mandibularesectie resulteert in minder morbiditeit voor de patiënt.

Aanbeveling-2
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Bij uitgebreide invasie van het corticale of medullaire bot of betrokkenheid van de canalis mandibularis is het aannemelijk dat een segmentale mandibularesectie nodig is om een veilige oncologische marge te behalen.

Onderbouwing

Achtergrond

Mandibulaire botinvasie bij primaire plaveiselcelcarcinomen van de mondholte is geassocieerd met een slechtere prognose. Bij de chirurgische behandeling van mondholtecarcinomen met mandibulaire botinvasie kan gekozen worden voor een marginale of een segmentale mandibularesectie. Een marginale mandibularesectie zorgt meestal voor een kleiner chirurgisch en een makkelijker te reconstrueren defect, maar gaat mogelijk ten koste van de chirurgische marges ten opzichte van de tumor. Het is daarom belangrijk om te bepalen wat het verschil in tumorcontrole is tussen een marginale en segmentale mandibularesectie bij carcinomen met invasie van het bot.

Conclusies

Very low GRADE	The evidence is very uncertain about the effect of marginal resection on the **disease-specific survival rate,** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. *Sources: (Gou, 2018; Stoop, 2020)*

Very low GRADE	The evidence is very uncertain about the effect of marginal resection on the **overall survival rate,** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. *Sources: (Gou, 2018; Qiu, 2018; Sproll, 2020)*

Very low GRADE	The evidence is very uncertain about the effect of marginal resection on the **local control,** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. *Sources: (Gou, 2018)*

Very low GRADE	The evidence is very uncertain about the effect of marginal resection on the **recurrence rate,** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. *Sources: (Qiu, 2018; Sproll, 2020; Stoop, 2020)*

Very low GRADE	The evidence is very uncertain about the effect of marginal resection on the **surgical margin free resection,** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. *Sources: (Alam; 2019)*

Very low GRADE	The evidence is very uncertain about the effect of marginal resection on the **oral function** (speech difficulty, trismus, mastication problems, and respiratory problems)**,** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. *Sources: (Alam, 2019)*

- GRADE	No evidence was found regarding the effect of marginal resection on **duration of surgery and complications** when compared with segmental resection in patients with bone invasion in mandible due to oral cavity carcinoma. These outcome measures were not studied in the included studies.

Samenvatting literatuur

<u>Description of studies</u>
First, the systematic literature review is described. The additional observational studies are described thereafter.

The systematic review by Gou (2018) investigated the differences in survival rate and disease control in patients undergoing marginal mandibulectomy versus segmental mandibulectomy. RCTs and/or cohort studies in line with the research question of the SR were eligible for inclusion. The Cochrane Oral Health Group Trials Register, the Cochrane Central Register of Controlled Trials, MEDLINE (via OVID), Embase, Cumulative Index for Nursing and Allied Health literature (CINAHL), Latin American and Caribbean Health Sciences Information (LILACS), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang Database, Sciencepaper Online, System for Information on Grey Literature in Europe (SIGLE), and the World Health Organization (WHO) International Clinical Trials Registry Platform, were searched to identify relevant studies until May 2016. Primary outcomes were "disease-free survival", defined the length of time after primary treatment for a cancer until the time at which the patient was confirmed to have local, regional, or distant recurrence of the cancer, and "overall survival", defined as the length of time that the patient diagnosed with the disease was still alive, starting from either the date of diagnosis or the start of treatment for the disease. Secondary outcomes were the 2-year/5-year survival rate and local control. In total data of 15 studies, including 1672 participants, were identified. Patient characteristics were not reported in 3 of the 15 studies. If it was reported, in total 873 males compared with 380 females aged (range) between 21-93 years were studied. All included studies were retrospective cohorts performed in Australia (n=2), Canada (n=1), China (n=1), Japan (n=1) Spain (n=1), UK (n=1), USA (n=8). Subgroup analyses are performed for patients with bone invasion. Important limitations of the current SR are (1) analyses were based on different types of mandibular invasion and different types of data (whether or not adjusted to the other independent prognostic factors), and (2) the article reported that all included studies had a high risk of bias.

Alam (2019) performed a prospective cohort study to investigate surgical outcomes and post-operative complications in patients undergoing marginal - or segmental resection for oral squamous cell carcinoma in Bangladesh. Between September 2008 and august 2013, 32 patients (9 males; median age of 40.5 years) were included, 20 of them underwent marginal resection and 12 a segmental resection. Mandibular invasion was present in 3 of the 20 patients in the marginal group compared to 10 of the 12 patients in the segmental group. Tumor stage was higher in patients who underwent segmental resection. The number of patients with margin free resection were reported per group, even as the number of patients with post-operative complications (i.e., speech difficulty, trismus, mastication problem, respiratory problem) per group. The current study is limited by the fact that data was not reported separately for patients with bone invasion, and no adjusted were made for potential prognostic factors.

Sproll (2020) conducted a retrospective cohort study to investigate results after marginal and segmental mandibulectomies in patients with oral squamous cell carcinoma. Between 1996 and 2010 259 patients (178 male; mean age of 62.3 years) were included. Of them 35 underwent marginal versus 224 segmental mandibulectomy. Mandibular infiltration was found in 5 of the 35 patients undergoing marginal resection versus 105 of the224 patients undergoing segmental resection. The tumor stage was higher in patients receiving segmental mandibulectomy compared to marginal. Although the authors mentioned that there was no significant difference between patients receiving marginal mandibulectomy and those receiving segmental mandibulectomy regarding prognostic factors. The number of patients with oral squamous cell carcinoma recurrence were reported, and percentages of patients achieving a 5-year overall survival were described. Although, the precise follow-up time was not mentioned for recurrence, only that the minimal follow-up time

was 3-years. No information about function and/or quality of life was reported. The current study is limited by the fact that data was not reported separately for patients with bone invasion, and no adjusted were made for potential prognostic factors.

Stoop (2020) conducted a retrospective cohort study in the Netherlands. In total 229 patients undergone mandibular resection for oral squamous cell carcinoma between January 2000 and December 2017. Of them 19 were lost to follow-up. Therefore, analyses were based on 210 patients (127 males; mean age of 66.0 years), 59 had a marginal resection and 151 a segmental resection. Mandibular bone invasion was present in all patients. The group receiving a segmental resection had more defects classified as Ic, II, and IV (Brown's classification, p=0.000), had larger tumors (p=0.001), and had a larger infiltration depth (p=0.000) compared to patients receiving a marginal resection. Local recurrence rates and disease-specific survival rates after 3 (and 5) years were reported. No information about surgery (for example duration), function and/or quality of life was reported. The current study is limited by the fact that no adjusted were made for potential prognostic factors.

Qiu (2018) conducted a retrospective cohort study of 82 patients (61 males; median age of 52 years) with oral squamous cell carcinoma who underwent mandibulectomy between January 2001 and January 2015. In total 39 underwent marginal mandibulectomy, and 43 underwent segmental mandibulectomy. Mandibular involvement was present in 29 of the 39 patients in the marginal resection group versus 23 of the43 patients in the segmental group. Patient and tumor characteristics were not different between the two groups at baseline. Local recurrence rates and survival rates after 3 (and 5) years were reported. No information about surgery (for example duration), function and/or quality of life was reported. The current study is limited by the fact that data was not reported separately for patients with bone invasion, and no adjusted were made for potential prognostic factors.

Results
Results are described per outcome measure, if possible relative risks (RR) were presented for a specific follow-up (i.e., achieving a specific outcome at a specific time). Subgroup analyses are performed for patients with bone invasion in line with the systematic review (SR) of Gou (2018). As it was not possible to obtain data which was adjusted for prognostic factors, no pooled effect estimates were illustrated.

Disease-specific survival rate
Disease-specific survival (DFS) was defined as 'the length of time after primary treatment for a cancer until the time at which the patient was confirmed to have local, regional, or distant recurrence of the cancer' by Gou (2018). Stoop (2020) did not specifically describe this outcome.

1.1 Disease-specific survival rate at 2-year
Three studies in the systematic review (Gou, 2018) reported the number of patients achieving DFS at 2-year, see Figure 11.2.1. Results showed that the relative risk point estimates of the individual studies were slightly in favor of in the intervention (i.e., marginal resection) group when compared to the control (i.e., segmental resection) group.

Figure 11.2.1 Forest plot for disease-specific survival rate at 2-year; marginal versus segmental resection

Study or Subgroup	Marginal Events	Total	Segmental Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Totsuka, 1991	18	21	23	28	1.04 [0.82, 1.33]	
Wald, 1983	16	21	18	26	1.10 [0.78, 1.56]	
Werning, 2001	131	182	24	40	1.20 [0.92, 1.57]	

0.5 0.7 1 1.5 2
Favours segmental   Favours marginal
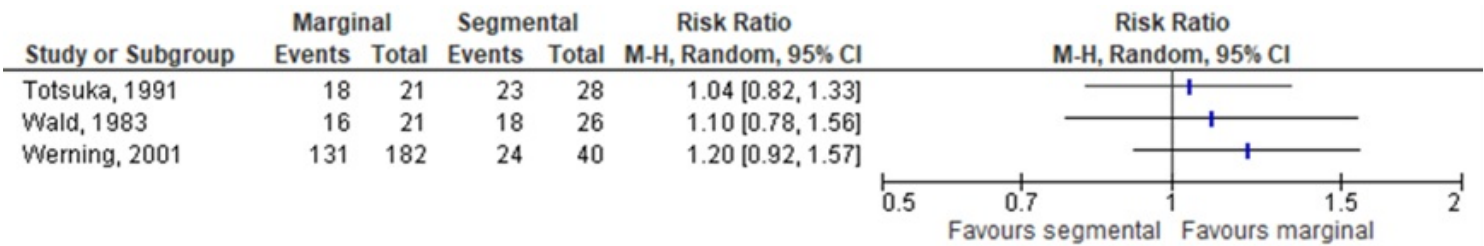
1.2 Disease-specific survival rate at 3-year with bone invasion.

One study (Stoop, 2020) reported the number of patients achieving DFS at 3-year. Results showed that the relative risk was slightly in favor of the intervention (i.e., marginal resection) group when compared to the control (i.e., segmental resection) group, with a relative risk of 1.10 (95%CI 0.91 to 1.33). The risk difference was 0.07 (95%CI -0.07 to 0.20). Importantly, only patients with bone invasion were included in this analysis.

1.3 Disease-specific survival rate at 5-year

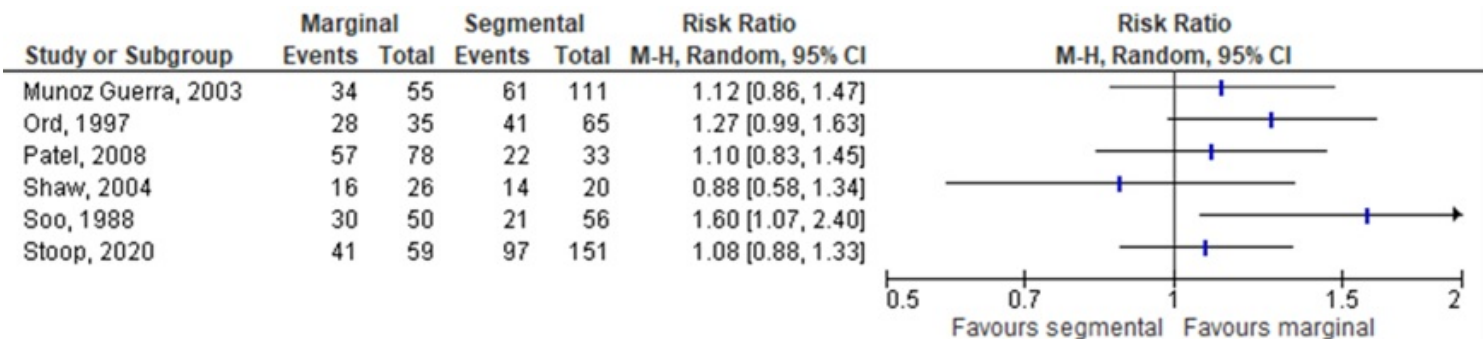Five studies in the systematic review by Gou (2018) and the study of Stoop (2020) reported the number of patients achieving DFS at 5-year, see Figure 11.2.2 Results showed that the point estimates of the relative risks in individual studies were slightly in favor of the intervention (i.e., marginal resection) group compared to the control (i.e., segmental resection) group in 5 of the 6 studies.

Figure 11.2.2 Forest plot for disease-specific survival rate at 5-year; marginal versus segmental resection

Study or Subgroup	Marginal Events	Total	Segmental Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Munoz Guerra, 2003	34	55	61	111	1.12 [0.86, 1.47]	
Ord, 1997	28	35	41	65	1.27 [0.99, 1.63]	
Patel, 2008	57	78	22	33	1.10 [0.83, 1.45]	
Shaw, 2004	16	26	14	20	0.88 [0.58, 1.34]	
Soo, 1988	30	50	21	56	1.60 [1.07, 2.40]	
Stoop, 2020	41	59	97	151	1.08 [0.88, 1.33]	

0.5 0.7 1 1.5 2
Favours segmental   Favours marginal

1.3.1 Disease-specific survival rate at 5-year with bone invasion.

Two studies in the systematic review by Gou (2018) and the study of Stoop (2020) reported the number of patients achieving DFS at 5-year in patients with bone invasion, see Figure 11.2.3. Results showed no differences between the intervention (i.e., marginal resection) group and control (i.e., segmental resection) group.

Figure 11.2.3 Forest plot for disease-specific survival rate at 5-year in patients with bone invasion; marginal versus segmental resection

Study or Subgroup	Marginal Events	Total	Segmental Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Patel, 2008	23	36	20	31	0.99 [0.69, 1.42]	
Soo, 1988	5	11	23	52	1.03 [0.50, 2.10]	
Stoop, 2020	41	59	97	151	1.08 [0.88, 1.33]	

0.2   0.5   1   2   5
Favours segmental   Favours marginal

2. Overall survival rate

Overall survival (OS) was defined as 'the length of time that the patient diagnosed with the disease was still alive, starting from either the date of diagnosis or the start of treatment for the disease' by Gou (2018). 'Death associated with primary disease was the evaluated outcome used to determine the survival rate' by Qiu (2018). Sproll (2020) did not specifically describe this outcome.

2.1 Overall survival rate at 2-year

Three studies in the systematic review by Gou (2018) reported the outcome OS at 2-year, see Figure 11.2.4. Results showed no differences between the intervention (i.e., marginal resection) group and control (i.e., segmental resection) group in 2 of the 3 studies. One of the 3 studies reported a relative risk indicating a more favorable effect in the segmental resectiongroup.

Figure 11.2.4 Forest plot for overall survival rate at 2-year; marginal versus segmental resection.

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Munoz Guerra, 2003	32	50	34	56	1.05 [0.78, 1.42]	
Totsuka, 1991	20	23	25	30	1.04 [0.83, 1.31]	
Wald, 1983	14	21	21	26	0.83 [0.58, 1.18]	

0.5   0.7   1   1.5   2
Favours segmental   Favours marginal

2.2. Overall survival rate at 5-year

Four studies in the systematic review by Gou (2018), the study by Qiu (2018), and by Sproll (2020) reported the outcome OS at 5-year, see Figure 11.2.5. Results of the individual trials were not consistent. Three of the 6 studies showed that the intervention group was more favorable (i.e., RR> 1), and the other 3 studies reported a more favorable outcome for the control group (i.e., RR< 1).

Figure 11.2.5 Forest plot for overall survival rate at 5-year; marginal versus segmental resection

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Munoz Guerra, 2003	30	50	21	56	1.60 [1.07, 2.40]	
Nie, 2000	43	82	92	166	0.95 [0.74, 1.21]	
Pascoal, 2007	11	20	11	22	1.10 [0.62, 1.96]	
Qui, 2018	22	39	26	43	0.93 [0.65, 1.35]	
Sproll, 2020	24	35	128	224	1.20 [0.93, 1.54]	
Totsuka, 1991	17	23	23	30	0.96 [0.71, 1.32]	

0.5   0.7   1   1.5   2
Favours segmental   Favours marginal

3. Local control
No specific definition of local control was given by Gou (2018).

3.1 Local control at 2-year
Four studies in the systematic review by Gou (2018) reported the outcome local control at 2-year, see Figure 11.2.6. Results showed that the relative risk was slightly in favor of the intervention (i.e., marginal resection) group compared to the control (i.e., segmental resection) group in 2 of the 4 studies.
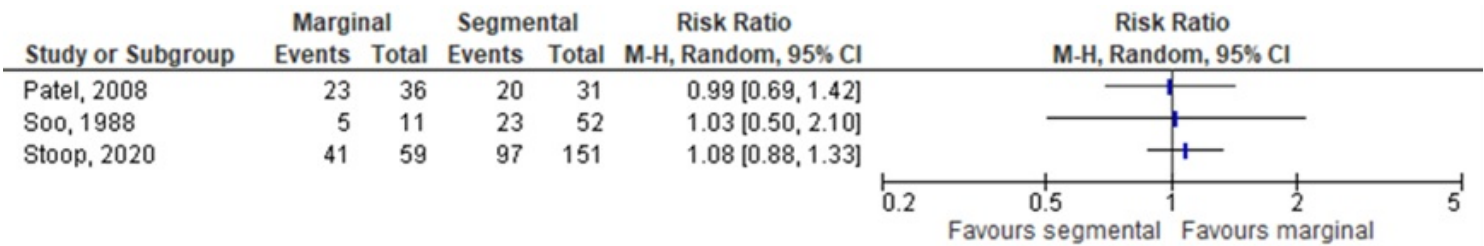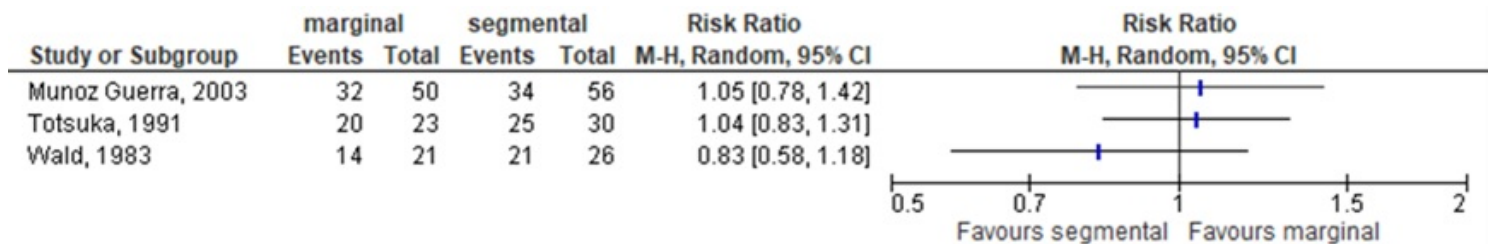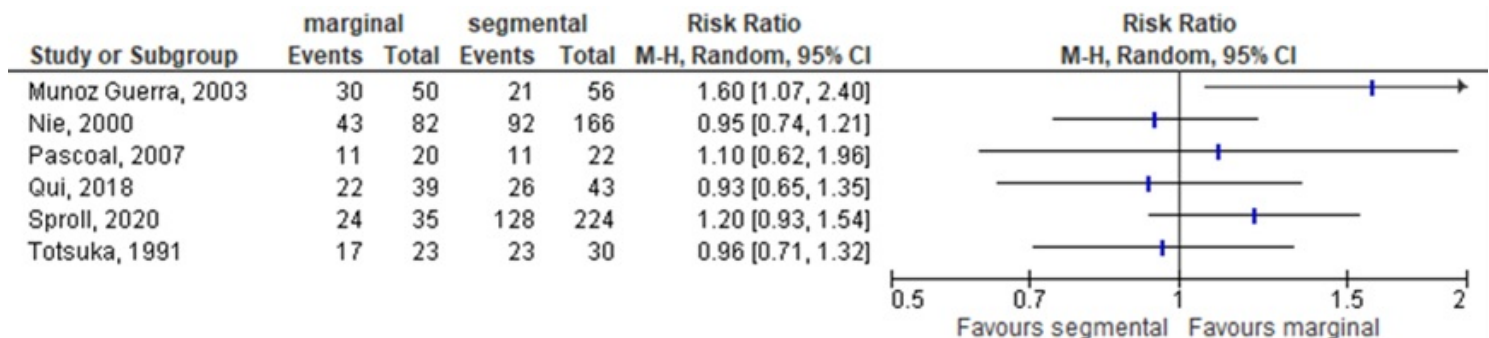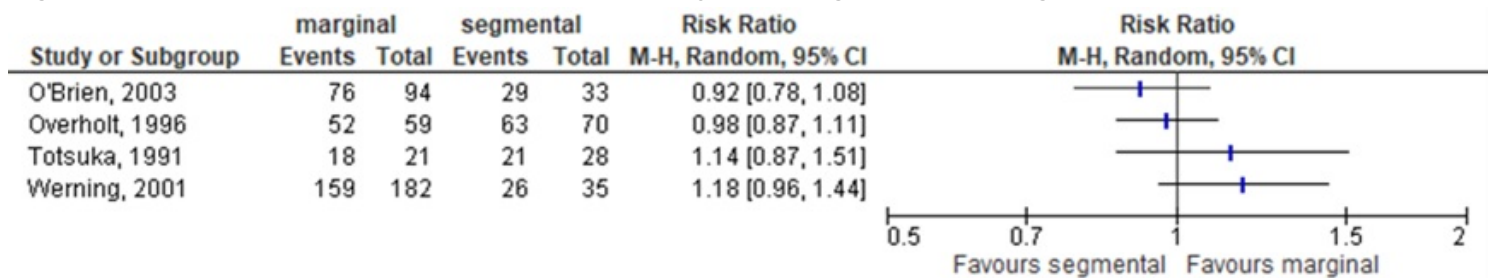
Figure 11.2.6 Forest plot for local control over 2-year; marginal versus segmental resection.

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI
O'Brien, 2003	76	94	29	33	0.92 [0.78, 1.08]
Overholt, 1996	52	59	63	70	0.98 [0.87, 1.11]
Totsuka, 1991	18	21	21	28	1.14 [0.87, 1.51]
Werning, 2001	159	182	26	35	1.18 [0.96, 1.44]

3.2 Local control at 5-year
Eight studies in the systematic review by Gou (2018) reported the local control at 5-year, see Figure 11.2.7. Results showed that the relative risk point estimates were slightly in favor of the intervention (i.e., marginal resection) group compared to the control (i.e., segmental resec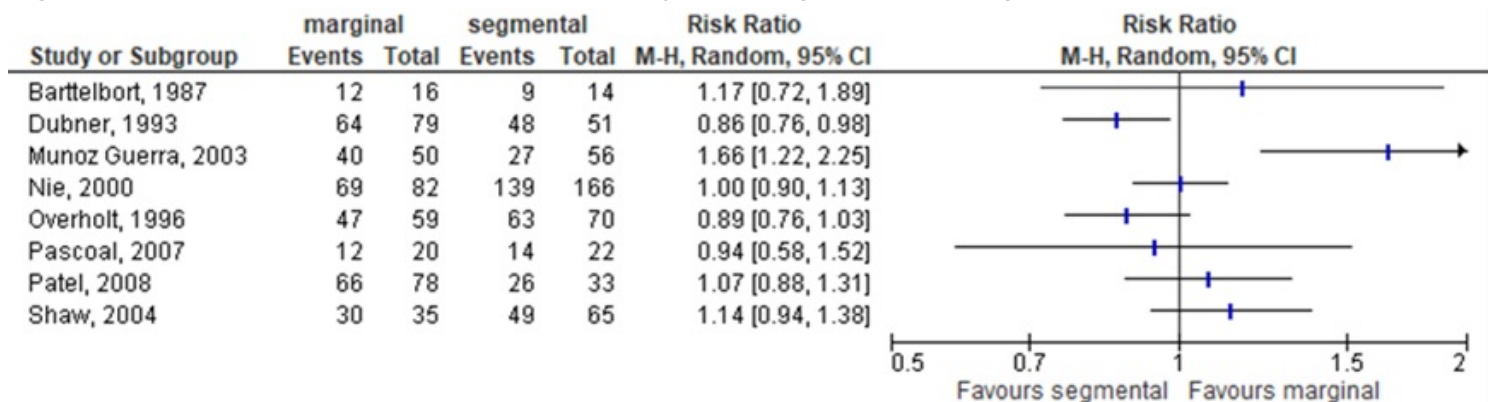tion) group in 4 of the 8 studies. No differences were observed in 1 study, and 3 studies showed a relative risk point estimate favoring the intervention group.
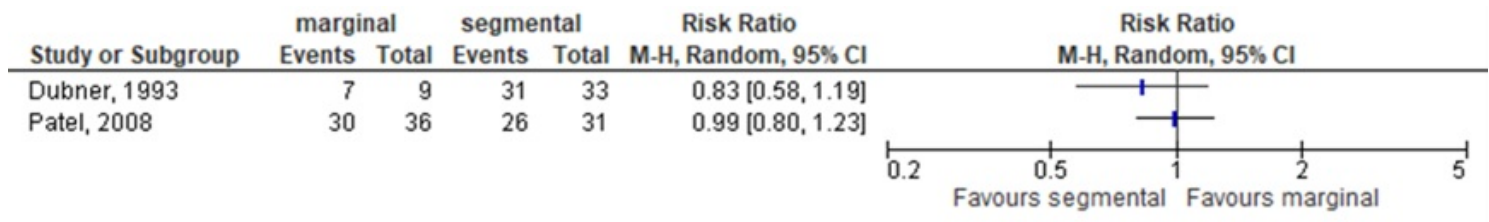
Figure 11.2.7 Forest plot for local control at 5-year; marginal versus segmental resection

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI
Barttelbort, 1987	12	16	9	14	1.17 [0.72, 1.89]
Dubner, 1993	64	79	48	51	0.86 [0.76, 0.98]
Munoz Guerra, 2003	40	50	27	56	1.66 [1.22, 2.25]
Nie, 2000	69	82	139	166	1.00 [0.90, 1.13]
Overholt, 1996	47	59	63	70	0.89 [0.76, 1.03]
Pascoal, 2007	12	20	14	22	0.94 [0.58, 1.52]
Patel, 2008	66	78	26	33	1.07 [0.88, 1.31]
Shaw, 2004	30	35	49	65	1.14 [0.94, 1.38]

3.2.1 Local control at 5-year in patients with bone invasion.
Two studies in the SR reported the outcome local control at 5-year in patients with bone invasion, see Figure 8. Results showed that the relative risks were slightly lower in the intervention (i.e., marginal resection) group compared to the control (i.e., segmental resection) group.

Figure 11.2.8 Forest plot for local control at 5-year in patients with bone invasion; marginal versus segmental resection

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI
Dubner, 1993	7	9	31	33	0.83 [0.58, 1.19]
Patel, 2008	30	36	26	31	0.99 [0.80, 1.23]

Risk Ratio M-H, Random, 95% CI
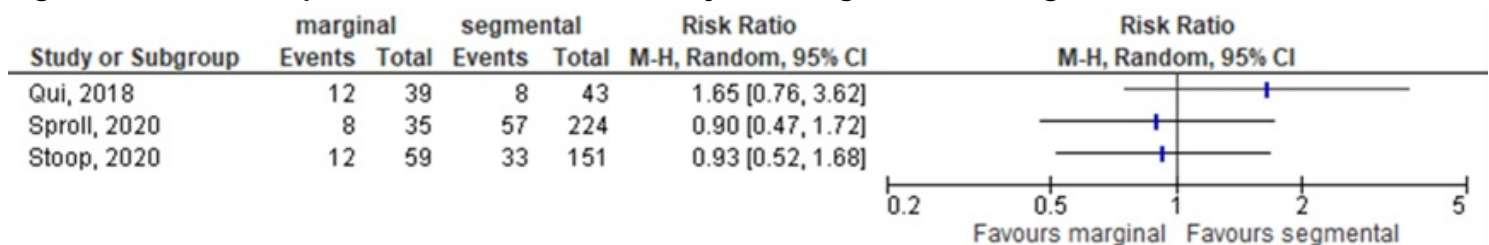0.2   0.5   1   2   5
Favours segmental   Favours marginal

4. Recurrence rate

No specific definition of the recurrence rate was given by Qiu (2018), Sproll (2020) and Stoop (2020).

<u>4.1 Recurrence rate at 3-year</u>

Three studies (Qiu, 2018; Sproll, 2020; Stoop, 2020) reported the outcome recurrence rate at 3-year, see Figure 11.2.9. Results showed that the relative risk was in favor of the intervention (i.e., marginal resection) group compared to the control (i.e., segmental resection) group in 1 of 3 studies. The relative risk point estimape were slightly favouring the marginal resection in 2 of the 3 studies. Importantly, the study of Stoop (2020; RR 0.93 (95%CI 0.52 to 1.68) was performed in patients with bone invasion.

Figure 11.2.9 Forest plot for recurrence rate at 3-year; marginal versus segmental resection

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI
Qui, 2018	12	39	8	43	1.65 [0.76, 3.62]
Sproll, 2020	8	35	57	224	0.90 [0.47, 1.72]
Stoop, 2020	12	59	33	151	0.93 [0.52, 1.68]

Risk Ratio M-H, Random, 95% CI
0.2   0.5   1   2   5
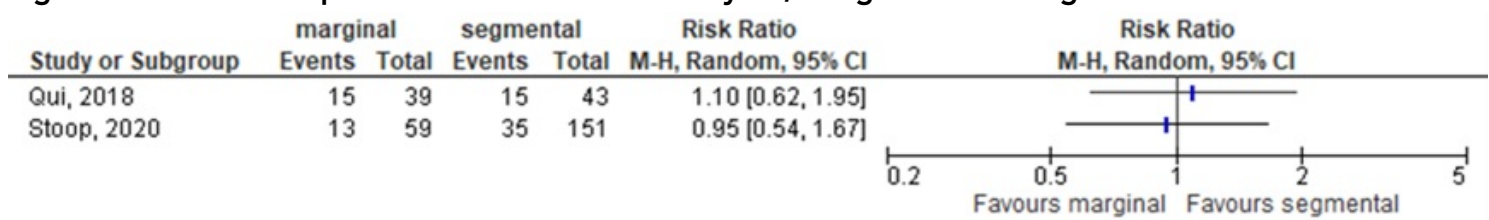Favours marginal   Favours segmental

<u>4.2 Recurrence rate at 5-year</u>

Two studies (Qiu, 2018; Stoop, 2020) reported the outcome recurrence rate at 5-year, see Figure 7.2.10. Results showed no differences between the intervention (i.e., marginal resection) group and control (i.e., segmental resection) group.

Importantly, the study of Stoop (2020; RR 0.95 (95%CI 0.52 to 1.53) was performed in patients with bone invasion.

Figure 11.2.10 Forest plot for recurrence rate at 5-year; marginal versus segmental resection

Study or Subgroup	marginal Events	Total	segmental Events	Total	Risk Ratio M-H, Random, 95% CI
Qui, 2018	15	39	15	43	1.10 [0.62, 1.95]
Stoop, 2020	13	59	35	151	0.95 [0.54, 1.67]

Risk Ratio M-H, Random, 95% CI
0.2   0.5   1   2   5
Favours marginal   Favours segmental

5. Surgical margin free resection

One study (Alam, 2019) reported the outcome surgical margin free resection. Results showed that the RR was slightly in favor of the intervention (marginal resection) group compared to the control (segmental resection) group, with a relative risk of 1.07 (95%CI 0.72 to 1.58).

6. Oral function
Data about function was reported in one study (Alam, 2019). Although, Alam (2019) did not report specific information about how this data was assessed, for example via questionnaires.

6.1 Speech difficulty
The outcome 'speech difficulty' was reported in one (1/20) patients in the intervention (marginal resection) group and two (2/12) patients in the control (segmental resection) group, resulting in a relative risk of 0.33 (95%CI 0.03 to 2.97).

6.2 Trismus
Trismus was reported in eight (8/20) patients in the intervention group (marginal resection) group compared to seven (7/12) patients in the control (segmental resection) group, resulting in a relative risk of 0.69 (95%CI 0.33 to 1.41).

6.3 Mastication problems
The outcome 'mastication problem' was observed in nine (9/20) patients in the intervention (marginal resection) group and in eight (8/12) patients in the control (segmental resection) group, resulting in a relative risk of 0.68 (95%CI 0.36 to 1.27).

6.4 Respiratory problems
The outcome 'respiratory problem' was observed in two (2/20) patients in the intervention (marginal resection) group and in one (1/12) patient in the control (segmental resection) group, resulting in an RR of 1.20 (95%CI 0.12 to 11.87).

Level of evidence of the literature
The level of evidence (GRADE method) is determined per comparison and outcome measure and is based on results from observational studies and therefore starts at level "low". Subsequently, the level of evidence was downgraded if there were relevant shortcomings in one of the several GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. It was upgraded if there was a strong association, or a dose-response relation, and/or plausible (residual) confounding.

The level of evidence regarding the outcome measures **duration of surgery, complications** could not be assessed with GRADE. The outcome measures were not studied in the included studies.

The level of evidence regarding the outcome measure **disease-specific survival rate, local control** was downgraded by 3 levels because of imprecision (2 levels, 95%CI of the relative risk crosses both thresholds of clinical relevance), and risk of bias (1 level, high risk in the included studies due to inadequate adjustment for all important prognostic factors).

The level of evidence regarding the outcome measure **overall survival, recurrence rate, surgical margin free resection, oral function** was downgraded by 4 levels because of imprecision (2 levels, 2 levels, 95%CI of the relative risk crosses both thresholds of clinical relevance, and not meeting the optimal information size), indirectness (1 level, no subgroup analyses could be performed for patients with bone invasion) and risk of bias (1 level, high risk in the included studies due to inadequate adjustment for all important prognostic factors).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the benefits and harm of segmental resection versus marginal resection on tumor-free resection, recurrence rate, disease-specific survival, overall survival rate, function (for example oral rehabilitation, dental rehabilitation, swallowing function), duration surgery, or complications in patients with bone invasion in the mandible due to oral cavity carcinoma?

P: Patients with bone invasion in the mandible due to oral cavity carcinoma.
I: Marginal resection.
C: Segmental resection.
O: Tumor-free resection, recurrence rate, disease-specific survival, overall survival rate, oral function (i.e., oral rehabilitation, dental rehabilitation, swallowing function), duration surgery, complications.

Relevant outcome measures
The guideline working group considered tumor-free resection, recurrence rate, disease-specific survival, overall survival rate as a critical outcome measure for decision making; and function (i.e., oral rehabilitation, dental rehabilitation, swallowing function), duration surgery, complications as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

A difference of 25% in the relative risk for dichotomous outcomes (i.e., RR 0.80 to 1.25) and 0.5 standard deviation (reported as SMD) for continuous outcomes was taken as a minimal clinically important difference.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 19, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 388 hits. Studies were selected based on the following criteria: patients had bone invasion in mandible due to oral cavity carcinoma, a segmental resection was compared to a marginal resection of the mandibula, and at least one of the outcomes of interest was reported.
Twenty-five studies were initially selected based on title and abstract screening. After reading the full text, twenty studies were excluded (see the table with reasons for exclusion under the tab Methods), and five studies (i.e., 1 systematic review and 4 additional studies) were included.

Results

Five studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Alam, Mohammad Deedarul. "Influence of marginal and segmental bony resection on the local control of oral Squamous cell carcinoma involving the mandible." Bangladesh Journal of Medical Science 18.4 (2019): 801-807.

Gou L, Yang W, Qiao X, Ye L, Yan K, Li L, Li C. Marginal or segmental mandibulectomy: treatment modality selection for oral cancer: a systematic review and meta-analysis. Int J Oral Maxillofac Surg. 2018 Jan;47(1):1-10. doi: 10.1016/j.ijom.2017.07.019. Epub 2017 Aug 18. PMID: 28823905.

Qiu Y, Lin L, Shi B, Zhu X. Does Different Mandibulectomy (Marginal versus Segmental) Affect the Prognosis in Patients With Oral Squamous Cell Carcinoma? J Oral Maxillofac Surg. 2018 May;76(5):1117-1122. doi: 10.1016/j.joms.2017.11.014. Epub 2017 Nov 21. PMID: 29227794.

Sproll CK, Holtmann H, Schorn LK, Jansen TM, Reifenberger J, Boeck I, Rana M, Kübler NR, Lommen J. Mandible handling in the surgical treatment of oral squamous cell carcinoma: lessons from clinical results after marginal and segmental mandibulectomy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Jun;129(6):556-564. doi: 10.1016/j.oooo.2019.11.011. Epub 2019 Nov 27. PMID: 32102765.

Stoop CC, de Bree R, Rosenberg AJWP, van Gemert JTM, Forouzanfar T, Van Cann EM. Locoregional recurrence rate and disease-specific survival following marginal versus segmental resection for oral squamous cell carcinoma with mandibular bone invasion. J Surg Oncol. 2020 Jun 9;122(4):64652. doi: 10.1002/jso.26054. Epub ahead of print. PMID: 32516499; PMCID: PMC7496367.

Definitie resectiemarge mondholtecarcinomen

Uitgangsvraag

Hoe wordt een laag-, intermediair- en hoog-risico resectiemarge gedefinieerd voor plaveiselcelcarcinomen in de mondholte?

Aanbeveling

Gebruik de volgende indeling van de grootte van de chirurgische marge in relatie tot het risico op het optreden van tumor recidief van een carcinoom van de bovenste adem en voedingsweg:

- Hoog risico: < 1mm.
- Intermediair risico: 1 tot 5 mm.
- Laag risico: > 5mm.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De meeste geïncludeerde studies gebruikten een afkapwaarde voor de resectie marge in millimeters, maar twee studies berekenden een marge-tumordikte ratio en onderzochten afkapwaarden voor deze methode (Heiduschka, 2016; Huang, 2019). Samenvattingen van de resultaten op elke uitkomstmaat zijn te vinden in Tabellen 11.3.1.1 tot 11.3.1.5 in de literatuursamenvattingen onder het tabblad 'Onderbouwing'. Alle geïncludeerde studies in deze richtlijnmodule waren observationeel van aard. De zekerheid in het gevonden bewijs was zeer laag voor elke afkapwaarde op elke vooraf gedefinieerde uitkomstmaat, ongeacht of het een afkapwaarde in millimeters of in marge-tot-tumordikte ratio was. Verder werden er op elke afkapwaarde voor de resectiemarge weinig patiënten met elkaar vergeleken. Hierdoor nam de zekerheid in de gevonden schatters af. Daarnaast definieerden de meeste studies niet a priori de plausibele confounders en in een aantal studies werden alleen significante predictoren voor de uitkomst van interesse behouden in het multivariabele model ter correctie. Hierdoor is het vertrouwen in de gevonden uitkomsten uit de literatuur zeer laag.
Hoewel deze module zich specifiek richt op de definitie van de resectiemarge zijn er, naast de resectiemarge status, andere factoren die een rol spelen bij de lokale controle en overleving. Hierbij is, bijvoorbeeld, te denken aan lymfkliermetastase(n) met kapseldoorbraak, meerdere lymfkliermetastasen, lymfangio invasie, T3-4 tumoren, en/of perineurale groei.

Aanvaardbaarheid, haalbaarheid en implementatie
Het lijkt dat de onderbouwing ontbreekt om de bestaande indeling van de margestatus van hoog (< 1mm), intermediair (1 tot 5mm) en laag (> 5mm) risico op tumor recidief aan te passen. De gangbare definitie lijkt voor nu gehandhaafd te moeten blijven. Inschatting van het risicoprofiel op tumor recidief blijft voor de gemiddeld-risicogroep een individuele afweging.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Er lijkt geen verdere verfijning van het marge interval van 1 tot 5 mm mogelijk met de voor handen zijnde data. De literatuur ondersteunt onvoldoende de mogelijkheid van toepassen van een gradiënt in risico in het interval van 1 tot 5 mm marge. De betrouwbaarheid intervallen zijn te breed en daarnaast zijn de data van de studies niet samen te voegen. Vermoedelijk is de marge niet de enige voorspeller voor het risico op tumor recidief en is onvoldoende rekening gehouden hiermee in de voorhanden zijnde studies.

Onderbouwing

Achtergrond

De resectiemarge van mondholtecarcinomen wordt conventioneel gedefinieerd als laag risico op recidief tumor wanneer er infiltrerende tumorcellen worden gevonden op een afstand van 5 millimeter of meer ten opzichte van het sneevlak. Dit wordt beschreven als een radicale of complete tumor resectie. Er wordt vanuit gegaan dat er een gemiddeld risico aanwezig is op recidief tumor wanneer er infiltrerende tumorcellen worden gevonden tussen de één en vijf millimeter ten opzichte van het sneevlak. Dit wordt beschreven als een krappe marge. Een hoog risico op recidief tumor zou bestaan als er infiltrerende cellen worden waargenomen binnen één millimeter ten opzichte van de resectiemarge en wordt derhalve geduid als een positieve marge. Chirurgen streven naar een radicale resectie marge van minimaal 5 mm bij het verwijderen van de tumor. Minder dan één mm marge heeft een hoog risico op recidief en behoeft adjuvante behandeling in geval van een curatieve behandeling. Het is onduidelijk of een marge tussen de 1 en 5 mm wellicht tot hetzelfde risicoprofiel zou kunnen hebben als een radicale resectie van 5 mm of meer wat betreft de kans op recidief van tumoren en de overleving van patiënten.

Conclusies

Very low GRADE	We are unsure of the effects of different cut-off values for the resection margin on the local recurrence of tumors in patients with a resected oral cavity tumor. *Sources: (Brinkman, 2020; Heiduschka, 2016; Tsai, 2011; Wong, 2012; Yamada, 2016; Yanamoto, 2012)*

Very low GRADE	We are unsure of the effects of different cut-off values for the resection margin on the (local) recurrence-free survival of patients with a resected oral cavity tumor. *Sources: (Zanoni, 2017)*

Very low GRADE	We are unsure of the effects of different cut-off values for the resection margin on the disease-specific survival of patients with a resected oral cavity tumor. *Sources: (Brinkman, 2020; Heiduschka, 2016; Tsai, 2011; Wong, 2012)*

Very low GRADE	We are unsure of the effects of different cut-off values for the resection margin on the disease-free survival of patients with a resected oral cavity tumor. *Sources: (Chiou, 2010; Huang, 2019; Tsai, 2011)*

Very low GRADE	We are unsure of the effects of different cut-off values for the resection margin on the overall survival of patients with a resected oral cavity tumor. *Sources: (Brinkman, 2020; Nason, 2009; Tsai, 2011)*

Samenvatting literatuur

<u>Description of studies</u>

Brinkman (2020) selected patients who underwent primary surgery for oral cavity carcinomas between 2009 and 2018 from a database. Patients that had a second primary tumor, had a previous history of radiotherapy or head and neck cancer, or resection without curative intent were excluded. The sample consisted of 224 patients (164 males; 80 females) with a median age of 63 years (range 27-93). Primary tumor locations were at the tongue (n=105), floor of the mouth (n=71), buccal (n=20), alveolus/retromolar trigone/palate (n=37), or lip (n=11). Of the 244 patients, 149 had a bone resection and 196 had a neck dissection (unilateral: n=142, bilateral: n=54). Patients had either T1 (n=59), T2 (n=91), T3 (n=38), or T4 (n=56) carcinomas. Nodal stage in the sample was N0 (n=103), N1 (n=30), N2a (n=9), N2b (n=13), N2c (n=4), N3b (n=37), or cN0 (n=48). The 8th edition of the AJCC TNM-staging system was used. Surgical margins were extracted from pathology reports, without taking intraoperative frozen sections or extra tumor bed margins in to account. Multivariable analyses were conducted for a resection margin at 3 millimeters, where < 3 millimeters was a close margin and ≥ 3 millimeters was a clear margin.

Chiou (2010) selected 110 patients from a database. To be eligible, patients with buccal mucosa carcinoma had to be treated between 2000 and 2008. Patients were excluded when solely treated with radiotherapy or concurrent chemoradiotherapy, had neoadjuvant treatment and surgery, or had a second synchronous primary tumor. The 110 patients (103 males; 7 females) had a pT-stage of pT1-2 (n=70) or pT3-4 (n=40), and a pN-stage of pN0 (n=84) or pN1-3 (n=26). The 6th edition of the AJCC TNM-staging system was used. Sixty-six participants were aged above 50 years old. Tumor differentiation was well (n=6), moderate (n=90), poor (n=12), or was not specified (n=2). Other characteristics were tobacco use (n=93 smoked) and betel nut chewing (n=93 chewed betel nuts, n=2 unknown). Patients underwent surgery alone (n=32), surgery with radiotherapy (n=38), or surgery with concurrent chemoradiotherapy (n=40). Pathology reports were reviewed. Cut-offs of 1 millimeter (close: ≤ 1mm, clear: >1mm), 2 millimeter (close: ≤ 2mm, clear: > 2mm), 3 millimeter (close: ≤ 3mm, clear: > 3mm), 4 millimeter (close: ≤ 4mm, clear: > 4mm) and 5 millimeter (close: ≤ 5mm, clear: > 5mm).

Heiduchka (2016) selected patients treated for oral squamous cell carcinoma between 1987 and 2014 from a database. Patients were excluded when insufficient data was available. A total of 501 participants (289 males; 212 females) with a median age of 63.6 years (IQR: 53.2-72.9) were included. Tumor differentiation was well (n=81), moderate (n=307), or poor (n=77). There was perineural invasion (in n=151), lymphovascular invasion

(in n=69), and extracapsular spread (in n=83) in the sample. The patients had a T1 (n=170), T2 (n=180), T3 (n=43), or T4 (n=108). The nodal stage was N0 (n=303), N1 (n=140), or N3 (n=2). It was unclear which staging system was used. Radiotherapy was given for 225 patients, and 29 patients received chemotherapy. A resection margin to tumor size ratio (margin/tumor diameter in millimeters) and a resection margin to tumor thickness ratio (margin/tumor thickness in millimeters) was calculated. A margin to thickness cut-off (MTR) of 0.3 was used in a multivariable analysis to compare MTR< 0.006 with MTR> 0.3, and MTR 0.06-0.3 with MTR> 0.3.

Huang (2019) selected 302 patients from a database. To be eligible, patients should have had a newly diagnosed oral squamous cell carcinoma, underwent radical surgery (either with or without adjuvant treatment), and had sufficient pathologic data available. Patients that were treated with chemotherapy or radiotherapy as an initial treatment were excluded. Furthermore, patients with previous cancer in their history or distant metastases upon diagnoses were excluded as well. A resection margin to tumor thickness ratio (MTR) was calculated by: margin +0.1/tumor thickness +0.1 in millimeters. The log(MTR) of 33% was used as a cut-off in multivariable analyses (close: log(MTR)≤ 33%, clear: log(MTR)> 33%). There were 100 patients (93 males; 7 females) in the log(MTR)≤33% group with a median age of 51 years (range: 33-88). In this group, the tumor site was at the tongue (n=41) or buccal mucosa (n=59). There was perineural invasion (in n=48) and lymphovascular invasion (in n=14). Tumor differentiation was well (n=7), moderate (n=79), or poor (n=14). Other characteristics were tobacco use (in n=88) and alcohol use (in n=70). This group received no adjuvant therapy (n=35), radiotherapy (n=35), chemotherapy (n=7), or chemoradiotherapy (n=28). The pT-stage in the log(MTR)≤33% group was T1 (n=8), T2 (n=43), T3 (n=10), or T4 (n=39), while the pN-stage was N0 (n=44), N1 (n=41) or N2 (n=41). The log(MTR)>33% group consisted of 202 patients (187 males; 15 females) with a median age of 54 years (range: 28-92). The tumor site was either the tongue (n=88) or buccal mucosa (n=114). Perineural invasion was present in 6 patients and lymphovascular invasion in 6 patients as well. Tumor differentiation was well (n=38), moderate (n=150), or poor (n=14). There was tobacco use in 179 patients and alcohol use in 150 patients. Patients in this group received no adjuvant treatment (n=107), radiotherapy (n=22), chemotherapy (n=22), or chemoradiotherapy (n=28). Their pT-stage was T1 (n=63), T2 (n=91), T3 (n=10), or T4 (n=36), while their pN-stage was N0 (n=136), N1 (n=22), or N2 (n=44). The 7th edition of the AJCC TNM-staging system was used. There were proportional differences between the groups on the following characteristics: perineural invasion, lymphovascular invasion, pT-stage, pN-stage, tumor differentiation, and adjuvant therapy.

Nason (2009) selected patients from a database which had biopsy-proven and previously unteasted oral cavity squamous cell carcinoma and were managed with surgery (with or without adjuvant radiotherapy). Patients with incomplete data, which were seen in consultation only, were treated with radiotherapy only, or were treated with palliative intent were excluded. The sample consisted of 277 patients with a mean age of 63.3 years (SD: 12). Ninety percent used alcohol and seventy percent used tobacco. Other relevant sample characteristics were not described. Staging was performed with the 6th edition of the IUAC TNM-staging system. Margin status was extracted from pathology reports. A cut-off value of 3 millimeter was used, where clear margins (> 3mm) were compared to close margins (≥3mm) and positive margins (undefined).

Tsai (2011) selected patients with a surgical margin ≤ 3 millimeter who underwent postoperative radiotherapy or concurrent chemoradiotherapy between 2000 and 2008 from a database. Patients were excluded when

they had positive margins, had not received postoperative therapy, or when the radiotherapy dose was below 45 Gy. Thirty patients were selected (26 males; 4 females) with a median age of 51.5 years (range: 35 to 82). Medical record were reviewed. The EGOC-status was either 0 to 1 (in n=21) or > 2 (in n=9). Tumor differentiation was well to moderate (n=28) or poor (n=2). Twenty-four patients smoked and twenty-tree patients chewed betel nuts. The pT-stage was categorized in either T1-3 (n=20) or T4 (n=10). Similarly, the pN-stage was categorized in N0 (n=25) and N1-2 (n=5). The 6th edition of the AJCC TNM-staging system was used. Sixteen patients received ≤66 Gy dose for radiotherapy and fourteen patients received > 66 Gy. A resection margin cut-off value of 1 millimeter was used in multivariable analyses (close: ≤ 1mm, clear: > 1mm).

Wong (2012) selected previously untreated patients with oral or oropharyngeal squamous cell carcinomas between 2001 and 2007 from a database. Paraffin-embedded sections of 4 micrometer were stained and measured under a microscope. The sample consisted of 192 patients (122 males; 70 females) with a mean age of 61 years (SD: 11). Tumor site was oral in 160 patients and oropharyngeal in 32 patients. Tumor differentiation was well (n=21), moderate (n=134), or poor (n=27). There was perineural invasion (in n=28), vascular invasion (in n=36), lymphatic invasion (in n=26), and bony invasion (in n=31). Invasive front was assessed as being either cohesive (n=56) or non-cohesive (n=105). The cT-stage was T1 (n=72), T2 (n= 38), T3 (n=16), or T4 (n=56). Nodal stage was cN0 (n=119), cN1 (n=28), cN2 (n=44), or cN3 (n=1). It remained unclear which staging system was used. ROC analyses identified a cut-off value of 1 (close: ≤ 1mm, clear: > 1mm) and 1.6 millimeter (close: ≤ 1.6mm; clear: > 1.6mm). The cut-off values were used un multivariable analyses.

Yamada (2016) selected previously untreated patients with oral squamous cell carcinomas who had planned radical resection (with or without adjuvant radiotherapy and/or chemotherapy) between 1990 and 2007. Patients with T4b tumors or dysplastic epithelium at the mucosal margin were excluded. Pathology reports were reviewed for the margin status. A total of 127 patients (73 males; 54 females) with a median age of 66 years (range 27-84) were selected. Tumor locations were the tongue (n=59), lower gum (n=2), upper gum (n=16), cheek mucosa (n=16), floor of the mouth (n=14), or hard palate (n=1). Tumor differentiation was micro-invasive (n=4), well (n=79), moderate (n=38), or poor (n=6). Furthermore, the mode of invasion was YK-2 (n=18), YK-3 (n=55), YK4C (n=41), or YK4D (n=13). Eighty-three patients received preoperative therapy, while thirty-five patients received postoperative radiotherapy > 50 Gy. T-stage was T1 (n=20), T2 (n=39), T3 (n=22), or T4a (n=46), while the N-stage was N0 (n=72), N1 (n=20), N2b (n=26), N2c (n=8), or N3 (n=1). It was unclear which staging system was used. Resection margin cut-offs of 0 (involved, clear: > 0), 1 (involved, close: ≤ 1mm, clear: > 1mm), 2 (involved, close: ≤ 2mm, clear: > 2mm), 4 (involved, close: ≤ 4mm, clear: > 4mm), and 5 millimeters (involved, close: ≤ 5mm, clear: > 5mm) were used in multivariable analyses. An involved margin was defined as evidence of carcinoma at the margin (including carcinoma in situ).

Yanamoto (2012) retrospectively reviewed 187 patients who underwent radical surgery for histologically confirmed oral squamous cell carcinoma between 2001 and 2010 and with a minimal follow-up period of 12 months (exclusion criteria were not reported). Mean age in the total sample (102 males; 85 females) was 67.3 years (range: 28-95). Tumor stage was T1 (n=52), T2 (n=92), T3 (n=14), or T4 (n=29). N-stage was N0 (n=141), N1 (n=26), N2a (n=2), N2b (n=12), or N2c (n=6). Staging was performed using the 6th edition of the UICC staging system. Tumor differentiation was well in 166 patients, moderate in 20, and poor in 1 patient. A portion of the patients (n=63) received neoadjuvant chemotherapy and some patients received postoperative

adjuvant radiotherapy (n=15). Tumor site was at the tongue (n=73), the oral floor (n=26), upper gingiva (n=36), lower gingiva (n=44), or buccal mucosa (n=63). Resection margin cut-off used was 4 millimeter (close: ≤4 mm, clear: > 4mm) for both the superficial and deep margin.

Zanoni (2017) selected patients who underwent primary surgery for squamous cell carcinoma of the tongue between 2000 and 2012 from a database. Histopathological slides had to be available to be included. Archived tumor specimens were assessed by head and neck pathologists. The pathologists were blinded for the patient outcomes. The sample consisted of 381 patients (222 males; 159 females) with a mean age of 58 years (SD: 14.7). One hundred and twenty-one patients had never used tobacco. The cT stage was T1 (n=193), T2 (n=135), T3 (n=34), T4 (n=15), or cTX (n=4). Nodal stage was cN0 (n=275), cN1 (n=40), cN2 (n=64), or cN3 (n=2). It was unclear which staging system was used. A 5-millimeter cut-off (positive, close: 0.01-2mm; clear: > 5mm) and 2.2 millimeter cut-off (positive, close: 0.01-2mm, clear: > 2mm) resection margin was used in multivariable analyses. Positive margins were defined as invasive carcinoma at the margin of the resected specimen.

Results
Local failure
Results of the included studies reporting the local recurrence in multivariable models are summarized in Table 11.3.1.1

Brinkman (2020) selected 224 patients, however it was unclear how large both groups were (i.e. < 3mm-group and ≥ 3mm-group) and how disease characteristics were distributed between groups. It was not completely clear which other variables were added to the model.

Heiduschka (2016) selected 501 patients and calculated the margin-to-thickness ratio (MTR). It was unclear how large groups were (i.e. < 0.06 MTR-group, 0.06 to 0.3 MTR-group, and MRR> 0.3-group) and how characteristics were distributed among the groups. Sub-analyses were performed, where patients with positive margins (n=79) were removed from analysis. Perineural invasion, lymphovascular invasion, and nodal status were other variables in the model besides the MTR.

Tsai (2011) selected 30 patients. It was unclear how large both groups were at the cut-off point (i.e. the ≤ 1mm-group and < 1mm-group) and how characteristics were distributed among the groups. Besides the resection margin, other variables in the model were age, gender, ECOG PD, smoking, betel nut chewing, tumor differentiation, invasion depth, perineural invasion, lymphovascular invasion, extracapsular spread, pT-stage, pathology stage, and radiotherapy dose.

Wong (2012) selected 192 patients, of which 107 had close margins (as defined by the standard definition of 1 to 5mm). It was unclear how large the groups were at the cut-off point and how disease characteristics were distributed among both groups. Other variables in the model were cN-stage, lymphatic invasion, histopathological involved nodes, extracapsular spread, and tumor depth.

Yamada (2016) selected 127 patients and reported group sizes at the 0 millimeter (involved: n=10, > 0mm: n=117), 1 millimeter (involved: n=10, 0-1mm: n=6, > 1mm: n=111), 2 millimeter (involved: n=10, 0-2mm: n=14, >2mm: n=103), 4 millimeter (involved: n=10, 0-4mm: n=19, > 4mm: n=98), and 5 millimeter cut-off

values (involved: n=10, 0-5mm: n=24, > 5mm: n=93). It was unclear how disease characteristics were distributed among groups at the various cut-off points. The 2-year local recurrence was reported. Other variables in the model besides surgical margin were T-stage, tumor differentiation, mode of invasion, preoperative therapy, and postoperative therapy over 50 Gy.

Yanamoto (2012) reported the local recurrence using a cut-off value of 4 millimeter for the superficial margin (≤ 4mm: n=31, > 4mm: n=156) and deep margin (≤ 4mm: n=25, > 4mm: n=162). It was unclear how disease characteristics were distributed among groups. For superficial margin, other variables in the model were pattern of invasion, preoperative treatment, deep surgical margin, and postoperative adjuvant radiotherapy. For deep margin, Other variables in the model were pattern of invasion, preoperative treatment, superficial surgical margin, and postoperative adjuvant radiotherapy.

Table 11.3.1.1 Local recurrence at surgical margin cut-off values. The reference group is labeled with '*(ref)*'

| Author, year (tumor locations) | Cut-off value in millimeters | | | | | | | Cut-off value for MTR* |
	>0 mm	>1 mm	>2 mm	>3 mm	≥3 mm	>4 mm	>5 mm	>0.3
Brinkman 2020 (tongue, FOM, buccal)	-	-	-	-	<3mm versus ≥3m(ref): HR = 1.63 (95%CI: 0.90-2.96)	-	-	-

Heiduschka 2016 (oral)	-	-	-	-	-	-	-	**<0.06MTR versus >0.3MTR(ref):** HR = 1.92 (95%CI: 1.02-3.61) **<0.06MTR versus >0.3MTR(ref), (positive margins excluded):** HR = 2.63 (95%CI: 1.05-6.63) **0.06-0.3MTR versus >0.3MTR(ref):** HR = 1.22 (95%CI: 0.62-2.41)
Tsai 2011 (buccal mucosa)	-	**≤1mm versus >1mm(ref):** HR = 14.02 (95%CI: 1.13-29.76)	-	-	-	-	-	-
Wong 2012 (oral and oropharyngeal)	-	**≤1mm versus >1mm(ref):** HR = 2.86 (95%CI: 1.20-6.85)	-	-	-	-	-	-

Yamada 2016 (tongue, gums, cheek mucosa, FOM, hard palate)	Involved versus >0mm(ref): HR = 10.74 (95%CI: 3.07-37.54)	Involved versus >1mm(ref): HR = 17.00 (95%CI: 4.49-64.42) 0-1mm versus >5mm(ref): HR = 23.69 (95%CI: 3.38-166.15)	Involved versus >2mm(ref): HR = 13.22 (95%CI: 3.73-46-85) 0-2mm versus >5mm(ref): HR = 4.37 (95%CI: 1.04-18.42)	-	-	Involved versus >4mm(ref): HR = 14.42 (95%CI: 3.95-53.73) 0-4mm versus >4mm(ref): HR = 4.35(95%CI: 1.09-17.32)	Involved versus >5mm(ref): HR = 14.42 (95%CI: 3.82-54.36) 0-5mm versus >5mm(ref): HR = 3.32 (95%CI: 0.87-12.73)	-
Yanamoto 2012 (tongue, oral floor, upper and lower gingiva, buccal mucosa)	-	-	-	-	-	≤4mm versus >4mm(ref), (superficial margin): OR = 7.12 (95%CI: 2.28-22.35) ≤4mm versus >4mm(ref), (deep margin): OR = 4.90 (95%CI: 1.44-16.70)	-	-
*MTR: Margin to thickness ratio								

(Local) recurrence-free survival
Results of the included study reporting the (local) recurrence-free survival in multivariable models are summarized in Table 11.3.1.2.

Zanoni (2017) selected 381 patients, however group size and the distribution of characteristics was unclear for the groups at the cut-off values. Local recurrence-free survival was reported for 2.2 millimeter and 5 millimeter cut-off values. At the 2.2 millimeter cut-off value, the other variables in the model were tumor size, perineural invasion, and pN-stage. Other variables in the model for the 5 millimeter cut-off value were tumors size and adjuvant therapy besides resection margin.

Table 11.3.1.2 (Local) recurrence-free survival at surgical margin cut-off values. The reference group is labeled with _'(ref)'_

Author, year (tumor locations)	Cut-off value in millimeters						
	>0 mm	>1 mm	>2 mm	>2.2mm	>3 mm	>4 mm	>5 mm
Zanoni 2017 (tongue)	-	-	-	**Positive versus >2.2mm(ref):** HR = 5.73 (95%CI: 2.45-13.41) **0.01-2.2mm versus >2.2mm(ref):** HR = 2.00 (95%CI: 1.13-3.55)	-	-	**Positive versus >5mm(ref):** HR = 5.71 (95%CI: 2.8-15.65) **0.01-2.2mm versus >5mm(ref):** HR = 2.25 (95%CI: 1.03-4.92) **2.3-5mm versus >5mm(ref):** HR = 1.17 (95%CI: 0.51-2.66)

Disease-specific survival
Results of the included studies reporting the disease-specific survival in multivariable models are summarized in Table 11.3.1.3.

Brinkman (2020) selected 224 patients, however it was unclear how large both groups were (i.e. < 3mm-group and ≥ 3mm-group) and how disease characteristics were distributed between groups. T-stage, N-stage, extracapsular spread, and postoperative radiotherapy were variables in the model besides surgical margin.

Heiduschka (2016) selected 501 patients and calculated the margin-to-thickness ratio (MTR). It was unclear how large groups were (i.e. < 0.06 MTR-group and MRR> 0.3-group) and how characteristics were distributed among the groups. Sub-analyses were performed, where patients with positive margins (n=79) were removed from analysis. Perineural invasion, lymphovascular invasion, and nodal status were other variables in the model besides the MTR.

Tsai (2011) selected 30 patients. It was unclear how large both groups were at the cut-off point (i.e. the ≤ 1mm-group and < 1mm-group) and how characteristics were distributed among the groups. Besides the resection margin, other variables in the model were age, gender, ECOG PD, smoking, betel nut chewing, tumor differentiation, invasion depth, perineural invasion, lymphovascular invasion, extracapsular spread, pT-stage, pathology stage, and radiotherapy dose.

Wong (2012) selected 192 patients, of which 107 had close margins (as defined by the standard definition of

1-5mm). It was unclear how large the groups were at the cut-off point and how disease characteristics were distributed among both groups. Other variables in the model were cT-stage, cN-stage, lymphatic invasion, vascular invasion, histopathological involved nodes, extracapsular spread, and tumor depth.

Table 11.3.1.3 Disease-specific survival at surgical margin cut-off values. The reference group is labeled with (ref)

| Author, year (tumor locations) | Cut-off value in millimeters | | | | | | | | Cut-off value for MTR* |
	>0 mm	>1 mm	>1.6mm	>2 mm	>3mm	≥3 mm	>4 mm	>5 mm	>0.3
Brinkman 2020 (tongue, FOM, buccal)	-	-	-	-	-	**<3mm versus ≥3m(ref):** HR = 1.86 (95%CI: 1.06-3.27)	-	-	-
Heiduschka 2016 (oral)	-	-	-	-	-	-	-	-	**<0.06MTR versus >0.3MTR(ref), (positive margins excluded):** HR = 2.27 (95%CI: 1.07-4.81)
Tsai 2011 (buccal mucosa)	-	**≤1mm versus >1mm(ref):** HR = 16.52 (95%CI: 0.88-36.46)	-	-	-	-	-	-	-
Wong 2012 (oral and oropharyngeal)	-	-	**≤1.6mm versus >1.6mm(ref)** HR = 2.43 (95%CI: 1.21-4.88)	-	-	-	-	-	-
*MTR: Margin to thickness ratio									

Disease-free survival
Results of the included studies reporting the disease-free survival in multivariable models are summarized in Table 11.3.1.4.

Chiou (2010) selected 110 patients and reported the 3-year disease-free survival at various cut-off values for the resection margin. Group sizes and distribution of characteristics among the groups at the cut-off values were unclear. It was unclear which models were entered in the model besides surgical margin.

Huang (2019) selected 302 patients and separated the sample by using a margin-to-thickness ratio (MTR). Here, the sample was divided into log(MTR)≤ 33% (n=100) and log(MTR)> 33% (n=202). Groups differed in proportions on the following variables: perineural invasion, lymphovascular invasion, T-stage, N-stage, tumor differentiation, and adjuvant therapy. Variables in the model for 5-year disease-free survival other than surgical margin were perineural invasion, lymphovasculat invasion, pT-stage, pN-stage, and tumor differentiation. Sub-analyses were performed for a subsample of 97 patients with T3-4 tumors. Besides surgical margin, the multivariable model for 5-year disease-free for patients with T3-4 tumors contained pN-stage and adjuvant therapy.

Tsai (2011) selected 30 patients. It was unclear how large both groups were at the cut-off point (i.e. the ≤ 1mm-group and < 1mm-group) and how characteristics were distributed among the groups. Besides the resection margin, other variables in the model were age, gender, ECOG PD, smoking, betel nut chewing, tumor differentiation, invasion depth, perineural invasion, lymphovascular invasion, extracapsular spread, pT-stage, pathology stage, and radiotherapy dose.

Wong (2012) selected 192 patients, of which 107 had close margins (as defined by the standard definition of 1-5mm). It was unclear how large the groups were at the cut-off point and how disease characteristics were distributed among both groups. Other variables in the model were cN-stage, lymphatic invasion, histopathological involved nodes, extracapsular spread, and tumor depth.

Table 11.3.1.4 Disease-free survival at surgical margin cut-off values. The reference group is labeled with (ref)

Author, year (tumor locations)	Cut-off value in millimeters						Cut-off value for log(MTR)*
	>0 mm	>1 mm	>2 mm	>3 mm	>4 mm	>5 mm	>33%
Chiou 2010 (buccal mucosa)	-	≤1mm(ref) versus >1mm: HR = 0.2 (95%CI: 0.06-0.72)	≤2mm(ref) versus >2mm: HR = 0.1 (95%CI: 0.01-0.60)	≤3mm(ref) versus >3mm: HR = 0.2 (95%CI: 0.03-1.86)	≤4mm(ref) versus >4mm: HR = 0.3 (95%CI: 0.04-2.16)	≤5mm(ref) versus >5mm: HR = 0.5 (95%CI: 0.07-4.22)	-
Huang 2019 (tongue, buccal)							Log(MTR)≤33% versus log(MTR)>33% (ref): HR = 1.73 (95%CI: 1.16-2.57) Log(MTR)≤33% versus log(MTR)>33% (ref), (T3-4 only): HR = 2.67 (95%CI: 4.95)
Tsai 2011 (buccal mucosa)	-	≤1mm versus >1mm(ref): HR = 12.78 (95%CI: 1.93-25.22)	-	-	-	-	-
*MTR: Margin to thickness ratio							

Overall survival
Results of the included studies reporting the overall survival in multivariable models are summarized in Table 11.3.1.5.

Brinkman (2020) selected 224 patients, however it was unclear how large both groups were (i.e. < 3mm-group and ≥3mm-group) and how disease characteristics were distributed between groups. T-stage, N-stage, extracapsular spread, and postoperative radiotherapy were variables in the model besides surgical margin.

Nason (2009) selected 277 patients. Group sizes and distribution of characteristics between groups at the cut-off value were unclear. Variables in the multivariable models were gender, age, and tumor stage, besides resection margin.

Tsai (2011) selected 30 patients. It was unclear how large both groups were at the cut-off point (i.e. the ≤ 1mm-group and < 1mm-group) and how characteristics were distributed among the groups. Besides the resection margin, other variables in the model were age, gender, ECOG PD, smoking, betel nut chewing, tumor differentiation, invasion depth, perineural invasion, lymphovascular invasion, extracapsular spread, pT-stage, pathology stage, and radiotherapy dose.

Table 11.3.1.5 Overall survival at surgical margin cut-off values. The reference group is labeled with '(ref)'

Author, year (tumor locations)	Cut-off value in millimeters						
	>0 mm	>1 mm	>2 mm	>3 mm	≥3mm	>4 mm	>5 mm
Brinkman 2020 (tongue, FOM, buccal)	-	-	-	-	<3mm versus ≥3m(ref): HR = 1.78 (95%CI: 1.18-2.70)	-	-
Nason 2009 (oral)	-	-	-	Positive versus >3mm(ref): HR = 2.5 (95%CI: 0.95-2.70) ≤3mm versus >3mm(ref): HR = 1.54 (95%CI: 0.95-2.70)	-	-	-
Tsai 2011 (buccal mucosa)	-	≤1mm versus >1mm(ref): HR = 15.88 (95%CI: 0.54-35.98)	-	-	-	-	-

<u>Level of evidence of the literature</u>
GRADE for interventions starts at 'LOW' for a body of evidence with observational studies. The level of evidence regarding the outcome measure local failure was downgraded by 3 levels because of study limitations (1 level for risk of bias: 4/9 studies excluded non-significant variables from the model; most studies did not define plausible confounders a priori); number of included patients (2 levels for imprecision: individual cut-off values have a low number of participants).

GRADE for interventions starts at 'LOW' for a body of evidence with observational studies. The level of evidence regarding the outcome measure (local) recurrence-free survival was downgraded by 3 levels because of study limitations (1 level for risk of bias: 4/9 studies excluded non-significant variables from the model; most studies did not define plausible confounders a priori); number of included patients (2 levels for

imprecision: individual cut-off values have a low number of participants).

GRADE for interventions starts at 'LOW' for a body of evidence with observational studies. The level of evidence regarding the outcome measure disease-specific survival was downgraded by 3 levels because of study limitations (1 level for risk of bias: 4/9 studies excluded non-significant variables from the model; most studies did not define plausible confounders a priori); number of included patients (2 levels for imprecision: individual cut-off values have a low number of participants).

GRADE for interventions starts at 'LOW' for a body of evidence with observational studies. The level of evidence regarding the outcome measure disease-free survival was downgraded by 3 levels because of study limitations (1 level for risk of bias: 4/9 studies excluded non-significant variables from the model; most studies did not define plausible confounders a priori); number of included patients (2 levels for imprecision: individual cut-off values have a low number of participants).

GRADE for interventions starts at 'LOW' for a body of evidence with observational studies. The level of evidence regarding the outcome measure overall survival was downgraded by 3 levels because of study limitations (1 level for risk of bias: 4/9 studies excluded non-significant variables from the model; most studies did not define plausible confounders a priori); number of included patients (2 levels for imprecision: individual cut-off values have a low number of participants).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of alternatively defined surgical resection margins (i.e. other than < 1 mm, 1 tot 5mm, >5mm) on the recurrence-free survival, overall survival, local failure, and local recurrence-free survival in patients with surgically resected oral cavity carcinomas?

P: Patients with oral cavity squamous cell carcinomas where the carcinoma is surgically resected.
I: Surgical resection margin (cutoff point(s)) other than those defined as usual (usual definition: < 1mm, 1 tot 5mm, > 5mm).
C: Surgical resection margin (cut-off points) compared.
O: Local failure, (local) recurrence-free survival, disease-specific survival, disease-free survival, overall survival.

<u>Relevant outcome measures</u>
The guideline development group considered local failure and (local) recurrence-free survival as a critical outcome measures for decision making; and disease-specific survival, disease-free survival, and overall survival as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk/odds ratios for local failure.

- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival, (local) recurrence-free survival, and overall survival.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 4th of June, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 411 hits. Studies were selected based on the following criteria: patients had an oral cavity carcinoma, a different definition (or cut-off) of the low/intermediate/high risk resection margins were used and compared, multivariable models were used to correct for confounding. Fifty-seven studies were initially selected based on title and abstract screening. After reading the full text, 49 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 8 studies were included. One relevant study (Brinkman, 2020) was published shortly after the search date and was included. A systematic review (Bungum, 2020) published after the search date identified another relevant study which was not found in our search strategy. This study (Yanamoto, 2012) was included as well, resulting in a total of 10 included studies.

Results

Ten studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Behandeling intermediair risico resectiemarge

Uitgangsvraag

Wat is het management bij patiënten met een plaveiselcelcarcinoom in de mondholte na excisie van het mondholtecarcinoom resulterend in een intermediair-risico resectiemarge?

Aanbeveling

Overweeg, samen met de patiënt, adjuvante behandeling middels radiotherapie of chirurgische re-resectie bij patiënten met een intermediair risico (op basis van resectiemarge) op tumor recidief na chirurgische verwijdering van een carcinoom in de mondholte.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er werden geen gerandomiseerde studies gevonden die antwoord gaven op de zoekvraag. Eén studie (Fridman, 2018) gebruikte databases van meerdere centra, maar het vertrouwen in de resultaten was zeer laag. De studie droeg gecorrigeerde data aan door middel van een multivariabel model over de lokale recidief-vrije overleving voor de vergelijking tussen chirurgie met postoperatieve radiotherapie (n=78) en alléén chirurgie (n=130). Het model bevatte daarnaast leeftijd, geslacht en invasiediepte als variabelen. De variabelen in de multivariabele analyse werden geselecteerd op basis van univariabele analyses. Plausibele confounders werden daarom niet a priori gedefinieerd en aan het model toegevoegd. Het betrouwbaarheidsinterval om de gerapporteerde puntschatter van de hazard ratio was daarnaast breed (95%BHI: 0,38 tot 1,26). De vergelijking tussen de interventies werd gemaakt in een subgroep van de steekproef en bestond uit deelnemers met een intermediair risico resectiemarge (tumorcellen tot 5 millimeter) én deelnemers met een positieve resectiemarge (tumorcellen in de marge van het specimen). Hierdoor bestaat er enige indirectheid ten opzichte van de populatie zoals gedefinieerd in de zoekvraag. Wanneer alle deelnemers met positieve marges in één groep zouden zitten, zou in het meest indirecte scenario de adjuvante radiotherapie groep bestaan uit 42,3% (33/78) deelnemers met positieve marges. Voor de groep die alléén chirurgie ontving zou dit in het meest indirecte scenario 25,4% (33/130) zijn. Karakteristieken van de deelnemers met een intermediair risico marge werden niet afzonderlijk gerapporteerd van de deelnemers met een positieve marge. Hierdoor konden eventuele baseline-verschillen tussen de groepen niet worden beoordeeld. Er werden geen sub-analyses gerapporteerd over het effect van de postoperatieve radiotherapie voor groepen met of zonder specifieke risicofactoren, zoals lymfangioinvasies of perineurale groei.

Best (2019), Ivaldi (2019) en Liu (2018) voerden systematische reviews uit naar het gebruik van postoperatieve radiotherapie na een chirurgische resectie maar hierin werden geen sub-analyses gevonden specifiek voor patiënten met een intermediair risico resectiemarge. Best (2019) includeerde vijf retrospectieve studies specifiek voor patiënten met een stadium I-II plaveiselcelcarcinoom in de wang. De auteurs concludeerden op basis van de beperkte body of evidence dat er géén overduidelijke voordelen zouden bestaan voor het toevoegen van radiotherapie, maar dat een gerandomiseerde trial noodzakelijk is om dit te bevestigen. Ivaldi (2019) includeerde 15 retrospectieve studies naar het gebruik van postoperatieve radiotherapie bij vroeg-stadium mondholtecarcinomen (pT1-2N0-1). De auteurs concludeerden dat er geen data van hoge kwaliteit beschikbaar was die richting kon geven aan de indicaties voor postoperatieve radiotherapie bij vroeg-stadium

mondholtecarcinomen. Liu (2018) includeerde 6 retrospectieve studies om de rol van postoperatieve radiotherapie bij patiënten met laag-risico mondholtecarcinomen en histologische risicofactoren te onderzoeken. De auteurs concludeerden dat er geen bewijs werd gevonden om postoperatieve radiotherapie te geven op basis van alléén de aanwezigheid van histologische risicofactoren en dat voorzichtigheid is geboden bij het geven van postoperatieve radiotherapie om letsel door onnodige blootstelling aan radiatie te vermijden.

Vier studies (Brown, 2007; Dik, 2014; Jang, 2017; Welinder, 2018) rapporteerden data over de vergelijking tussen postoperatieve radiotherapie en alléén chirurgie bij patiënten met een intermediair risico resectiemarge. Deze studies hebben waarschijnlijk een hoog risico op vertekening door confounding door gebrek aan correctie. De resultaten dienen met voorzichtigheid te worden geïnterpreteerd. Welinder (2018) observeerde, bijvoorbeeld, dat de adjuvante radiotherapie groep significant meer nodale betrokkenheid had (53%, 9/17) dan de groep die alleen chirurgie had ontvangen (16%, 6/37; p=0,009). Er werden door Welinder (2019) tevens verschillen gevonden in het ziektestadium (adjuvante radiotherapie: 9/17 stage III-IV; alléén chirurgie: 8/36 stage III-IV (missing: n=1); p=0.03) en in het vóórkomen van perineurale invasie (adjuvante radiotherapie: 10/15 (missing: n=2); alléén chirurgie: 9/34 (missing: n=3); p=0.03). Een samenvatting van de studies is te vinden in Tabel 1.

Tabel 11.3.2.1 Ongecorrigeerde, niet-gerandomiseerde studies die data rapporteren over chirurgie met adjuvante radiotherapie versus alléén chirurgie bij patiënten met een intermediair risico resectiemarge

Auteur, jaartal	In- en exclusiecriteria	Tumor locatie(s) in de steekproef	Definitie intermediair risico resectie marge	Vergelijking	Steekproef-grootte met intermediair risico resectiemarge	Resultaten

Brown, 2007	Inclusie: Patiënten die primaire chirurgie voor orale tumoren tussen 1992-2002 ondergingen	Niet beschreven	1-5 millimeter	Interventie: Chirurgie en adjuvante radiotherapie	Interventie: N=56	Lokale terugkeer (in patiënten met pN0 en pN+):
					Controle: N=67	I: 11/56 C: 7/67
	Exclusie: Sterfte binnen 90 dagen na initiële chirurgie, minder dan 2 jaar follow-up			Controle: Alléén chirurgie		Lokale terugkeer (alleen in patiënten met pN0, n=91): I: 5/29 C: 5/62
						Lokale terugkeer (alleen in patiënten met pN+, n=32): I: 6/27 C: 2/5
Dik, 2014	Inclusie: Patiënten ondergingen primaire chirurgie voor stadium 1-2 carcinomen van de tong, tussen 2004 en 2010	Tong, mondbodem, wang	>0-5 millimeter	Interventie: Chirurgie en adjuvante radiotherapie	Interventie: N=34	Lokale recidief: I: 4/34 C: 1/77
				Controle: Alléén chirurgie	Controle: N=77	
	Exclusie: Behandeling van een voorafgaande hoofd-hals maligniteit, het ondergaan van zowel re-excisie als radiotherapie voor dezelfde tumor, regionale radiotherapie in het geval van lymfeklier metastasen					

Jang, 2017	Inclusie: Pathologisch bewezen plaveiselcel carcinoom van de mondholte, het ondergaan van chirurgische resectie als initiële behandeling, behandeld tussen 1996 en 2012 Exclusie: Salvage cases, metastases op afstand op moment van diagnose	Tong, mondbodem, wang	<5 millimeter tussen het invasiefront en de marge (voor positief: de aanwezigheid van tumorcellen op de marge)	Interventie: Chirurgie en ajduvante radiotherapie Controle: Alléén chirurgie	Interventie: N=33 Controle: N=28	Lokalerecidief rate in patiënten met T1-2 tumoren: Geen significant verschil met de log-rank test (p=0.628) bij de Kaplan-Meier curve
Welinder 2018	Inclusie: Behandeld tussen januari 2010 en december 2011 en als laatst gevolgd tot 31 mei 2015. Exclusie: Presentatie met terugkeer van een orale plaveiselcel-carcinoom, wanneer de biopsie de tumor al voldoende had verwijderd, wanneer de patiënt voordien al werd behandeld met radiotherapie in het hoofd-hals gebied. Wanneer er histologisch enkel sprake was van carcinoma in situ, wanneer de tumor een metastase was.	Tong, mondbodem, tandvlees, retromolaire ruimte	1 tot 5 millimeter	Interventie: Chirurgie en adjuvante radiotherapie Controle: Alléén chirurgie	Interventie: N=17 Controle: N=37	Terugkeer op de lokale of op een nodale site: I: 4/17 C: 11/37

Bulbul (2019) voerde een 'individual patient data' meta-analyse uit waarbij patiënten die re-resecties ondergingen voor positieve (< 1 millimeter) of intermediaire (1 tot 5 millimeter) marges bij mondholtecarcinomen werden vergeleken met patiënten met vrije resectiemarge (> 5 millimeter). In totaal werden 1427 deelnemers geïncludeerd uit 8 retrospectieve studies waarbij de resectiemarge intra-operatief werd bepaald met frozen section analyse voor de verschillende vergelijkingen. Bulbul (2019) gaf de volgende limitaties van de studie: analyses werden gebaseerd op retrospectieve studies, disbalans tussen groepen

maken het interpreteren van de resultaten uitdagend, de analyse werd beperkt tot de vijf-jaren lokale terugkeervrije overleving, en er kon niet worden gecorrigeerd voor een aantal variabelen (waaronder het effect van bestraling). De auteurs concludeerden desondanks dat een re-resectie van een initieel positieve marge naar een vrije marge op basis van een intra-operatieve frozen section analyse niet gelijk zou staan aan een initieel vrije marge en dat het niet voor een significante verbetering van de lokale controle zou zorgen. Ook rapporteerden de auteurs een slechtere vijf-jaren terugkeervrije overleving in de groep waarvan re-resectie na een initieel positieve marge resulteerde in een intermediaire of vrije marge, ten opzichte van de groep die initieel al een vrije marge bereikte.

Twee observationele studies (Dik, 2014; Azzopardi, 2019) waarin geen correctie lijkt te zijn toegepast rapporteerden over de vergelijking tussen chirurgie met re-resectie en alléén chirurgie bij patiënten met een intermediair risico resectiemarge. De resultaten dienen met voorzichtigheid te worden geïnterpreteerd. Een samenvatting van deze studies is te vinden in Tabel 11.3.2.2.

Tabel 11.3.2.2 Ongecorrigeerde, niet-gerandomiseerde studies die data rapporteren over chirurgie met re-resectie versus alléén chirurgie bij patiënten met een intermediair risico resectiemarge

Auteur, jaartal	In- en exclusiecriteria	Tumor locatie(s) in de steekproef	Definitie intermediair risico resectie marge	Vergelijking	Steekproef-grootte met intermediair risico resectiemarge	Resultaten
Dik, 2014	Inclusie: Patiënten ondergingen primaire chirurgie voor stadium 1-2 carcinomen van de tong, tussen 2004 en 2010 Exclusie: Behandeling van een voorafgaande hoofd-hals maligniteit, het ondergaan van zowel re-excisie als radiotherapie voor dezelfde tumor, regionale radiotherapie in het geval van lymfeklier metastasen	Tong, mondbodem, wang	>0-5 millimeter	Interventie: Chirurgie met re-resectie Controle: Alléén chirurgie	Interventie: N=15 Controle: N=77	Lokale terugkeer: I: 0/15 C: 1/77
Azzopardi 2019	Inclusie: Patiënten die met curatieve intentie werden geopereerd voor orale plaveiselcel-carcinomen tussen 1999 en 2009. Hieronder vielen ook de patiënten die postoperatief binnen drie maanden een re-excisie ondergingen. Exclusie: Niet beschreven	Niet beschreven	1-4.9mm	Interventie: Chirurgie met re-resectie Controle: Alléén chirurgie	Interventie: N=7 Controle: N=307	Lokale terugkeer: I: 0/7 C: 33/307

De bovenstaande summatie van de beschikbare literatuur laat zien dat de gebruikte methodiek in de studies niet van voldoende kwaliteit is om een conclusie te trekken. Er wordt niet voldoende rekening gehouden met andere prognostische factoren en deze zijn daarnaast verschillend geanalyseerd in de literatuur. Er is een groot risico op confounding. De studies zijn ook niet poolbaar. De studie van Fridman (2018) kan als voorbeeld dienen voor het lastige interpreteren van de data. De hazard ratio voor adjuvante radiotherapie is 0,71 waarmee een voordeel lijkt te bestaan voor deze behandeling, echter het betrouwbaarheidsinterval is er breed (95%BHI: 0.38 tot 1.26) waarmee ook een negatief effect van radiotherapie aanwezig zou kunnen zijn.

Daarnaast kan een patiënt een recidief krijgen, zelfs na een adjuvante behandeling. Het is denkbaar dat er ook andere predictieve factoren zijn, naast de status van resectiemarge, die het risico op een recidief kunnen verhogen. Bekende andere histopathologische factoren die gepaard gaan met een verhoogd risico op een lokaal recidief zijn sprieterige groei, perineurale groei, vasoinvasieve groei. Andere mogelijke predictieve (epi)genetische en/of moleculair biologische kenmerken van de tumor worden nog niet in de dagelijkse praktijk gebruikt.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
Voor patiënten heeft een adjuvante behandeling mogelijk een impact die kan variëren van beperkt tot zeer ingrijpend. Als adjuvante behandeling worden re-excisie van het operatiegebied of postoperatieve radiotherapie beschreven. Een re-excisie betekent een nieuwe operatie voor de patiënt met mogelijk meer functieverlies doordat ook meer normaal weefsel wordt meegenomen. Daarnaast is de het bepalen van de locatie waar precies de re-resectie dient plaats te vinden moeilijk en vindt deze waarschijnlijk niet altijd op de juiste locatie plaats. Postoperatieve radiotherapie kan gepaard gaan met mucositis, fibrose, xerostomie, trismus, dysfagie en osteoradionecrose. Het is belangrijk om met de patiënt de blijvende bijwerkingen van de twee adjuvante strategieën te bespreken en samen tot een besluit te komen. Hierbij zou de keuze moeten gaan over wel of geen adjuvante behandeling en welke van beide het best past bij de patiënt.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
De beschreven adjuvante behandelingen worden al toegepast in de hoofd-hals centra in Nederland, derhalve zijn de haalbaarheid en implementatie geen item in de overwegingen van deze richtlijnmodule. Hoewel deze module zich richt op de adjuvante behandeling na het behalen van een intermediair risico resectiemarge, zijn er andere factoren die een rol spelen bij de lokale controle en overleving en een indicatie kunnen vormen voor adjuvante therapie. Hierbij is, bijvoorbeeld, te denken aan lymfkliermetastase(n) met kapseldoorbraak, meerdere lymfkliermetastasen, lymfangio invasie, T3-4 tumoren, en/of perineurale groei.

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Op basis van de beschikbare literatuur is niet duidelijk wanneer bij een (op basis van resectiemarge) intermediair risico op lokaal recidieftumor een adjuvante radiotherapie nodig. Tevens is niet duidelijk wanneer deze adjuvante behandeling moet bestaan uit een chirurgische re-resectie of radiotherapie. Een adjuvante behandeling reduceert de kans op een lokaal recidief, maar kan een recidief niet helemaal voorkomen. Beide adjuvante behandelingen hebben voor- en nadelen, die gezamenlijk met de patiënt overwogen moeten worden.

Onderbouwing

Achtergrond

Chirurgen streven naar een radicale resectie marge van minimaal 5 mm bij het verwijderen van de tumor. Minder dan één mm marge heeft een hoog risico op recidief en behoeft adjuvante behandeling in geval van een curatieve behandeling. Het is onduidelijk of een marge tussen de 1 en 5 mm ook adjuvante behandeling behoeft door middel van radiotherapie of een re-resectie.

Conclusies

Postoperative radiotherapy

NO GRADE	GRADEing could not be performed for **local recurrence** after postoperative radiotherapy, since no studies were included in the current literature analysis for this outcome.

VERY LOW GRADE	The evidence is very uncertain regarding the effects of surgery with postoperative radiotherapy on the local recurrence-free survival when compared to surgery alone in patients with oral cavity carcinomas and an intermediate risk resection margin (1-5 millimeters) resulting from surgery. *Source: (Fridman, 2018)*

Re-resection

NO GRADE	GRADEing was not performed for **local failure** and **local recurrence-free survival** after adjuvant re-excision, since no studies were included in the current literature analysis for this outcome.

Samenvatting literatuur

Description of studies

Fridman (2018) used databases from centers in Italy, Brazil, Germany, United States of America, Israel, Australia, Taiwan, and India to select patients treated for T1-2N0 oral cavity squamous cell carcinoma (lip, tongue, buccal mucosa, floor of mouth, hard palate, or alveolar ridge). Patients had to be treated between 1970 and 2011 with primary surgery with or without adjuvant (chemo)radiotherapy. Exclusion criteria were not reported. From the databases, 1257 patients (931 males, 323 females, 3 missing data) were selected with a mean age of 56.1 (SD: 13.1). Median follow-up was 56 months (range: 0 to 302). All patients underwent a neck dissection (levels I to III, I to IV, or I to V). The margin status was either clear (n=995, free margin of ≥ 5 millimeters), close (n=205, tumor cells at a distance < 5 millimeters), or positive (n=33, presence of tumor cells in the resected margin) while the margin status was missing in n=2. The resection margin was determined on the resected specimen. The pT-stage in the sample was T1 (n=461) or T2 (n=796). Adjuvant treatment consisted of radiotherapy (n=284), chemoradiotherapy (n=50), radiotherapy with cetuximab (n=21), while n=900 did not receive any adjuvant therapy (n=2 missing data). Surgical procedures other than the neck dissection levels and postoperative radiotherapy procedures were not described. A multivariable analysis for local recurrence-free survival was performed on a subset of the sample (n=208) consisting of patients with both close and positive resection margins. Characteristics of the subset were not provided, thus in a worst-case scenario the subset in the analysis consisted of n=33 (33/208, 15.9%) with positive margins. Variables that had predictive potential were identified through univariable analyses and were selected for the multivariable model. Plausible confounders to use as variables in the multivariable model were therefore not defined a priori.

Results
Postoperative radiotherapy

No (sub)group analyses were found comparing the outcomes in patients receiving postoperative radiotherapy with and without specific disease characteristics, such as multiple lymph node metastases, lymph node(s) with extra capsular invasion, lymphovascular invasion, T3-4 tumors, and perineural growth.

Local failure
No studies were included in the current literature analysis that reported data on local failure when comparing surgery with adjuvant radiotherapy to surgery alone.

Local recurrence-free survival
Fridman (2018) used a multivariable analysis to estimate the hazard ratio for local recurrence-free survival in 208 patients with positive (most indirect scenario: n=33, 15.9%) or close resection margins that received surgery with (n=78) or without (n=130) adjuvant postoperative radiotherapy. It was unclear how sample characteristics were distributed among both groups. Besides the adjuvant treatment variable, the model contained the following variables: sex, age, and depth of invasion. A hazard ratio of 0.71 (95%CI: 0.38 to 1.26) was reported, with the point estimate favoring surgery with postoperative radiotherapy.

Re-resection
No (sub)group analyses were found comparing the outcomes in patients receiving a re-resection with and without specific disease characteristics, such as multiple lymph node metastases, lymph node(s) with extra capsular invasion, lymphovascular invasion, T3-4 tumors, and perineural growth.

Local failure
No studies were included in the current literature analysis that reported data on local failure when comparing surgery with adjuvant re-excision to surgery alone.

Local recurrence-free survival
No studies were included in the current literature analysis that reported data on local recurrence-free survival when comparing surgery with adjuvant re-excision to surgery alone.

Level of evidence of the literature
Postoperative radiotherapy
GRADEing was not performed for local recurrence after postoperative radiotherapy since no studies were included in the current literature analysis that reported data on local recurrence when comparing surgery with adjuvant re-excision to surgery alone.

GRADE starts at 'LOW' for non-randomized intervention study designs. The level of evidence regarding the outcome measure local recurrence-free survival was downgraded by 4 levels because of study limitations (1 level for risk of bias: the multivariable model was not built on pre-defined confounders); applicability (1 level due to indirectness: in the most indirect scenario, 15.9% of the used subgroup in the multivariable analysis had positive resection margins while the distribution of margins status among groups was not provided (most indirect scenario per group: 25.4% in the surgery-alone group, or 42.3% in the surgery + radiotherapy group)); number of included patients (2 levels for imprecision: low number of participants in the analysis and the 95%CI crosses both 0.8 and 1.25); publication bias was not assessed.

Re-resection
GRADEing was not performed for outcomes of re-resection, since no studies were included in the current literature analysis that reported data on any of the outcomes when comparing surgery with adjuvant re-excision to surgery alone.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of adjuvant therapy (using radiation therapy or re-resection) compared to no adjuvant therapy on the local recurrence and (local) recurrence-free survival in patients with a surgically resected oral cavity squamous cell carcinoma resulting in a resection margin of one to five millimeters?

P: Patients with a surgically resected oral cavity squamous cell carcinomas resulting in a resection margin of 1 to 5 millimeters.
I: Adjuvant treatment with radiation therapy or re-resection.
C: No adjuvant treatment after initial resection.
O: Local failure, local recurrence-free survival.

Relevant outcome measures
The guideline development group considered local failure and (local) recurrence-free survival as critical outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk/odds ratios for local failure.
- 5% difference or more (absolute) and HR< 0.7 in local recurrence-free survival

Available (sub)analyses regarding the outcomes in (sub)groups with and without specific characteristics will be extracted when reported in the included studies. Characteristics of interest were factors such as multiple lymph node metastases, lymph node(s) with extra capsular invasion, lymphovascular invasion, T3-4 tumors, and perineural growth.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until October 21, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 544 hits. In a pre-screening of the results, 368 obvious non-relevant hits (for example neo-adjuvant treatment, carcinomas outside the oral cavity, diagnostic studies) were excluded leaving 176 hits.

Studies were selected based on the following criteria: Patients underwent surgical resection of the primary

oral cavity carcinoma, patients had an intermediate risk resection margin (presence of tumor cells within 1 to 5 millimeters), patients either had surgery with adjuvant therapy (consisting of postoperative radiotherapy or surgical re-resection) or surgery alone, at least one outcome of interest was measured, and corrections for potential bias (for example multivariable analyses, propensity scores) were performed when a non-randomized study design was used.

Twenty-two studies (including systematic reviews) were initially selected based on title and abstract screening. After the full-text screening of the potentially relevant systematic reviews (Best, 2019; Ivaldi, 2019; Liu, 2018), six primary observational studies (Brown, 2007; Dik, 2014; Dixit, 1998; Fridman, 2018; Jang, 2017; Katz, 2017) identified in the systematic reviews were added for full-text screening. Thus, in total 28 studies were screened for eligibility. One study was included in the literature analysis based on its full text, while the remaining studies were excluded (see the table with reasons for exclusion under the tab Methods).

<u>Results</u>
One relevant study (Fridman, 2018) was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Invasiediepte (negatieve hals)

Uitgangsvraag

Welke rol speelt de mate van invasiediepte (of tumordikte) van het primaire plaveiselcelcarcinoom van de mondholte voor de behandelbeslissing van de klinisch negatieve hals?

Aanbeveling

Aanbeveling-1
Gebruik invasiediepte bij het bepalen van de kans op occulte lymfekliermetastasen van mondholtecarcinomen.

Aanbeveling-2
Overweeg geen watchful waiting in te zetten bij een invasiediepte hoger dan 3 tot 4 millimeter door een toenemend risico op lymfekliermetastasen.

Overwegingen

De zekerheid in het bewijs uit de geïncludeerde studies met multivariabele modellen was laag voor het risico op de aanwezigheid van metastasen. De geïncludeerde studies bevatten in geen enkel geval vooraf gedefinieerde confounders en de betrouwbaarheidsintervallen waren breed. Voor het classificeren van de aan- of afwezigheid van (occulte) halskliermetastasen aan de hand van een afkapwaarde voor invasiediepte (of tumordikte) was er een redelijk vertrouwen in het gevonden bewijs, met uitzondering van een zeer laag vertrouwen op specifieke afkappunten waar zeer weinig data voor beschikbaar was.

Invasiediepte is voorspellend voor de aanwezigheid van lymfekliermetastasen. In de beschreven studies werd een verhoogd risico gevonden voor lymfekliermetastasen bij een invasiediepte boven de gekozen afkapwaarde. Wanneer deze studies vergeleken worden, is geen duidelijke trend richting een hogere odds ratio te zien bij een hogere afkapwaarde. De studiepopulaties kunnen echter sterk verschillen.

Wanneer invasiediepte of tumordikte gebruikt wordt om de aanwezigheid van lymfekliermetastasen te voorspellen, nemen met een lagere afkapwaarde de sensitiviteit en negatief voorspellende waarde toe. Bij de veel gebruikte afkapwaarde van 4 mm voor het verrichten van een electieve halsklierdissectie is de sensitiviteit 70 tot 95% en de negatief voorspellende waarde 61 tot 99%. Dit betekent dat als een electieve halsklierdissectie alleen wordt verricht wanneer de invasiediepte groter is dan 4 millimeter, het risico op aanwezigheid van (occulte) lymfekliermetastasen 1 tot 39% is in de groep met een invasiediepte kleiner dan 4 millimeter. De sensitiviteit en negatief voorspellende waarde voor een afkapwaarde van 3 mm zijn 71-96% en 67 tot 98%.

Na de zoekactie voor deze module is nog een studie verschenen waarin de waarde van invasiediepte voor het voorspellen van lymfekliermetastasen is onderzocht bij 222 patiënten met een T1-2 mondholtecarcinoom (Aaboubout, 2021). De referentiestandaard was een electieve halsklierdissectie (n=166) of observatie (n=56). Hierbij werd een odds ratio van 1,3 per mm invasiediepte gevonden en was bij een afkapwaarde van 4 mm de sensitiviteit 74% en de negatief voorspellende waarde 81% (zie tabel 6).

Tabel 6 Sensitiviteit en negatief voorspellende waarde, uit Aaboubout 2021

Accuratesse parameter	Afkapwaarde (millimeter)									
	1	2	3	4	5	6	7	8	9	10
Sensitiviteit	1.00	1.00	0.90	0.74	0.59	0.54	0.46	0.28	0.13	0.00
Negatief voorspellende waarde	1.00	1.00	0.88	0.81	0.80	0.81	0.82	0.79	0.77	0.77

Belangrijke factoren die van invloed kunnen zijn op de gevonden waarde zijn de onderzoeken die verricht zijn voordat gesproken wordt over een klinisch negatieve hals, de daarmee samenhangende incidentie van lymfekliermetastasen.

Indien de hals na uitgebreid beeldvormend onderzoek negatief is, is de kans dat toch lymfekliermetastasen aanwezig zijn kleiner dan wanneer de hals na palpatie alleen als negatief beschouwd wordt. Aangezien het risico op lymfekliermetastasen ook afhankelijk is van vele andere factoren als T-stadium en tumor lokalisatie, kan de incidentie van lymfekliermetastasen verschillen indien de samenstelling van in studies onderzochte cohorten anders is. De incidentie van lymfekliermetastasen kan invloed hebben op de negatief voorspellende waarde.

Ook de referentiestandaard kan van invloed zijn op de resultaten. Bij routinematig onderzoek van een halsklierdissectiepreparaat kunnen namelijk tot 15% van de (micro)metastasen gemist worden. Door stapsgewijze doorsnijdingen en immunohistochemie kunnen bij de schildwachtklierprocedure micrometastasen beter gedetecteerd worden. Het is alleen te arbeidsintensief om dit routinematig bij alle lymfeklieren in een halsklierdissectiepreparaat te doen. Bij een watch and wait strategie (observatie) van een onbehandelde hals zullen alle lymfekliermetastasen tijdens follow-up uiteindelijke manifest worden. Derhalve is observatie van de onbehandelde hals de beste referentiestandaard, gevolgd door de schildwachtklierprocedure (die indien negatief gevolgd wordt door observatie) en daarna het histopathologisch onderzoek van een electieve halsklierdissectie.

In de beschreven studies zijn met name tumoren van de tong onderzocht. Het is goed mogelijk dat de gevonden resultaten bij andere tumorlokalisaties als de mondbodem anders zullen zijn.

In de beschreven studies wordt invasiediepte op twee verschillende manieren gemeten: van een denkbeeldig intact (alsof er geen ulceratie of exofytische groei aanwezig is) mucosale oppervlak tot het diepste punt van tumorinfiltratie of van de basaalmembraan tot het diepste punt van tumorinfiltratie. Daarnaast is in andere studies tumordikte in plaats van invasiediepte gebruikt. Dikte kan mogelijk als surrogaat voor invasiediepte gebruikt worden aangezien Dirven (2017) in een cohort van 456 patiënten met een mondholtecarcinoom een gemiddeld verschil van 0,7 mm vonden.

Invasiediepte is voorspellend voor het optreden van lymfekliermetastasen. De sensitiviteit en negatief voorspellende waarde (per afkapwaarde) verschilt echter sterk per studie. Naast invasiediepte zijn er andere voorspellende factoren voor aanwezigheid van lymfekliermetastasen. Toch kan invasiediepte gebruikt worden bij de keuze voor het al dan niet electief behandelen van de hals. Invasiediepte kan histopathologisch

bepaald worden op het resectiepreparaat en is derhalve voor de patiënt niet belastend. Nadeel is dat de uitslag niet voor of tijdens de operatie van de primaire tumor beschikbaar is, zodat dan in tweede instantie eventueel een halsklierdissectie verricht zou moeten worden. Aangezien een incisiebiopt slechts sample van de hele tumor is, zal onduidelijk zijn of de gemeten invasiediepte in het biopt ook de maximale invasiediepte van de tumor is. Preoperatief kan de invasiediepte met MRI en echografie betrouwbaar bepaald worden. MRI en echografie van de hals worden vaak al routinematig gemaakt waardoor het weinig belastend voor de patiënt is. Voor bepaling van invasiediepte met echografie is alleen wel een speciale probe voor in de mondholte nodig. Dit laatste is het enige dat extra aangeschaft hoeft te worden. De overige onderzoeken worden routinematig verricht. De metingen zijn gemakkelijk te aan te leren.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Aanbeveling-1
Invasiediepte is een voorspeller voor de kans op lymfekliermetastasen. Gezien de grote variatie in sensitiviteit en negatief voorspellende waarde kan moeilijk een keuze gemaakt worden voor een optimale afkapwaarde waaronder voor een afwachtend beleid en waarboven voor een electieve halsklierdissectie gekozen dient te worden. Dit is onder andere afhankelijk van incidentie van lymfekliermetastasen, welke deels bepaald wordt door de accuratesse voor het detecteren van (occulte) lymfekliermetastasen van de tevoren verrichte diagnostische onderzoeken.

Aanbeveling-2
Gezien de grote variatie in sensitiviteit en negatief voorspellende waarde kan moeilijk een keuze gemaakt worden voor een optimale afkapwaarde waaronder voor een afwachtend beleid en waarboven voor een electieve halsklierdissectie gekozen dient te worden. Wanneer de hals alleen op basis van palpatie als klinisch negatief beoordeeld wordt zal waarschijnlijk voor een lagere afkapwaarde gekozen moeten worden om een acceptabel risico op gemiste metastasen te houden. In het algemeen lijken afkapwaarden tussen 3 en 4 mm acceptabel te zijn.

Onderbouwing

Achtergrond

De mate van invasiediepte (en tumordikte) van het primaire plaveiselcelcarcinoom van de mondholte is geassocieerd met de ontwikkeling van cervicale lymfekliermetastasen. Wanneer lymfekliermetastasen klinisch niet gedetecteerd worden, maar de kans aanzienlijk is dat deze wel aanwezig zijn, ontstaat een dilemma om de hals uit voorzorg (electief) te behandelen of af te wachten totdat deze eventueel manifest worden. Het verwijderen van lymfeklieren in de hals kan echter, naast pijn, oedeemvorming en bloedingen, ook potentieel gevolgen hebben voor de nek- en schouderfunctie van de patiënt. Wanneer gewacht wordt totdat de nog niet gedetecteerde (occulte) lymfekliermetastasen manifest worden, is de behandeling vaak uitgebreider of zelfs soms niet meer mogelijk. Het is daarom belangrijk om te bepalen aan de hand van de invasiediepte (en tumordikte) van de primaire tumor hoe hoog het risico op lymfekliermetastasen is, zodat voor een patiënt het beste beleid ten aanzien van het beleid van de hals (electief behandelen of afwachten en observeren) gekozen kan worden.

Conclusies

LOW GRADE	The evidence is uncertain about the **risk of lymph node metastasis** as at various cut-off points of depth of invasion of oral tongue carcinomas using a sentinel node biopsy, elective neck dissection and/ or a watch and wait strategy as reference standard. There was no data included for other subsites of oral cavity carcinomas. *Sources: (Faisal, 2018; Wu, 2019; Xu 2020)*

MODERATE GRADE	There is moderate certainty about the **sensitivity** at various cut-off points of depth of invasion (or tumor thickness) with enough data in oral cavity carcinomas using a sentinel node biopsy, elective neck dissection, or a watch and wait strategy as reference standard for the prediction of lymph node metastases. However, the evidence is very uncertain about specific cut-off points where there is a lack of data (1.5 mm/ 1.6mm/ 2.2mm/ 2.7mm/ 3.8mm). *Sources: (den Toom, 2019; Goerkem, 2010; Melchers, 2012; Sahoo, 2020; van Lanschot, 2020; Warburton, 2007; Yeh, 2014; Zhang, 2014)*

MODERATE GRADE	There is moderate certainty about the **negative predictive value** at various cut-off points of depth of invasion (or tumor thickness) with enough data in oral cavity carcinomas using a sentinel node biopsy, elective neck dissection, or a watch and wait strategy as reference standard for the prediction of lymph node metastases. However, the evidence is very uncertain about specific cut-off points where there is a lack of data (1.5 mm/ 1.6mm/ 2.2mm/ 2.7mm/ 3.8mm). *Sources: (Goerkem, 2010; Melchers, 2012; van Lanschot, 2020; Warburton, 2007; Yeh, 2014)*

Samenvatting literatuur

<u>Description of studies</u>
Den Toom (2019) included patients with cT1-2N0 oral carcinomas who underwent transoral excision and sentinel lymph node biopsy (examined with histopathology). Exclusion criteria were not reported. Patients (n=199, 100 males, 99 females) had a median age of 63 years (range 27 to 87). Tumor site in the sample was at the tongue (n=121), floor of mouth (n=53), buccal mucosa (n=160), inferior alveolar process (n=5), or other (n=4). T-stage was either T1 (n=132) or T2 (n=67). Persons with a negative sentinel lymph node biopsy were considered positive for metastasis when metastases developed during follow-up (i.e. the SLNB was false negative). There was a follow-up in the sample of 19 months (central tendency measure was unclear, range: 1 to 104). Depth of invasion was measured as being the mass beneath the basement membrane. A theoretical reconstruction of the basement membrane was made for exophytic lesions or ulceration. Depth of invasion was correlated with (true positive and false negative) lymph node metastatic rate. It was argued that the combination of sentinel node biopsy and follow-up was a better reference standard than routine histopathological examination of neck dissections specimens.

Faisal (2018) selected patients with histopathologically proven T1-2 tongue carcinomas from a database. Patients had to have a clinically negative neck and had to be treated with surgery (including level I-III/IV elective neck dissection) followed by adjuvant (chemo)radiotherapy. Exclusion criteria were not reported. Patients (n= 179, 57% male, 43% female) had a mean age of 57.92 years (SD: 11.93). Pathological T-stage was either T1 (63.69%) or T2 (36.31%), with a tumor differentiation of poor (5.59%), moderate (39.66%), or well (54.75%). Postoperative radiotherapy was provided for patients with pathologically involved lymph nodes or close (< 5mm) resection margins. Three patients received re-excision followed by radiotherapy. Patients with extranodal extension received chemoradiation. Depth of invasion was measured from the basement membrane of adjacent normal mucosa to the deepest point of invasion by a pathologist.

Goerkem (2010) selected patients from a database with biopsy-proven cT1-2 oral cavity carcinomas without evidence of lymph node metastases after physical examination and imaging. Exclusion criteria were not reported. Transoral tumor resection and sentinel lymph node biopsy was performed in all patients. Patients (n=78, 52 males, 26 females) had a mean age of 60 years (range: 34 to 87). T-stage was either T1 (n=40) or T2 (n=38) with the tumor location at the tongue (n=55) or floor of mouth (n=23). Lymphatic invasion was observed in 10 persons, perineural invasion in 15 persons, vascular invasion in 3 persons, and muscular invasion in 55 patients. Mode of infiltration was observed to be grade 1 (n=11), grade 2 (n=12), grade 3 (n=25), grade 4C (n=16), or grade 4D (n=14). Lymphoplasmacytic infiltration in the sample was grade 1 (n=31), grade 2 (n=41), or grade 3 (n=6). Tumor depth was measured from the mucosal surface to the deepest point of infiltration. Tumor thickness was measured from a virtual line (tangentially placed at the most exophytic tumor area) to the deepest point of infiltration.

Melchers (2012) selected patients with a histologically proven T1-2 oral squamous cell carcinoma from a database. Patients had to be treated by resection of the primary tumor without prior head-neck systemic oncological treatment. All clinicopathologic data regarding the nodal status had to be available. Patients were excluded when there were synchronous tumors, when HE-slides were irretrievable, or when there was an unreliable assessment of depth of invasion. Included patients (n=212, 119 males, 93 females) had a mean age of 61.5 years (range: 25 to 94) with tumors at the tongue (n=108), gum (n=15), floor of mouth (n=64), cheek mucosa (n=7), retromolar area (n=12), or other (n=6). Pathological T-stage was T1 9n=123) or T2 (n=89). The patients were treated with neck dissection (n=174, with n=106 with cN0) or underwent an observation period of at least 2 years (n=38). Clinical nodal stage was assessed with palpation and imaging (CT or MRI, while PET or ultrasound could be performed on indication). Patients with cN0 (n=106) were selected for the accuracy analyses. Pathological N-stage was considered as the true N-stage, after neck dissection. Patients who received the observation strategy were examined for the development of nodal metastases in the follow-up with return visits every 6 weeks. Maximum infiltration depth of the tumor below the mucosal surface was considered as the depth of invasion. The mucosal surface was reconstructed for ulcerated or exophytic tumors when measuring the depth of invasion. Of note is that the group of patients who underwent elective neck dissection differs from the observation group, e.g. true N0 status 58% versus 82%. This difference in incidence may affect negative predictive values.

Sahoo (2020) selected patients older than 35 years with histologically proven oral squamous cell carcinomas from a database. Patients had to be treated with a wide excision of the primary tumor and with elective neck dissection. Patients who had metastatic tumors, recurrent tumors in the oral cavity, immune-compromised

diseases and tumors, or who were under treatment with chemotherapy or radiotherapy were excluded. The sample (n=150) consisted of 88 men and 51 females, where 110 patients were younger than 40 years old. The tumor stage was either cT1 (n=27) or cT2 (n=41), with a tumor differentiation of well (n=27), moderate (n=60), or poor (n=3). Lymphovascular invasion was present in 35 patients, while perineural invasion was present in 41 patients. Tumor thickness was measured from the level of the surface of the mucosa or the ulcer base to the deepest point of invasion (without superficial keratin or inflammatory debris). Depth of invasion was measured in two ways from the bottom of the adjacent dysplastic rete ridge to the deepest point of invasion and from the epithelial junction of most superficial adjacent connective tissue papilla to the deepest point of invasion

Van Lanschot (2020) included patients with pT1-2 primary oral squamous cell carcinomas from a database. Patients with synchronous multiple tumors or with clinically positive neck nodes were excluded. Patients (n=300, 158 males, 142 females) were surgically treated and received an elective neck dissection (n=173) or observation (n=127). Median age was 66.5 years (range: 25 to 94). Tumor site was at the tongue (n=162), floor of mouth (n=77), buccal mucosa (n=27), lower (n=12) or upper (n=7) alveolus and gingiva, lip (n=7), retromolar area (n=5), or hard palate (n=3). Infiltrative grows was present in 179 patients, vasoinvasion in 28 patients, and perineural invasion in 52 patients. Pathological T-stage according to the TNM7-staging system was pT1 (n=197) and pT2 (n=90). Some patients were staged according to the TNM8-staging system (pT1: n=5, pT2: n=8). Patients were surgically treated. Elective neck dissection was performed when the depth of invasion of the primary tumor was ≥ 4 millimeters. Patients staged with clinically negative lymph nodes and < 4 millimeters depth of invasion received an observation strategy. The mean follow-up in the observation group was 23.4 months (range: 0 to 62) and consisted of physical examinations and regular ultrasound of the neck in the first two years. Depth of invasion was measured from the basement membrane of the adjacent normal mucosa to the deepest point of infiltration.

Warburton (2007) selected patient with T1-2N0M0 tongue or floor of mouth carcinomas from a database. Patients had to be treated with resection of the primary tumor, without neck dissection or irradiation. Cases were excluded when there was insufficient tumor tissue on the archived slides. The sample consisted of 27 patients (18 males, 9 females) with a mean age of 64 years (range: 39 to 86). T-stage was either T1 (n=19) or T2 (n=8) with tumors located at the floor of mouth (n=15) or tongue (n=12). Depth of invasion was measured from the surface of the epithelium to the deepest points of invading tumor island or cell by using a reconstructed line, excluding exophytic components and including thickness lost to ulceration.

Wu (2019) Included patients with pathologically confirmed tongue squamous cell carcinoma by biopsy. Patients with T1-2 tumors and without cervical lymph node relapse (N0) were included. TNM stage was assessed with a clinical check, CT, and ultrasound. Exclusion criteria were not reported. Patients received neck dissection (n=69) or observation (n=72) after tumor resection. The sample (n=141, 75 males, 66 females) had a mean age of 55 years. Tumor location carcinoma was on the anterior (n=14), middle (n=103) or back (n=24) of the tongue. Tumor differentiation was well (n=48), moderate/poor (n=93). Eighteen patients had neurovascular invasion. Patients were followed for a maximum of 60 months and examined every 3 months (first 24 months), then every 6 months (for the following 36 months). Examination consisted of physical inspection and CT or MRI. Nodal relapses were pathologically proven. It was unclear how the depth of invasion was measured.

Xu (2020) selected adult patients (≥ 18 years) with primary cT1N0M0 tongue squamous cell carcinoma. Patients were selected when MRI and follow-up data were available. Exclusion criteria were not reported. Elective neck dissection was routinely provided after primary tumor excision, while patients with very early-stage disease did not undergo neck dissection. After therapy, the patients were examined every 3 months (in the first 12 months), every 6 months (in the following 12 months), and once yearly thereafter (mean follow-up: 70.4 months, range: 8 to 103). The sample (n=151, 111 males, 40 females) had a mean age of 57.1 years (range: 30 to 78). A portion of the sample had perineural invasion (n=23) and/or lymphovascular invasion (n=19). The observed growth pattern was either ulcerative (n=71), invasive (n=20), or exogenous (n=49). Depth of invasion as measured on MRI was defined as the distance between the deepest point of invasion and the simulated normal mucosal junction. The depth of invasion was determined by at least two radiologists. Pathological depth of invasion was measured from the level of normal adjacent mucosa to the deepest point of infiltration.

Yeh (2014) recruited 272 consecutive patients with newly diagnosed T1-2 cN0 oral squamous cell carcinoma who underwent curative surgery. Patients were excluded when there was previous cancer, unless the patient was more than 2 years disease-free. Nineteen patients (who underwent observation) were excluded because of adjuvant therapy was provided (n=7), there was local recurrence before neck recurrence (n=1), or the follow-up period was too short (n=11). Included patients (n=253) had either pT1 (n=128) or pT2 (n=125) with a well (n=171) or moderate/poor (n=82) tumor differentiation. The clinically negative neck status was determined with clinical examination and imaging (MRI or CT). A total of n=176 received neck dissection and n=77 received observation. Node positivity was defined as the pathological diagnosis of lymph node metastasis (for neck dissection) or the neck recurrence within 2 years without antecedent or synchronous local recurrence (for observation). Patients with high-risk features in the neck dissection group received postoperative adjuvant treatment (n=31). Patients were followed every month (first year), every 2 months (following year), and every 3 months (thereafter). Persons who received the observation strategy and remained free from neck recurrence had a mean follow-up of 61.9 months (range: 24 to 130). Tumor thickness was measured vertically from the tumor surface or ulcer base to the deepest point of invasion on serial sections.

Zhang (2014) selected patients with a biopsy proven cT1N0M0 squamous cell carcinoma of the tongue without previous treatment. Patients had to be treated with surgery, the staging of the neck was performed with palpation and contrast-enhanced CT, no other malignancies were present in the head and neck, and sufficient data was recorded. Cases were excluded when there was a carcinoma in situ, verrucous carcinoma, or carcinoma at the base of the tongue. The sample (n=65, 32 males, 33 females) had a mean age of 60.7 years (range: 24 to 91). Tumor was located at the dorsal (n=2), lateral (n=54), or ventral (n=9) part of the tongue with a poor (n=5), moderate (n=18), well (n=37), or unknown (n=5) tumor differentiation. Perineural invasion was present in four patients. Patients received observation when biopsy results showed < 3 millimeters depth of invasion. Delayed neck dissection was recommended within 4 to 6 weeks when pathological depth of invasion was ≥ 3 millimeters (while the biopsy showed < 3 mm). When the depth of invasion was ≥ 3mm on biopsy, the patients received selective neck dissection. Thirty-six patients received simultaneous or delayed neck dissection, while the other (n=29) did not receive neck dissection. Pathological tumor depth was measured from the normal adjacent mucosa to the deepest point of invasion.

Overviews of how depth of invasion was measured, whether tumor thickness was measured, and which reference standard(s) were used in the included studies are reported in Tables 1 and 2.

Table 1 Overview of how depth of invasion measured in the included studies and whether tumor thickness was measured

Author, year	Depth of invasion		Tumor thickness
	From basement membrane of intact mucosa	**From surface of intact mucosa**	
Den Toom 2019	x		
Faisal 2018	x		
Goerkem 2010		x	x
Melchers 2012		x	
Sahoo 2020	x		x
Van Lanschot 2020	x		
Warburton 2007		x	
Wu 2019	Unclear	Unclear	
Xu 2020		x	
Yeh 2014			x
Zhang 2014		x	

Table 2 Overview of how the included studies assessed the occurrence (i.e. presence or development) of neck metastases

Author, year	Reference standard			
	Follow-up	**Sentinel node biopsy**	**Sentinel node + follow-up**	**Neck dissection**
Den Toom 2019			x	
Faisal 2018	x			I - III/IV
Goerkem 2010		x		
Melchers 2012	x			x
Sahoo 2020				x
Van Lanschot 2020	x			x
Warburton 2007	x			
Wu 2019	x			x
Xu 2020	x			x
Yeh 2014	x			x
Zhang 2014	x			x

Results

Risk of lymph node metastases

Three studies used a multivariable model (Faisal, 2018; Wu, 2019; Xu 2020). All studies solely included patients with oral tongue carcinomas. Results are summarized in Table 3.

Table 3 Adjusted odds ratios from multivariable models at specific cut-off points

Author, year, tumor sites	Reference strategy	TT / DOI*	Adjusted risk per cut-off (millimeters		
			4 mm	5 mm	7.5 mm
Faisal 2018 *Tongue*	ND	DOI		≤5 mm (ref) versus 6-10mm OR not reported (95%CI: 0.52 – 2.00) *Other variables in the model: cT-stage, perineural invasion, extracapsular spread* ≤5mm (ref) versus >10mm OR = 1.69 (95%CI: 0.80 – 3.58) *Other variables in the model: cT-stage, perineural invasion, extracapsular spread*	
Wu 2019 *Tongue*	ND/WW*	DOI	≤4 mm (ref) versus ≥4 mm OR = 12.23 (95%CI: 1.31 – 113.90) *Other variables in the model: gender, age, mode of invasion, pathological differentiation, neurovascular invasion, location, T-stage, smoking, drinking, treatment*		

Xu 2020 *Tongue*	ND/WW*	DOI			≤5 mm(ref) versus >5 mm (pathological DOI) OR = 3.112 (95%CI: 1.812 – 9.668) *Other variables in the model: lymphovascular invasion, pathologic tumor grade, MRI-measured depth of invasion.*	<7.5mm (ref) versus ≥7.5 mm (MRI-measured DOI) OR = 2.978 (95%CI: 1.574 – 7.332) *Other variables in the model: lymphovascular invasion, pathologic tumor grade, pathologic depth of invasion.*

DOI: Depth of invasion
mm: millimeter(s)
ND: Neck dissection
SLNB: Sentinel lymph node biopsy
TT: Tumor thickness
WW: Watch and wait
*: ND and WW were not separately distinguishable from the reported results

Sensitivity
Study results for sensitivity using several reference strategies at specific cut-off points are summarized in Table 4. Overall the sensitivity ranged from 0.13 to 1.00, depending on the reference strategy and the cut-off point. Studies used tumor thickness measurements and/or depth of invasion measurements for specific cut-off points in millimeters.

Using watch and wait as the reference strategy, the sensitivity ranged from 0.375 to 1.00 (Warburton, 2007; Melchers 2012) depending on the cut-off point.

Two studies reported the sensitivity for both the neck dissection and observation strategies combined as one group (Zhang, 2014; Van Lanschot 2020). From another study, the sensitivity for the group receiving neck dissection or watch and wait could be calculated from the presented data (Yeh, 2014). The sensitivity ranged from 0.545 to 1.00, depending on the cut-off.

When using neck dissection as a reference strategy, two studies reported the sensitivity at various cut-off points (Melchers, 2012; Sahoo, 2020). Depending on the cut-off point, the sensitivity ranged from 0.50 to 1.00.

Sentinel lymph node biopsy was used as a reference strategy in two studies (Goerkem, 2010; Den Toom 2010). The sensitivity ranged from 0.13 to 1.00, depending on the different cut-off points.

Negative predictive value
Study results for the negative predictive value are summarized in Table 5. Overall, the negative predictive value using different reference strategies at specific cut-off points ranged from 0.464 to 1.00 in five studies

(Warburton, 2007; Goerkem, 2010; Melchers, 2012; Yeh, 2014; Van Lanschot, 2020). Studies used tumor thickness measurements and/or depth of invasion measurements for specific cut-off points in millimeters. When using watch and wait as a reference strategy in two studies (Warburton, 2007; Melchers, 2012), the negative predictive value ranged from 0.783 to 1.00 depending on the cut-off point.

In two studies, the study samples received neck dissection or watch and wait as a reference strategy which could not be distinguished (Yeh, 2014; Van Lanschot, 2020). One study reported the negative predictive value (Van Lanschot, 2020), while the negative predictive value could be calculated from the reported data in the other study (Yeh, 2014). Depending on the cut-off points, the negative predictive value ranged from 0.815 to 1.00.

One study also used neck dissection as the reference strategy in a study group (Melchers, 2012). The negative predictive value ranged from 0.889 (at the 7 millimeters cut-off point) to 1.00 (at the 1 millimeter cut-off point).

Sentinel lymph node biopsy was used as a reference strategy in one study reporting the negative predictive value (Goerkem, 2010). Here, the negative predictive value ranged from 0.649 to 1.00 (tumor thickness) and from 0.464 to 0.75 (depth of invasion), depending on the cut-off points.

Table 4 Summary of the sensitivity for predicting of lymph node metastasis using several reference standards at specific cut-off points of tumor thickness or depth of invasion

Author, year, tumor sites	Reference strategy	TT / DOI	Sensitivity at specific cut-off points												
			1 mm	1.5 mm	1.6 mm	2 mm	2.2 mm	2.7 mm	3 mm	3.4 mm	3.8 mm	4 mm	4.59 mm	5 mm	6 mm
Warburton 2007 *Floor of mouth, tongue*	WW	DOI	-	1.00	1.00	0.875	0.875	0.75	0.5	-	0.375	-	-	-	-
Melchers 2012 *Tongue, gum, floor of mouth, cheek mucosa, retromolar area, other (oral)*	WW	DOI	1.00	-	-	0.857	-	-	0.714	-	-	0.714	0.714	0.571	0.571
	ND	DOI	1.00	-	-	0.944	-	-	0.889	-	-	0.833	0.833	0.722	0.667

Sahoo 2020 *Gingivobuccal sulcus, tongue, floor of mouth, retromolar area, maxilla*	ND	DOI	-	-	-	-	-	-	-	-	-	-	-	-	-
		TT	-	-	-	-	-	-	-	-	-	-	-	-	-
Van Lanschot 2020 *Tongue, Floor of mouth, buccal mucosa, lower and upper alveolus and gingiva, lip, retromolar area, hard palate*	ND/WW*	DOI	1.00	-	-	1.00	-	-	0.951		-	0.951	-	0.878	0.805
Yeh 2014 *Oral*	ND/WW*	TT	-	-	-	-	-	-	-	-	-	-	-	-	0.545
Zhang 2014 *Tongue*	ND/WW*	DOI	-	-	-	1.00	-	-	0.929	-	-	0.786		0.643	-

Den Toom 2019 *Tongue, floor of mouth, buccal mucosa, inferior alveolar process, other (oral)*	SLNB+follow-up**	DOI	0.97	-	-	0.89	-	-	0.83	0.83	-	0.70	-	0.50	0.34
Goerkem 2010 *Tongue, floor of mouth*	SLNB	DOI	0.964	-	-	0.929	-	-	0.857	-	-	0.643	-	0.607	0.464
		TT	1.00	-	-	1.00	-	-	0.964	-	-	0.786	-	0.679	0.536

DOI: Depth of invasion
mm: millimeter(s)
ND: Neck dissection
SLNB: Sentinel lymph node biopsy
TT: Tumor thickness
WW: Watch and wait
*: ND and WW were not separately distinguishable from the reported results
**: When a regional metastasis developed during follow-up after a negative SLNB, the negative SLNB wa

Table 5 Summary of negative predictive values for the prediction of lymph node metastasis using several reference standards at specific cut-off points of tumor thickness or depth of invasion

Author, year, tumor sites	Reference strategy	TT / DOI	Negative predictive value at specific cut-off points												
			1 mm	1.5 mm	1.6 mm	2 mm	2.2 mm	2.7 mm	3 mm	3.8 mm	4 mm	4.59 mm	5 mm	6 mm	7 mm
Warburton 2007 *Floor of mouth, tongue*	WW	TT	-	1.00	1.00	0.933	0.938	0.889	0.818	0.783	-	-	-	-	-

Study	Type	Metric													
Melchers 2012 *Tongue, gum, floor of mouth, cheek mucosa, retromolar are, other (oral)*	WW	DOI	1.00	-	-	0.857	-	-	0.889	-	0.923	0.923	0.889	0.897	0.906
	ND	DOI	1.00	-	-	0.938	-	-	0.939	-	0.943	0.948	0.918	0.915	0.889
Van Lanschot 2020 *Tongue, Floor of mouth, buccal mucosa, lower and upper alveolus and gingiva, lip, retromolar area, hard palate*	ND/WW*	DOI	1.00	-	-	1.00	-	-	0.978	-	0.986	-	0.971	0.958	-
Yeh 2014 *Oral*	ND/WW*	TT	-	-	-	-	-	-	-	-	-	-	-	0.815	-
Goerkem 2010 *Tongue, floor of mouth*	SLNB	DOI	0.75	-	-	0.75	-	-	0.667	-	0.615	-	0.607	0.464	-
		TT	1.00	-	-	1.00	-	-	0.80	-	0.625	-	0.625	0.649	-

DOI: Depth of invasion
mm: millimeter(s)
ND: Neck dissection
SLNB: Sentinel lymph node biopsy
TT: Tumor thickness
WW: Watch and wait
*: ND and WW were not separately distinguishable from the reported results

<u>Level of evidence of the literature</u>
The level of evidence regarding the outcome measure risk of lymph node metastases was downgraded by two levels because of study limitations (1 levels for risk of bias: confounders were not predefined, but models were developed based on significance as predictors in the model); imprecision (1 level for imprecision: wide confidence intervals); publication bias was not assessed.

The level of evidence regarding the outcome measure sensitivity was downgraded by one level because of study limitations (1 level for risk of bias: unclear whether there were inappropriate exclusions in most studies, and in some studies not every patient received the same reference standard); not downgraded for conflicting results (already downgraded for risk of bias: different reference tests used within one group may explain some heterogeneity); Not downgraded for overall number of included patients (There is imprecision due to a very low number of included patients (n=27) at: 1.5mm/ 1.6mm/ 2.2 mm/ 2.7 mm/ 3.8 mm); publication bias was not assessed.

The level of evidence regarding the outcome measure negative predictive value was downgraded by 1 level because of study limitations (1 level for risk of bias: unclear whether there were inappropriate exclusions in most studies, and in some studies not every patient received the same reference standard); conflicting results (already downgraded for risk of bias: different reference tests used within one group may explain some heterogeneity); number of included patients (There is imprecision due to a very low number of included patients (n=27) at: 1.5mm / 1.6mm / 2.2 mm / 2.7 mm / 3.8 mm); publication bias.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:
What is the risk of lymph node metastases, sensitivity, and negative predictive value per millimeter tumor depth of invasion (or tumor thickness) of the primary tumor for a sentinel lymph node biopsy, an elective neck dissection, or a watch and wait strategy in patients with cT1-2N0 oral cavity carcinomas?

P: patients with a cT1-2N0 oral cavity carcinoma;
I/R: watch and wait, sentinel lymph node biopsy or elective neck dissection;
C: -;
O: risk of lymph node metastases (radiologically or pathologically confirmed), sensitivity, and negative predictive value per millimeter depth of invasion (or tumor thickness) of the primary tumor.

<u>Relevant outcome measures</u>
The guideline development group considered sensitivity and negative predictive value as a critical outcome

measure for decision making; and the risk of lymph node metastases as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for lymph node metastases risk or odds ratios.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until September 23rd,2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 612 hits.

Studies reporting the risk of lymph node metastases to the neck were selected based on the following criteria: patients had a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy/ elective neck dissection/ watch and wait was performed, at least one outcome of interest was reported at a specific cut-off (millimeter), and a multivariable model was used to estimate adjusted risk/odds ratios.

Studies reporting the accuracy (sensitivity/negative predictive value) were selected based on the following criteria: patients had a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy / elective neck dissection/ watch and wait was performed, and at least one outcome of interest was reported at a specific cut-off (millimeter).

Seventy-one studies were initially selected based on title and abstract screening. After reading the full text, 60 studies were excluded (see the table with reasons for exclusion under the tab Methods) and 11 studies were included.

Results
Eleven studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Beleid (negatieve hals)

Uitgangsvraag

Wat is het beleid bij patiënten met een mondholtecarcinoom en een klinisch negatieve hals?

Aanbeveling

Aanbeveling-1
Verricht bij patiënten met een kleine mondholtecarcinoom (cT1-T2) en een klinisch negatieve hals (cN0) bij voorkeur een electieve halsklierdissectie in plaats van een "watch-and-wait" beleid.

Aanbeveling-2
Neem specifieke tumor- en patiëntfactoren mee bij de keuze voor een "watch-and-wait" beleid.

Aanbeveling 3
Gebruik bij een "watch-and-wait" beleid bij voorkeur echografie voor het opvolgen van de hals.

Overwegingen

Uit de meta-analyse van Ibrahim (2020) bleek dat er een significant voordeel was voor een electieve halsklierdissectie op de terugkeer van halskliermetastasen in vergelijking met een 'watch and wait' strategie (RR = 0.36, 95%CI: 0.20 tot 0.66). De zekerheid in dit bewijs was laag, aangezien Massey (2019) het risico op vertekening van de uitkomst in de studies in de meta-analyse beoordeelde als redelijk tot hoog. Twee beoordelaars gaven onafhankelijk van elkaar deze beoordeling met de Cochrane risk of bias-tool, maar er werden geen beoordelingsredenen en individuele beoordelingen op de domeinen van de Cochrane tool gerapporteerd.

In de originele rapportages van de RCT's werden verschillende maten van overleving gerapporteerd. De zekerheid van dit bewijs hing af van welk type overleving er werd gerapporteerd. Algehele overleving is een hardere maat dan ziektevrije overleving, waardoor een eventueel gebrek aan blindering minder risico op vertekening geeft. Daarnaast was er sprake van enige imprecisie door betrouwbaarheidsintervallen die een vooraf gedefinieerde grens van klinische besluitvorming overschreed of wanneer er zeer weinig patiënten in de steekproef zaten (per uitkomstmaat). Er werd een zeer lage (ziekte-specifieke overleving) tot lage (algehele overleving, ziektevrije overleving) zekerheid gevonden in het bewijs met betrekking tot overleving, hoewel de gevonden data een betere overleving lijkt te suggereren (al dan niet significant) bij een electieve halsklierdissectie wanneer vergeleken met een 'watch and wait' strategie.

Twee gerandomiseerde onderzoeken rapporteerden de sterfte (Kligerman, 1994; D'Cruz, 2015). Aan de hand van de gerapporteerde data uit Klingerman (1994) werd een relatief risico van 0,45 (95%BHI: 0,21 tot 0,97) berekend en met de data uit D'Cruz (2015) werd een relatief risico van 0,66 (95%BHI: 0.48-0.90) bepaald. Massey (2019) beoordeelde het risico op vertekening in deze studies als hoog. Daarnaast kruisten de gevonden betrouwbaarheidsintervallen de vooraf gedefinieerde grens van klinische besluitvorming. Het bewijs lijkt daarmee te suggereren dat er mogelijk een lagere mortaliteit zou kunnen zijn bij het uitvoeren van een electieve halsklierdissectie in plaats van een 'watch and wait' beleid.

Belangrijk bij het beoordelen van de verschillende studies is ook hoe de klinisch negatieve hals is vastgesteld. Is dit alleen door palpatie gedaan of met uitgebreid beeldvormend onderzoek inclusief echogeleide cytologische puncties van echografisch afwijkende lymfeklieren. Zo is de incidentie van lymfekliermetastasen in de 'watch and wait' arm in de studie van D'Cruz et al bijvoorbeeld 45%, terwijl 25 tot 30% na echogeleide cytologische puncties gebruikelijk is. Daarbij is het bij de 'watch and wait' strategie belangrijk om zo spoedig mogelijk de lymfekliermetastase tijdens de follow-up te detecteren. In de studie van D'Cruz et al waren de lymfekliermetastasen die tijdens follow-up gedetecteerd werden in 28% > 3cm en 18% > 6 cm en hadden 93% extranodale groei. Hierdoor kunnen bij de stringente follow-up die nodig is voor een goede 'watch and wait' strategie vraagtekens gezet worden in deze studie.

Het doel bij het kiezen voor een manier van management van de klinisch negatieve hals (cN0) is het bereiken van een lange (ziektevrije) overleving. Daarnaast zal vooral voor patiënten de kwaliteit van leven en functie na behandeling een grote rol spelen. Een voordeel van het uitvoeren van een halsklierdissectie is dat eventuele occulte metastasen verwijderd zijn. Het nadeel van het uitvoeren van een halsklierdissectie is de morbiditeit die hierbij een rol kan spelen, zoals bijvoorbeeld schouderklachten en lymfoedeem. Bij een "watch-and-wait" beleid speelt het voordeel dat er geen operatie nodig is met bijkomende risico's en bijwerkingen. Echter zoals reeds beschreven is de mortaliteit mogelijk hoger bij een "watch-and-wait" beleid omdat er een risico genomen wordt met het wachten op het ontstaan van een metastase. Bij ernstige co-morbiditeit van patiënten waarbij bijvoorbeeld een algehele narcose als risico niet opweegt tegen een "watch-and-wait" beleid of wanneer persoonlijke voorkeur van patiënt om bijvoorbeeld functionele redenen (muzikanten, mensen werkzaam in de bouw) uitgaat naar "watch-and-wait" kunnen hierin andere beslissingen genomen worden. Wanneer gekozen wordt voor een "watch and wait" beleid lijkt met een protocol met echogeleide cytologische puncties de overleving vergelijkbaar te zijn met een beleid met electieve halsklierdissectie, maar moeten de patiënten met lymfkliermetastasen uitgebreider behandeld (b.v. gemodificeerd radicale halsklierdissectie in plaats van selectieve halsklierdissectie en vaker adjuvante radiotherapie) te worden dan wanneer een electieve halsklierdissectie was verricht.

Uit de literatuur blijkt dat het uitvoeren van een halsklierdissectie een financieel voordeel oplevert ten opzichte van een "watch-and-wait" beleid. (Avecedo, 2016) Echter in de in Nederland uitgevoerde studie van Govers (2013) blijkt dat een "watch-and-wait" beleid en het uitvoeren van een schildwachtklier procedure kosteneffectiever zijn dan het uitvoeren van een electieve halsklierdissectie. De keuze om bij subgroepen zoals eerder genoemd te kiezen voor een "watch-and-wait" beleid zullen in Nederland niet op financiële gronden genomen worden. Het toevoegen van een schildwachtklierprocedure aan de diagnostische fase zou de kosten verder kunnen reduceren.

Een electieve halsklierdissectie of een "watch-and-wait" beleid voor een negatieve hals (cN0) horen reeds bij de standaard mogelijkheden van diagnostiek en behandeling van mondholtecarcinomen. Dit is beschikbaar in alle hoofd-halscentra en voor alle patiënten. Voor beide keuzes spreekt het voor zich dat het belangrijk is dat er behandelaars met voldoende ervaring betrokken zijn bij de behandeling (hoofd-halschirurg en radioloog). Er worden geen problemen verwacht in de aanvaardbaarheid, haalbaarheid en implementatie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Aanbeveling-1
Voor een klinisch negatieve hals (cN0) bij kleine plaveiselcelcarcinomen van de mondholte na beeldvorming ter stadiëring zijn er meerdere wegen om hiermee om te gaan. Twee hiervan zijn: 1) electieve halsklierdissectie, 2) "watch-and-wait" beleid. De electieve halsklierdissectie lijkt hierbij de voorkeur te hebben ten opzichte van een "watch-and-wait" in verband met de betere overleving en minder regionale recidieven. Wanneer er toch gekozen wordt voor een "watch-and-wait" beleid wordt dit bij voorkeur gedaan met regelmatige echografische controle van de hals.

Aanbeveling-2
Bij ernstige co-morbiditeit van patiënten waarbij bijvoorbeeld een algehele narcose als risico niet opweegt tegen een "watch-and-wait" beleid of wanneer persoonlijke voorkeur van patiënt om bijvoorbeeld functionele redenen uitgaat naar "watch-and-wait" kunnen hierin andere beslissingen genomen worden.

Aanbeveling 3
De electieve halsklierdissectie lijkt de voorkeur te hebben ten opzichte van een "watch-and-wait" in verband met de betere overleving en minder regionale recidieven. Wanneer er toch gekozen wordt voor een "watch-and-wait" beleid wordt dit bij voorkeur gedaan met regelmatige echografische controle van de hals. In een protocol met echogeleide cytologische puncties lijkt de overleving vergelijkbaar te zijn met een beleid met electieve halsklierdissectie, maar moeten de patiënten met lymfkliermetastasen uitgebreider behandeld (bijvoorbeeld gemodificeerd radicale halsklierdissectie in plaats van selectieve halsklierdissectie en vaker adjuvante radiotherapie) te worden dan wanneer een electieve halsklierdissectie was verricht.

Onderbouwing

Achtergrond

Plaveiselcelcarcinomen van de mondholte metastaseren primair lymfogeen naar de lymfeklieren van de hals. Aangetoonde metastasen worden doorgaans behandeld met een halsklierdissectie. Voor kleine mondholtetumoren (T1 en T2) die klinisch en radiologisch een negatieve hals laten zien (cN0) en waarbij de hals niet geopend hoeft te worden voor resectie van de primaire tumor of reconstructie van het defect zijn verschillende strategieën mogelijk aangaande behandeling van de hals. Er is bekend dat 30% van deze patiënten occulte metastasen heeft. Er kan gekozen worden voor een electieve halsklierdissectie dan wel voor "watch-and-wait" strategie waarbij de hals wordt opgevolgd bijvoorbeeld met echografische controle en pas behandeld wordt bij een manifeste metastase. Elke strategie heeft zijn eigen voor- en nadelen. Bij een electieve halsklierdissectie worden occulte metastasen direct verwijderd. In geval van grote chirurgische ingrepen zoals commando-procedures met of zonder reconstructies, wordt ongeacht de stadiering van de hals meestal een halsklierdissectie uitgevoerd vanwege de noodzakelijke chirurgische benadering. Bij een "watch-and-wait" strategie ondergaan minder patiënten een behandeling van de hals, maar bestaat het risico dat door de verlate diagnose van eventuele lymfekliermetastasen de behandeling uitgebreider moet zijn dan bij een electieve halsklierdissectie (bijvoorbeeld een gemodificeerd radicale halsklierdissectie met opoffen van structuren in de hals (bijvoorbeeld vena jugularis interna, nervus accessorius en/of musculus sternocleidomastoideus). Ook kan een niet-juiste stadiering van de hals leiden tot het niet uitvoeren van een (selectieve) halsklierdissectie of adjuvante radiotherapie of zelfs dat de metastasen door de delay van het

ontdekken inoperabele ziekte zou kunnen ontstaan. Verder moet een afweging moet gemaakt worden op basis van onder andere morbiditeit van een halsklierdissectie, verwijderen van een vangnet voor metastasen van een recidief of tweede primaire tumoren, gebruik van (schaarse) middelen en kosten.

Conclusies

LOW GRADE	The evidence suggests that elective neck dissection may reduce the number of neck recurrences in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Ibrahim, 2020 (meta-analysis of: Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015)*

LOW GRADE	The evidence suggests that elective neck dissection may improve the overall survival in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (D'Cruz, 2015)*

LOW GRADE	The evidence suggests that elective neck dissection may improve the disease-free survival in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Fakih, 1989; Kligerman, 1994; D'Cruz, 2015)*

VERY LOW GRADE	The evidence is very uncertain about the effects of elective neck dissection on disease-specific survival in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Yuen, 2009)*

LOW GRADE	The evidence suggests that elective neck dissection may reduce the mortality in patients with an oral cavity carcinoma and a clinically negative neck, when compared to a watch and wait strategy. *Sources: (Kligerman, 1994; D'Cruz, 2015)*

Samenvatting literatuur

Description of studies
Ibrahim (2020) performed a systematic review and included 24 articles, of which 4 were RCTs (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015). An exact search date was not provided and it was unclear how keywords were combined in the search. Excluded studies in the full-text selection phase were not described

or referenced and reasons for excluding literature were not provided. Data was extracted by two authors independently and was cross-checked. The authors did not perform a risk of bias appraisal of the included studies. Potential publication bias was assessed and the authors reported that there was no evidence of publication bias.

Massey (2019) included the same four RCTs. An exact search date was not provided, however it was reported that databases were searched from inception to June 2018. It was unclear how the key words were combined in the search. Excluded studies in the full-text selection phase were not described, however reasons for exclusion were provided in the flow-diagram describing the study selection. Some studies containing overlapping datasets were referenced and excluded in some analyses. Three authors extracted data independently which were checked for consistency. Two authors independently assessed the risk of bias of RCTs by using the Cochrane risk of bias tool. Discrepancies in data-extraction and risk of bias assessments were resolved by consensus. Massey (2019) also included one RCT that recruited patients with T3 disease, which was excluded for the current data-analysis. The authors assessed the potential for publication bias and reported that no publication bias was detected.

Study and/or sample characteristics reported by Ibrahim (2020) and Massey (2019) are summarized in Table 1. Other data about potentially important prognostic factors in the sample (such as depth of invasion, perineural invasion, extracapsular spread) was not reported in the systematic reviews. Data about the watch and wait procedures were extracted from the original RCT papers, separately from the systematic reviews.

Table 1 Summary of study and sample characteristics as reported in Ibrahim (2020) and/or Massey (2019). Data from the watch and wait strategy was extracted from the original papers (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015)

Author, year	Country	Sample size	Tumor location	Pre-operative staging method	Type of neck dissection	Type of watch and wait strategy*	Adjuvant therapy
Fakih 1989	India	END: 30 WW: 40	Tongue	Not reported	Radical neck dissection	**Strategy:** Therapeutic neck dissection **Regime:** Patients were seen regularly	Postoperative radiotherapy for positive resection margin and extracapsular spread
Kligerman 1994	Brazil	END: 34 WW: 33	Tongue, floor of mouth	Not reported	Supraomohyoid neck dissection	**Strategy:** Primary resection alone **Regime:** Not reported	Postoperative radiotherapy for pathologically positive lymph nodes

Yuen 2009	China	END: 36 WW: 35	Tongue	Ultrasound and ultrasound-guided fine needle aspirate cytology	Supraomohyoid neck dissection	**Strategy:** Observation (after transoral glossectomy) **Regime:** Every month in the first year, every two months in the second year, every 3 months in the third year, every 4 months in the fourth and fifth year. Every 6 months thereafter. Ultrasound examination was performed every three months in the first three years.	Postoperative radiotherapy for pathologically positive lymph nodes
D'Cruz 2015	India	END: 243 WW: 253	Tongue, floor of mouth, buccal mucosa	Physical examination and ultrasound	Supraomohyoid neck dissection	**Strategy:** Therapeutic neck dissection **Regime:** Every 4 weeks in the first 6 months, every 6 weeks for the next 6 months, every 8 weeks for the next 12 months, and thereafter every 12 weeks	Postoperative radiotherapy for pathologically positive lymph nodes, positive resection margins, and >10mm depth of invasion
*Extracted from the original RCT papers **END: Elective Neck dissection** **WW: Watch and Wait**							

Results

Neck recurrence

Ibrahim (2020) pooled data on neck recurrence from the four included RCTs which compared an elective neck dissection (45 events from n=343) to a watch and wait management (158 events from n=361). A pooled relative risk of 0.36 was found (95%CI: 0.20-0.66, random effects, I^2 = 69.24%), favoring an elective neck dissection. For the pooled risk difference, a fixed methods meta-analyses by Ibrahim (2020) found a difference of -0.302 (95%CI: -0.364 to -0.240, I^2 = 0%), favoring an elective neck dissection. A fixed-effects meta-analysis of risk differences by Ibrahim (2020) found a pooled risk difference of -0.302 (95%CI: -0.364 to -0.240, I^2 = 0.0%), favoring elective neck dissection.

Survival

Four randomized controlled trials reported several survival outcomes at different time-points (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015). Data is summarized in Table 2.

Table 2 Overview of survival outcomes

Variable	Author, year	Follow-up	Sample size	Survival
Overall survival	*D'Cruz 2015*	3 years	END: 243 WW: 253	END: 80% WW: 67.5% HR = 0.64 (95%CI: 0.45-0.92), p=0.01
Disease-free survival	*Fakih 1989*	Minimum of 12 months (median: 20 months)	END: 30 WW: 40	END: 63% WW: 52% Not significant (p-value not reported)
	Kligerman 1994	3 years	END: 34 WW: 33	END: 72% WW: 49% P=0.04
	D'Cruz 2015	3 years	END: 243 WW: 253	END: 69.5% WW: 45.9% HR = 0.45 (0.34-0.59), p<0.001
Disease-specific survival	*Yuen 2009*	5 years	END: 36 WW: 35	END: 89% WW: 87% P=0.89 (log rank test)

Mortality

Klingerman (1994) reported 7 deaths (7/34, 20.6%) in the elective neck dissection group (n=4 death related to the disease, n=2 death due to new primary tumor, n=1 unknown cause) and 15 deaths (15/33, 45.5%) in the observation group (n=14 disease related deaths (of which 2 brain and pleural metastases), n=1 heart failure) over the course of 3 years. From this data we calculated a relative risk of 0.45 (95%CI: 0.21-0.97), favoring an elective neck dissection.

D'Cruz (2015) reported 50 deaths in the elective neck dissection group (50/243, 20.6%) and 79 deaths in the observation group (79/253, 31.2%) over the course of the study (median follow-up: 39 months, IQR: 16-76). From the reported data, a relative risk of 0.66 (95%CI: 0.48-0.90) was calculated, favoring elective neck dissection.

<u>Level of evidence of the literature</u>

The level of evidence regarding the outcome measure neck recurrence was downgraded by 2 levels because of study limitations (2 level for risk of bias: Massey (2019) indicated that two RCTs had a moderate risk of bias and two RCTs had a high risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 4 RCTs which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure overall survival was downgraded by 1 level because of study limitations (1 level for risk of bias: Massey (2019) indicated that the RCT had a high risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool, however blinding is one of the domains in the tool which probably had a high risk of bias considering the 4 RCTs did not report any procedures regarding blinding. Blinding does not affect a hard outcome such as overall survival, and therefore we only subtracted 1 level); number of included patients (1 level for imprecision: event calculator revealed that for HR= 0.64 about 158 events were needed (alpha=0.05, beta=0.2, q1=0.49, q0=0.51, relative hazard = 0.64), over the course of the whole study 129 events were reported; furthermore the confidence interval crossed the pre-defined border of 0.7); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 1 RCTs which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure disease-free survival was downgraded by 2 levels because of study limitations (2 level for risk of bias: Massey (2019) indicated that one RCT had a moderate risk of bias and 2 RCTs had a high risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool); conflicting results (inconsistency); applicability (bias due to indirectness); we did not downgrade for number of included patients (imprecision, because: event calculator revealed that for HR= 0.45 about 49 events were needed (alpha=0.05, beta=0.2, q1=0.49, q0=0.51, relative hazard = 0.45), furthermore the confidence interval of the largest RCT did not cross the pre-defined border of 0.7); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 3 RCTs which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure disease-specific survival was downgraded by 2 levels because of study limitations (2 level for risk of bias: Massey (2019) indicated that the RCT had a moderate risk of bias. However, the authors did not provide reasons or appraisals on the individual domains of the risk of bias tool); number of included patients (2 levels for imprecision: the study only contained a sample of n=71); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 1 RCT which is not enough to reliably assess publication bias).

The level of evidence regarding the outcome measure mortality was downgraded by 2 levels because of study limitations (1 level for risk of bias: Massey (2019) indicated that the two RCTs had a high risk of bias. The authors did not provide reasons or appraisals on the individual domains of the risk of bias tool, however

blinding is one of the domains in the tool which probably had a high risk of bias considering the 4 RCTs did not report any procedures regarding blinding. Blinding does not affect a hard outcome such as mortality, and therefore we only subtracted 1 level); number of included patients (1 level for imprecision: Confidence intervals cross the pre-defined border of 0.75); publication bias was not assessed (although publication bias was assessed by the authors of both systematic reviews by using both randomized and non-randomized studies together (Ibrahim, 2020; Massey, 2019), we included 2 RCTs which is not enough to reliably assess publication bias).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of elective neck dissection on neck recurrence, survival, and mortality compared to an observation strategy in patients with cT1-2N0 oral cavity carcinomas?

P: patients with a resected primary cT1-2N0 oral cavity carcinoma;
I: Elective neck dissection;
C: watchful waiting;
O: neck recurrence, overall survival, disease-free survival, disease-specific survival, mortality.

Relevant outcome measures
The guideline development group considered neck recurrence and overall survival as a critical outcome measure for decision making; and disease-free survival, disease-specific survival, and mortality as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.
The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) and HR< 0.7 in overall survival.
- A difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Statistically significant less complications/adverse events.
- Statistically significant better functional outcomes, work participation.

Search and select (Methods)
The working group identified two published systematic reviews that included studies comparing elective neck dissection to watchful waiting (Ibrahim, 2020; Massey, 2019).

The combined reporting of both systematic reviews was used and only data from randomized studies were considered, even though both systematic reviews included observational studies.

Ibrahim (2020) searched Medline, Google Scholar and Scopus for relevant studies published from 1989 up to

2018. Keywords used in the search were reported in the published manuscript (Ibrahim, 2020). Studies were selected when published in English, patients had pathologically proven T1-2N0M0 oral squamous cell carcinoma (oral tongue, buccal mucosa, hard palate, alveolar ridge, floor of mouth, retromolar trigone), patients had a clinically and radiologically negative neck, patients only received surgical treatment without previous neck radiotherapy, and when elective neck dissection was compared to watchful waiting. Exclusion criteria were not reported. Over 1200 studies were identified by Ibrahim (2020) and, finally, 24 studies were selected (including 4 randomized studies).

Massey (2019) searched Medline, Google Scholar, and Scopus up to June 2018. Keywords used in the search were reported in the published manuscript (Massey, 2019). The reference lists of systematic reviews and meta-analyses deemed relevant were hand-searched. Two authors independently screened articles. Potentially relevant articles were assessed in detail by the two reviewers independently. Studies were selected when patients had T1-2N0M0 (clinical negative nodes) squamous cell carcinoma of the oral cavity with a verification of diagnosis, when the sample size was 30 or more, the oral cavity was defined in accordance with the AJCC or UICC, the TNM staging (AJCC or UICC) was used, patients did not have prior head and neck treatment (surgery, radiotherapy, chemotherapy), occult lymph node metastasis was clearly defined (as: the presence of a metastasis in the sampled lymph node of a clinically disease-free neck at elective neck dissection), and the techniques of neck dissection were well defined (as: a neck dissection in a patient without clinically detectable disease). Studies were excluded when cancers of the oral cavity were non-squamous cell, the primary tumor site was outside the oral cavity, patients had signs of clinical nodal disease, or when the study focused on laboratory application. Massey (2019) found 1840 search hits, eventually leading to the inclusion of 39 studies (including 5 randomized studies).

Results
Two systematic reviews (Ibrahim, 2020; Massey, 2019) were used to identify relevant randomized trials to be included in the analysis of the literature. Both systematic reviews included the same four randomized studies (Fakih, 1989; Kligerman, 1994; Yuen, 2009; D'Cruz, 2015). Massey (2019) included one additional randomized study, published in 1980, which included patients with T3 carcinomas. Ibrahim (2020) did not include that study because of their search period (from 1989 up to 2018). Due to the inclusion of T3 disease in the study's sample (21% in the elective neck dissection group; 6% in the therapeutic neck dissection group), it was decided not to consider the study in the current analysis of literature (Vandenbrouck, 1980). Important study characteristics and results are summarized in the evidence tables from the combined reporting of the two systematic reviews. The assessment of the risk of bias of the systematic reviews is summarized in the risk of bias tables. The risk of bias assessment for the individual randomized studies as reported by Massey (2019) was used for the GRADEing of outcomes.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Chirurgische interventie (negatieve hals)

Uitgangsvraag

Welke chirurgische interventie dient uitgevoerd te worden bij patiënten met een mondholtecarcinoom en een klinisch negatieve hals?

Aanbeveling

Verricht bij patiënten met een klein mondholtecarcinoom en een klinisch en/of bij beeldvorming negatieve hals een schildwachtklierprocedure of een electieve halsklierdissectie.

Overwegingen

De zekerheid in het bewijs uit de geïncludeerde gerandomiseerde trials was laag tot zeer laag voor de gerapporteerde uitkomstmaten. Procedures met betrekking tot de randomisatie werden niet (voldoende) beschreven. Daarnaast vonden blindering niet plaats, wat als risico heeft dat de 'zachtere' uitkomsten kunnen vertekenen in tegenstelling tot 'harde' uitkomstmaten zoals algehele overleving. Garrel (2020) stelde in het studieprotocol dat de kwaliteit van leven gemeten zou worden met de H&N35, QLQ-C30, SF-36 en EuroQoL EQ-5D, maar rapporteerde hierover geen resultaten in de geïncludeerde studierapportage. De geïncludeerde gerandomiseerde studies in de literatuuranalyse rapporteerden daarnaast geen data over de kosten en het ontstaan van hematomen en postoperatieve oedeemvorming.

In een systematische review van Crocetta (2020) over schildwachtklierprocedures versus halsklierdissecties werden géén gerandomiseerde onderzoeken gevonden tot 30 april 2019. In de geïncludeerde niet-gerandomiseerde onderzoeken werden geen significante verschillen gevonden op de volgende uitkomstmaten: recidief van lymfekliermetastasen in de hals, ziekte-specifieke overleving, algehele overleving, kwaliteit van leven (behalve op één sub-schaal uit één studie: kwaliteit van leven op de sub-schaal 'swallowing' was significant lager voor de electieve halsklierdissectie-groep), pijn, en postoperatief oedeemvorming. Eén studie, geïncludeerd door Crocetta (2020), observeerde dat er proportioneel meer mensen die een schilwachtklierprocedure ondergingen pijn ervaarden dan mensen die een halsklierdissectie ondergingen, maar dit verschil was niet statistisch significant. Voor de schouderfunctie werd gezien dat, indien gerapporteerd, groepen die de schildwachtklierprocedure ondergingen een statistisch significant betere schouderfunctie hadden zoals gemeten met de Constant-Murley score. Eén studie, opgenomen in de systematische review van Crocetta (2020), rapporteerde de schouderbeperkingen zoals gemeten met de Shoulder Disability Questionnaire. Hier leek het wellicht dat mensen die een schildwachtklierprocedure ondergingen minder beperkingen ervaarden, maar er werd geen statistisch significant verschil tussen de groepen geobserveerd. Twee studies in Crocetta (2020) rapporteerden over het ontstaan van bloedingen. Er werd door één studie geen statistisch significant verschil gevonden in het aantal bloedingen die revisie chirurgie noodzakelijk maakten (schildwachtklierprocedure: 0/33, 0%; halsklierdissectie: 5/29, 17.2%; OR=0,067, 95%BHI: 0,004-1,260 (+0,5 in alle cellen in verband met nul-waarde)), terwijl in de andere studie een significant verschil in het vóórkomen van hematomen werd gezien aan de hand van de Fischer's Exact test (schildwachtklierprocedure: 0/29, 0%; halsklierdissectie: 6/41, 14.6%; OR=0,093, 95%BHI: 0,005 tot 1,712 (+0,5 in alle cellen in verband met nul-waarde)). Beide studies zagen minder events in de groep die de schilwachtklierprocedure ontving ten opzichte van aanvullende halsklierdissectie of electieve

halsklierdissectie. De zekerheid in dit bewijs is waarschijnlijk laag tot zeer laag door de observationele aard van de studies. De auteurs van de systematische review rapporteerden voor 4 van de 5 geïncludeerde studies een hoog risico op vertekening doordat de groepen van elkaar verschilden op mogelijke confounders (door middel van de Newcastle-Ottawa Scale). De auteurs concludeerden dat er tot op het moment van zoeken een gebrek was aan gerandomiseerd bewijs. Zij waren van mening dat hun resultaten suggereerden dat er geen significante verschillen zijn tussen een beleid van de hals gebaseerd op de schildwachtklierprocedure en electieve halsklierdissectie op totale overleving, ziektevrije overleving en op het recidief van halskliermetastasen, maar dat de zekerheid in het geïncludeerde bewijs te laag is voor klinische besluitvorming.

Sundaram (2019) voerde een gerandomiseerde trial uit in India om de effecten van een schildwachtklierprocedure te vergelijken met electieve halsklierdissectie. Procedures rondom de randomisatie (bijvoorbeeld de blok-grootte, random sequence generation) werden niet of onvoldoende gerapporteerd. De studie werd geëxcludeerd uit de literatuuranalyse omdat er patiënten met cT3 tumoren werden geïncludeerd en omdat de enige relevante uitkomst als composiet werd gerapporteerd (nodal én distant metastases in de follow-up). Recidief in de halsklier kon niet afzonderlijk worden geanalyseerd. De auteurs rapporteerden drie recidieven in de halsklierdissectie-groep (3/30, 10%) tegenover één recidief in de schildwachtklierprocedure-groep (1/28, 3.6%). Hiermee is het volgende relatieve risico te berekenen: RR = 0.36 (95%BHI: 0.04-3.24).

De schildwachtklierprocedure is echter niet voor alle mondholtecarcinomen even betrouwbaar. In een studie waarbij retrospectief een cohort patiënten met een vroeg stadium mondholtecarcinoom een schildwachtklierprocedure ondergingen (n=488) werd vergeleken werd met een cohort patiënten die electieve halsklierdissectie ondergingen (n=399), was voor de detectie van occulte lymfekliermetastasen de sensitiviteit bij mondbodemcarcinomen statistisch significant lager: 63% (SLNB) versus 92% (END, p = 0.006). De negatief voorspellende waarde was 90% versus 97% (p = 0.057). De sensitiviteit was bij mondbodemcarcinomen lager dan voor de overige lokalisaties in de mondholte: 63% versus 86% (p = 0.008) (den Toom, 2020). Omdat de oorzaak van de mindere betrouwbaarheid met name gelegen lijkt te zijn in (radioactieve) overstraling van de schildwachtklieren door de hoge activiteit op de nabijgelegen injectielocatie (waardoor deze niet meer separaat detecteerbaar zijn) wordt bij mondbodemcarcinomen een aanvullende dissectie van level I geadviseerd, totdat met nieuwe technieken deze schildwachtklieren beter geïdentificeerd kunnen worden. Zodoende kan bij mondbodemcarcinomen de schildwachtklierprocedure waarschijnlijk even betrouwbaar verricht worden als bij andere tumorlokalisaties in de mondholte (Stoeckli, 2016).

Voordeel van een beleid gebaseerd op de schildwachtklierprocedure is dat een aanzienlijk aantal achteraf onnodige halsklierdissecties worden voorkomen. Een nadeel is dat bij een positieve schildwachtklierprocedure een tweede operatie nodig is voor de halsklierdissectie, terwijl deze bij een electieve ingreep in één keer tegelijk met de resectie van de primaire tumor verricht kan worden.

Seferin (2021) rapporteerde een cross-sectioneel onderzoek waarin de kwaliteit van leven 26 maanden na de ingreep gemeten met de University of Washington Quality of Life Questionnaire. Patiënten met een T1-2N0 mondholtecarcinoom die tussen 2014 en 2015 een ingreep ondergingen (n=51) werden bevraagd, maar slechts een deel kon worden geïncludeerd (n=15 met schildwachtklierprocedure, n=9 met selectieve

halsklierdissectie). De auteurs concludeerden dat patiënten die een schildwachtklierprocedure ondergingen op langere termijn een betere kwaliteit van leven ervaarden, specifiek op het gebied van uiterlijk en kauwfunctie.

Flach (2016) interviewde patiënten met een negatieve schildwachtklierprocedure en patiënten met een positieve schildwachtklierprocedure gevolgd door een halsklierdissectie. De meeste van deze patiënten prefereerden een beleid van de klinisch negatieve hals met een schildwachtklierprocedure in plaats van een halsklierdissectie.

De individuele keuze dient door behandelend arts en patiënt gezamenlijk gemaakt te worden.

Govers (2013) toonde modelmatig aan dat de schildwachtklierprocedure kosteneffectief is in vergelijking met electieve halsklierdissectie. Van de Linden (2016) bevestigde dit later in ieder geval voor de korte en middellange termijn. Hoe beter de accuraatheid van de schildwachtklier is hoe kosten-effectiever deze is. Het is mogelijk dat bij een hogere incidentie van occulte lymfekliermetastasen de schildwachtklierprocedure niet meer kosteneffectief is. In de Franse zorg-context werd een kostenanalyse gerapporteerd door De Kerangal (2021) waar de schildwachtklierprocedure (n=94) met de selectieve halsklierdissectie (n=77) vergeleken werd bij patiënten met een T1-2cN0 mondholte tumoren die tussen 2012 en 2017 werden behandeld. De volgende kosten werden gebruikt bij de berekening van de kosten: kosten van de ziekenhuisopname voor de initiële operatie, kosten voor de verlate aangepaste radicale halsklierdissectie en kosten voor elke ziekenhuisopname door postoperatieve complicaties tot 60 dagen na de initiële operatie. Na multivariabele correctie werd geschat dat een schildwachtklierprocedure €9.564,- (95%BHI: 7.646-11.483) kostte, ten opzichte van €10.562,- (95%BHI: 8.985-12.138) voor een selectieve halsklierdissectie. Het gemiddelde verschil was niet statistisch significant.

De verrichtingen schildwachtklierprocedure en electieve halsklierdissectie zijn voor iedereen toegankelijk. Beide vormen van beleid (schildwachtklierprocedure en electieve halsklierdissectie) kunnen in alle hoofd-halscentra routinematig verricht worden nadat door het behandelend team enige ervaring hiermee is opgedaan. De faciliteiten zijn in alle centra aanwezig. Binnen elk centrum kan een afweging gemaakt worden welk beleid de voorkeur in het betreffende centrum heeft. Voorzichtigheid is geboden bij mondbodemcarcinomen aangezien daarbij de schildwachtklierprocedure minder betrouwbaar is. In geval van mondbodem carcinomen is het nog steeds mogelijk een schildwachtklierprocedure te doen, echter, vanwege overstraling naar de hals van de tracer vanuit de inspuitplaats in de mondbodem (shine through phenomenon) kan het identificeren van de schildwachtklier lastig blijken. Hierbij wordt in de literatuur een duidelijk lagere negatief voorspellende waarde gevonden dan voor andere mondholte locaties. Indien een schildwachtklierprocedure wordt overwogen dan is het mogelijk de lymfeklieren uit het deel van level I anterieur van de glandula submandibularis te verwijderen, zoals beschreven door Stoeckli (2016) als onderdeel van de schildwachtklierprocedure.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Een beleid op basis van de schildwachtklierprocedure heeft als voordeel dat er wellicht een aanzienlijk deel achteraf onnodige halsklierdissecties voorkómen zouden kunnen worden. Het nadeel van een schildwachtklierprocedure is dat er een tweede operatie noodzakelijk is als er een positieve schildwachtklier

gevonden wordt. Een electieve ingreep is daartegenover in één verrichting mogelijk, namelijk gezamenlijk met de resectie van de primaire tumor. De zekerheid in het gevonden wetenschappelijk bewijs was laag tot zeer laag en op enkele uitkomstmaten werd geen gerandomiseerde data gevonden. Binnen elk centrum kan er een afweging gemaakt worden welk beleid de voorkeur heeft.

Onderbouwing

Achtergrond

Plaveiselcelcarcinomen van de mondholte metastaseren primair lymfogeen naar lymfeklieren in de hals. In het geval van aantoonbare lymfekliermetastase(n) wordt de hals van de patiënt doorgaans behandeld met een halsklierdissectie. Bij een klinisch (en bij beeldvorming) negatieve hals (cN0) zijn er twee opties: een electieve (profylactische) halsklierdissectie om occulte (dat wil zeggen klinisch en bij beeldvorming niet te detecteren) metastasen te verwijderen of een "watchful waiting" beleid waarbij de hals pas behandeld wordt bij manifeste metastasering tijdens follow-up. Dit dilemma doet zich met name voor bij kleine mondholtecarcinomen waarbij de hals niet geopend hoeft te worden voor resectie van de primaire tumor of reconstructie van het chirurgisch defect in de mondholte. Van patiënten met een klinisch of bij beeldvorming negatieve hals is het bekend dat ongeveer 30% van de patiënten occulte metastasen heeft. Van oudsher bestaat bij deze patiënten dan ook het dilemma of er een electieve halsklierdissectie dient te worden uitgevoerd (overbehandeling bij 70% van de patiënten met hierbij behorende postoperatieve morbiditeit zoals mogelijk een gestoorde schouderfunctie) of dat kan worden volstaan met een afwachtend beleid (onderbehandeling bij 30% van de patiënten met het risico dat een occulte metastase zich zal ontwikkelen tot een grotere metastase met mogelijk uitgebreide en zelfs inoperabele ziekte tot gevolg). Het risico op het ten onrechte afzien van een behandeling van de hals kan verminderd worden door de diagnostiek voorafgaand aan behandeling te verbeteren. Daarnaast is het als onderdeel van de diagnostische work-up mogelijk om een schildwachtklierprocedure (sentinel node procedure) uit te voeren, wat als voordeel heeft dat er een histologische bevestiging van de oncologische klierstatus (N) van de hals komt. Het nadeel van een schildwachtklierprocedure is dat indien een metastase gevonden wordt in tweede instantie een halsklierdissectie moet worden uitgevoerd. De voorliggende vraag is, indien er gekozen wordt voor een stadierende ingreep voor de hals, is een schildwachtklierprocedure dan gelijkwaardig aan een electieve halsklierdissectie bij patiënten met een mondholtecarcinoom en een negatieve hals?

Conclusies

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on **neck recurrences** compared to elective neck dissection. *Sources: (Hasegawa, 2021; Garrel, 2020)*

LOW GRADE	The evidence is uncertain about the effects of a sentinel node biopsy on **disease-specific survival** compared to elective neck dissection and may not result in relevant differences between treatments.. *Sources: (Garrel, 2020)*

LOW GRADE	The evidence is uncertain about the effects of a sentinel node biopsy on **overall survival** compared to elective neck dissection and may not result in relevant differences between treatments. *Sources: (Hasegawa, 2021; Garrel, 2020)*

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on **shoulder morbidity** compared to elective neck dissection. *Sources: (Hasegawa, 2021; Garrel, 2020)*

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on the **quality of life** compared to elective neck dissection. *Sources: (Hasegawa, 2021)*

VERY LOW GRADE	The evidence is very uncertain about the effects of a sentinel node biopsy on **pain** compared to elective neck dissection. *Sources: (Hasegawa, 2021)*

- GRADE	The outcomes **occurrence of hematomas**, **postoperative oedema**, and c**osts** could not be assessed since none of the included studies reported these outcomes.

Samenvatting literatuur

Description of studies

Hasegawa (2021) performed a multi-center randomized trial in Japan to assess the hypothesized noninferiority of a sentinel lymph node biopsy (SLNB) compared to elective neck dissection (ND). The border of clinical relevance for noninferiority was set at 12% for the three-year overall survival of patients with an oral cavity squamous cell carcinoma. Patients were included when they had a T1-2N0M0 oral cavity squamous cell carcinoma (according to the TNM 7th ed.), when there were no lymph node metastases on contrast enhanced CT of the head and neck, when the patient did not receive prior treatment, and when the patient was 18 years or older. Patients with T1 tumors having ≤ 4mm depth of invasion were excluded, as well as patients with a recurrence after definitive treatment, history of radiation to the neck, had planned or were currently pregnant or lactating, or had other disqualifying reasons as judged by the attending physician. Patients were allocated to a treatment through a stratified randomization (T-stage: T1 versus T2, tumor site: tongue versus other). The clinical neck status of patients was examined by CT and supplemented with ultrasound when necessary. The study center could decide to use MRI and PET/CT additionally at their own discretion. Four patients were excluded after randomization (n=3 did not fulfill the eligibility criteria (n=1 ND, n=2 SLNB), n=1 declined treatment (SLNB)). Tumor resection was performed during surgery. For the group undergoing SLNB, the sentinel lymph node identification was performed with ^{99m}Tc phytate and was injected in the peritumoral

mucosa the day before surgery. A gamma probe was used to identify the sentinel node on the day of surgery. During surgery a frozen section analysis was performed on 2mm blocks. When the result was negative, the blocks were paraffin embedded for staining analysis on 4mm sections (hematoxylin and eosin, and cytokeratin). Isolated tumor cells were treated as metastasis-positive. Patients with positive sentinel nodes on frozen section immediately underwent neck dissection (level I-IV or I-V). If the resected specimen was positive in pathological analysis, the neck dissection was performed within 6 weeks of the initial surgery. When no metastasis was detected in the sentinel node and if the resection required a pull-through resection, a supraomohyoid neck dissection was performed. Patients with a negative sentinel node on the contralateral side of the neck received a sentinel node basin dissection. The group undergoing neck dissection received a supraomohyoid neck dissection. Patients with a positive resection margin received a reoperation or radiontherapy (with or without chemotherapy) at the discretion of the study center. Radiotherapy was initiated within 6 weeks when patients had extracapsular spread of the lymph node metastasis. Concomitant chemotherapy was left at the discretion of the study center. Patients were followed up to a median of 3.1 years. Patients in the SLNB-group (n=134, 66.4% males) had a median age of 63 years (range: 21 to 90) and tumors located at the tongue (n=109), floor of mouth (n=13), lower gingiva (n=7), or buccal mucosa (n=5). Tumor stage was either T1 (n=26) or T2 (n=108) with a pN status of pN- (n=86), pN+ (n=46), or pNx (n=4). Four patients received postoperative radiation and/or chemotherapy. The group undergoing elective ND (n=137, 65.7% males) had a mean age of 63 years (range: 28 to 85). The primary tumor was located at the tongue (n=114), floor of mouth (n=14), lower gingiva (n=6), or buccal mucosa (n=3). Patients had a T-stage of either T1 (n=25) or T2 (n=112). The pN status was either pN- (n=99), pN+ (n=34), or pNx (n=4). Three patients received postoperative radiation or chemotherapy.

Garrel (2020) performed a multi-center open-label randomized controlled trial in France to investigate the equivalence of sentinel lymph node biopsy to elective neck lymph node dissection. The border of equivalence was defined at a recurrence rate difference of 0.10 (H_{null}: SLNB-END ≥ 0.10; $H_{alternative}$: SLNB-END < 0.10). Eligible patients had to be older than 18 years with health insurance, signed an informed consent, were not participating in another trial, and had an operable T1-2N0M0 primary oral or oropharyngeal squamous cell carcinomas (diagnosed by biopsy with histopathologic analysis in the month prior to inclusion). Patients were excluded when they had treatment for other cancers, non-invasive tumors (high grade dysplasia, in situ carcinoma), inadequate tumor resection, contraindications (for sentinel lymph node biopsy, lymph node dissection, radiotherapy, medical imaging), allergy or intolerance to contrast product, pregnancy, refusal to accept full treatment, when follow-up was not possible or when follow-up was refused, when already treated for the tumor, when chemotherapy or immunotherapy was received in the prior 6 months, or when there was a history of neck surgery or radiotherapy. Preoperatively a contrast enhanced CT or MRI (when there were contraindications for CT) was performed to check for the clinically negative neck (cN0). All participants (n=307) received excision of the primary tumor. After randomization 28 participants were excluded (intervention: n=15, control: n=13) due to high grade dysplasia (n=2), carcinoma in situ (n=10), history of surgery for oral cavity carcinoma (n=1), history of radiotherapy for oropharyngeal carcinoma (n=1), R1 margin without completion (n=1), refusal of surgery (n=1), decision for radiotherapy (n=1), refusal of random allocation (n=4), withdrawal of consent (n=1), synchronous lung cancer (n=1), urgent carotid surgery (n=1), erroneous inclusion of T4 tumor (n=2), investigator decision (n=1), or neck dissection despite ITC1 only (n=1). Participants in the intervention group received treatment with sentinel lymph node biopsy and neck dissection in case of positive sentinel lymph nodes (SLNB-group, n= 140 after exclusions). Preoperative

sentinel lymph node identification was performed with radiotracer injections and lymphoscintigraphy. A portable gamma probe was used to identify sentinel lymph nodus during surgery and intraoperative histopathology was performed by imprint cytology or frozen sections. Positive tumor invasion was defined as the presence of at least one micrometastasis (tumor tissue 200mm-2mm) or one macrometastasis (tumor tissue > 2mm). Isolated tumor cells (< 200mm) were not considered to be nodal invasion. When sentinel lymph node positivity was detected post-surgery, a neck dissection was performed. Eight persons in the SLNB-group received a neck dissection because sentinel lymph node biopsies failed and twelve patients received a neck dissection after initial negative intraoperative histopathological analysis (total neck dissections in SLNB-group: 21/140, 15%) The control group (END-group, n=139 after exclusion) received neck dissection. Patients received adjuvant radiotherapy if two or more lymph nodes (including the sentinel node, when applicable) were positive. Concomitant adjuvant chemotherapy was proposed when poor prognostic factors were present (for example vascular, perineural, or muscular invasion). Follow-up was performed by the surgeon every 2 months (first year), every 4 months (following year), and once yearly (up to the fifth year). Every visit had a clinical examination. A neck-thorax CT was performed at year 1 and year 2 post-surgery. Functional follow-up was performed at month 2, 4, 6, 12, and 24 post-surgery. Mean follow-up duration was 4.95 years (SD: 2.45).

Results

Neck recurrence
Hasegawa (2021) observed 15 regional recurrences (11.2%) in the sentinel lymph node biopsy-group, while 13 (9.5%) regional recurrences were observed in the neck dissection group. A relative risk was calculated from this data (RR=1.18, 95%CI: 0.58 to 2.38). In natural frequencies (using the baseline risk of 9.5%), a neck dissection results in 95 patients with regional recurrences from a group of 1000 patients compared to 113 patients (95%CI: 56 to 217) with regional recurrences out of 1000 patients for a sentinel lymph node biopsy. According to these numbers, sentinel lymph node biopsy can result in a range of 39 less patients to 122 more patients with regional recurrences per 1000 patients compared to neck dissection.

Garrell (2020) reported 13 recurrences without relapse of the primary tumor in the sentinel lymph node biopsy-group (9.3%), compared to 14 recurrences in the elective neck dissection-group (10.1%). There were no statistically significant differences when tested with a Chi^2-test (p=0.82). From this data a relative risk was calculated: RR = 0.92 (95%CI: 0.45 to 1.89) with the point estimate favoring the sentinel lymph node biopsy procedure. In natural frequencies (using the baseline risk of 10.1%), a neck dissection then results in 101 patients with regional recurrences from a group of 1000 patients compared to 93 patients (95%CI: 46 to 191) with regional recurrences out of 1000 patients for a sentinel lymph node biopsy. According to these numbers, sentinel lymph node biopsy can result in a range of 55 less patients to 90 more patients with regional recurrences per 1000 patients compared to neck dissection.

Disease-specific survival
Garrel (2020) reported the 2-year and 5-year disease specific survival. The 2-year specific survival in the sentinel lymph node biopsy-group was 93.0% (95%CI: 87 to 96), compared to 95.5% (95%CI: 90 to 98) in the neck dissection-group. The 5-year disease-specific survival was 87.1% (95%CI: 79 to 92) in the sentinel lymph node biopsy group versus 88.6 (95%CI: 82 to 93) in the neck dissection group. No statistically significant difference between groups were found (p=0.68).

Overall survival

Hasegawa (2021) reported the 3-year overall survival. In the sentinel lymph node biopsy-group the survival was 87.9% (one-sided lower limit of the 95%CI: 82.4%) compared to 86.6% (one-sided lower limit of the 95%CI: 80.9%) survival in the neck dissection group at three years.

Garrel (2020) investigated the 2-year and 5-year overall survival. The 2-year overall survival in the sentinel lymph node biopsy-group was 88.7% (95%CI: 82 to 93) versus 92.6% (95%CI: 87 to 96) in the neck dissection-group. The 5-year overall survival in the sentinel lymph node biopsy-group was 82.2% (95%CI: 74 to 88) compared to 81.8% (95%CI: 74 to 88) in the neck dissection-group. No statistically significant differences between groups were found (p=0.42).

Quality of life

Hasegawa (2021) reported the quality of life using the Neck Dissection Quality of Life Questionnaire. Subscales in this questionnaire that described outcomes of interest in this guideline module are described under the respective outcome (i.e. the subscales: pain, shoulder drop, reach above). The other quality of life subscales are described in Table 1 for 1, 3, 6, and 12 months postoperatively. Medians were calculated from the reported frequency table.

Table 1 Median scores on Quality of Life subscales as measured by Hasegawa (2021) with the Neck Dissection Quality of Life Questionnaire

QoL Subscale	Treatment	Median score at 1 month (sample size)	Median score at 3 months (sample size)	Median score at 6 months (sample size)	Median score at 12 months (sample size)
Stiffness	SLNB	4 (n=125)	4 (n=125)	4 (n=123)	4 (n=108)
	ND	3 (n=126)	3 (n=131)	4 (n=128)	4 (n=120)
	p-value*	<0.001	<0.001	0.00105	0.00108
Constriction	SLNB	4 (n=125)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	3 (n=125)	3 (n=131)	4 (n=128)	4 (n=120)
	p-value*	<0.001	<0.001	M0.001	0.00133
Numbness	SLNB	4 (n=124)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=131)	4 (n=128)	4 (n=120)
	p-value*	0.01345	<0.001	0.00077	<0.001
Neck appearance	SLNB	5	5	5	5
	ND	3	4	4	4
	p-value*	<0.001	<0.001	0.01852	0.04795
Measurement scale ranged from 1 to 5. Higher scores indicate a better quality of life. **ND: Neck dissection** **SLNB: Sentinel Lymph Node Biopsy*P-value: Bonferroni corrected alpha for multiple testing was set at 0.0125**					

Shoulder morbidity

Hasegawa (2021) measured 'shoulder drop' and 'reach above' using the Neck Dissection Quality of Life Questionnaire. Since these subscales specifically describe an aspect of shoulder morbidity, these subscales were described here. Hasegawa (2021) also used the shoulder abduction test. Results are presented in Table 2 for 1, 3, 6, and 12 months postoperatively. Median scores were derived from the reported data in a frequency table.

Table 2 Median scores for shoulder morbidity, from Hasegawa (2021)

Outcome	Treatment	Median score at 1 month (sample size)	Median score at 3 months (sample size)	Median score at 6 months (sample size)	Median score at 12 months (sample size)
Shoulder drop (QoL subscale)*	SLNB	5 (n=125)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=131)	5 (n=128)	5 (n=119)
	p-value**	<0.001	<0.001	0.004	0.04873
Reach above (QoL subscale)	SLNB	5 (n=124)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=130)	5 (n=128)	4.5 (n=120)
	p-value*	<0.001	<0.001	0.04327	0.09578
Arm abduction test†	SLNB	3 (n=38)	4 (n=33)	4 (n=26)	4 (n=19)
	ND	4 (n=68)	3 (n=73)	4 (n=41)	5 (n=31)
	p-value*	<0.001	<0.001	0.06219	0.099

ND: Neck dissection
SLNB: Sentinel Lymph Node Biopsy
QoL: Quality of life
*Measurement scale ranged from 1 to 5. Higher scores indicate a better quality of life.
**P-value: Bonferroni corrected alpha for multiple testing was set at 0.0125
†Measurement scale ranged from 0 to 5: 0 = up to <90°/ 1 = up to around 90°/ 2 = Up to more than 90° but < 150°/ 3 = Up to more than 150° but < 180°/ 4 = up to 180° with pain or effort/ 5 = up to 180° without pain or effort

Garrel (2020) assessed shoulder mobility with the neck-shoulder impairment scale (self-reported). Results were displayed in a figure and exact scores can only be approximated. Significance tests at different time points on the questionnaire's items are summarized in Table 3. Garrell (2020) also reported the proportion of patients capable of reaching 180° shoulder abduction without pain or effort. Results are summarized in Table 4.

Table 3 Approximated scores and statistical differences between groups on the neck-shoulder impairment scale as reported by Garrel (2020)

Item	2 months	4 months	6 months	12 months

Shoulder stiffness	SLNB: 17% ND: 34% p<0.01 (favouring SLNB)	SLNB: 15% ND: 36% p<0.01 (favouring SLNB)	SLNB: 18% ND: 35% p<0.01 (favouring SLNB)	SLNB: 16% ND: 17% NS
Shoulder pain	SLNB: 20% ND: 32% NS	SLNB: 22% ND: 32% NS	SLNB: 22% ND: 27% NS	SLNB: 22% ND: 13% NS
Constriction of the neck	SLNB: 26% ND: 37% NS	SLNB: 17% ND: 25% NS	SLNB: 20% ND: 39% p<0.01 (favouring SLNB)	SLNB: 17% ND: 24% NS
Limited ability to reach above head	SLNB: 15% ND: 39% p<0.01 (favouring SLNB)	SLNB: 18% ND: 29% NS	SLNB: 13% ND: 26% p=0.03 (favouring SLNB)	SLNB: 14% ND: 15% NS
Neck numbness	SLNB: 23% ND: 23% NS	SLNB: 19% ND: 15% NS	SLNB: 19% ND: 29% NS	SLNB: 10% ND: 14% NS
Shoulder drop	SLNB: 6% ND: 11% NS	SLNB: 6% ND: 11% NS	SLNB: 6% ND: 7% NS	SLNB: 5% ND: 5% NS
Bothered by appearance of neck	SLNB: 16% ND: 14% NS	SLNB: 15% ND: 18% NS	SLNB: 11% ND: 10% NS	SLNB: 5% ND: 17 p=0.04 (favouring SLNB)
Difficulty dressing	SLNB: 6% ND: 21% NS	SLNB: 10% ND: 17% NS	SLNB: 6% ND: 12% NS	SLNB: 5% ND: 5% NS
Difficulty combing hair	SLNB: 10% ND: 17% NS	SLNB: 7% ND: 12% NS	SLNB: 5% ND: 9% NS	SLNB: 6% ND: 6% NS
Limited in ability to do work	SLNB: 10% ND: 24% p<0.01 (favouring SLNB)	SLNB: 11% ND: 22% NS	SLNB: 13% ND: 13% NS	SLNB: 8% ND: 9% NS
Limited in ability to do leisure	SLNB: 11% ND: 24% p=0.01 (favouring SLNB)	SLNB: 11% ND: 21% p=0.05 (favouring SLNB)	SLNB: 11% ND: 24% p=0.03 (favouring SLNB)	SLNB: 9% ND: 11% NS

NS: Not significant
SLNB: Sentinel lymph node biopsy
Lower score indicates less impairment: Percentage of positive responses to the questions

Table 4 Proportion capable of reaching 180° shoulder abduction without pain or effort, from Garrell (2020)

	2 months	4 months	6 months	12 months	24 months
SLNB-group	71.03%	74.29%	76.29%	84.95%	87.8%
ND-group	50.51%	57.89%	60.23%	76.92%	78.38%
Significance testing	p<0.01	p<0.01	p<0.03	p=0.18	p=0.11

END: Elective Neck Dissection
SLNB: Sentinel Lymph Node Biopsy

Hematoma
None of the included studies reported the occurrence of hematomas as an outcome.

Pain
Hasegawa (2021) measured 'pain' using the Neck Dissection Quality of Life Questionnaire. Since this subscale specifically described the outcome of interest, the subscale was reported here. The measurement scale of the instrument was 1 to 5, where higher scores indicated a higher quality of life (i.e. less pain). Table 5 summarized the findings of Hasegawa (20201) at 1, 3, 6, and 12 months postoperatively. Median scores were derived from the reported data in a frequency table.

Table 5 Median scores of the pain subscale of th Neck Dissection Quality of Life Questionnaire, as measured by Hasegawa (2021)

Outcome	Treatment	Median score at 1 month (sample size)	Median score at 3 months (sample size)	Median score at 6 months (sample size)	Median score at 12 months (sample size)
Pain (QoL subscale)*	SLNB	4 (n=125)	5 (n=125)	5 (n=123)	5 (n=108)
	ND	4 (n=126)	4 (n=130)	4 (n=128)	4 (n=120)
	p-value**	0.00117	0.00086	0.01272	0.6394

ND: Neck dissection
SLNB: Sentinel Lymph Node Biopsy
QoL: Quality of life
*Measurement scale ranged from 1 to 5. Higher scores indicate a better quality of life (i.e. less pain).
**P-value: Bonferroni corrected alpha for multiple testing was set at 0.0125

Postoperative oedema
None of the included studies reported the occurrence of postoperative oedema as an outcome.

Costs
None of the included studies reported costs as an outcome.

Level of evidence of the literature
The level of evidence regarding the outcome measure neck recurrence was downgraded by 3 levels because of study limitations (1 level for risk of bias: unclear block size for randomization in one of the RCTs, unclear procedures for random sequence generation, unclear procedures for allocation concealment); number of included patients (2 levels for imprecision: the confidence interval of the pooled estimate crosses both borders of clinical decision-making (0.8 and 1.25)); publication bias was not assessed.

The level of evidence regarding the outcome measure disease-specific survival was downgraded by 2 levels because of study limitations (1 levels for risk of bias: unclear block size for randomization, unclear procedures for random sequence generation, unclear procedures for allocation concealment, no blinding in the RCT); number of included patients (1 level for imprecision: the trial protocol calculated 164 patients per arm in a sample size calculation, this number was not met in the actual inclusion); publication bias was not assessed.

The level of evidence regarding the outcome measure overall survival was downgraded by 2 levels because of study limitations (1 level for risk of bias: unclear block size for randomization in one of the RCTs, unclear procedures for random sequence generation, unclear procedures for allocation concealment); number of included patients (1 level for imprecision: Hasegawa (2021) calculated a sample size for a 12% difference (border of non-inferiority); using the sample size calculation provided in the protocol of Hasegawa (2021) a sample size for a 5% difference was calculated resulting in n=592 participants per arm ($D_{between-group}$=0.05, $Z_{one-sided\ alpha\ 0.05}$=1.65, $Z_{two-sided\ beta\ 0.2}$=1.28 P_a=0.85, P_b=0.85); SLNB arms consisted of n=134/n=137, ND arms consisted of n=137/n=139); publication bias was not assessed.

The level of evidence regarding the outcome measure shoulder morbidity was downgraded by 3 levels because of study limitations (2 levels for risk of bias: unclear block size for randomization in one of the RCTs, unclear procedures for random sequence generation, unclear procedures for allocation concealment, no blinding in the RCTs, outcomes on the shoulder impairment scale were not reported at 24 months in one RCT); number of included patients (1 level for imprecision: SLNB arms consisted of n=134/n=137, ND arms consisted of n=137/n=139); publication bias was not assessed.

The level of evidence regarding the outcome measure quality of life was downgraded by 3 levels because of study limitations (2 levels for risk of bias: unclear procedures for random sequence generation, unclear procedures for allocation concealment, no blinding in the RCT, missing data on the subscales at 12 months was 12.4% (ND) and 19.4% (SLNB)); number of included patients (1 level for imprecision: SLNB arms consisted of n=134, ND arms consisted of n=137); publication bias was not assessed.

The level of evidence regarding the outcome measure pain was downgraded by 3 levels because of study limitations (2 levels for risk of bias: unclear procedures for random sequence generation, unclear procedures for allocation concealment, no blinding in the RCT, 13.1% (ND) and 19.4%(SLNB) missing data at 12 months); number of included patients (1 level for imprecision: SLNB arms consisted of n=134, ND arms consisted of n=137); publication bias was not assessed.

The level of evidence regarding the outcome measures hematoma, postoperative oedema, and costs could not be GRADEd, since none of the included studies reported this outcome.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:
What are the (un)beneficial effects of a sentinel lymph node biopsy on neck recurrence, disease specific survival, overall survival, quality of life, shoulder morbidity, hematomas, pain, and postoperative oedema compared to an elective neck dissection in patients with cT1-2N0 oral cavity carcinomas?

P: patients with a cT1-2N0 oral cavity carcinoma;
I: sentinel lymph node biopsy;
C: elective neck dissection;
O: neck recurrence, disease specific survival, overall survival, quality of life, shoulder morbidity, hematomas, pain, and postoperative oedema, costs.

Relevant outcome measures
The guideline development group considered neck recurrence, disease-specific survival, and overall survival as critical outcome measures for decision making; and quality of life, shoulder morbidity, hematomas, pain, and postoperative oedema as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) and HR< 0.7 in overall survival.
- A difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Statistically significant less complications/adverse events.
- Statistically significant better functional outcomes.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until July 15th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 201 hits. Six systematic reviews were selected and screened for eligibility. Systematic reviews were selected based on the following criteria: concerns patients with a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy was compared to (elective) neck dissection, at least one outcome of interest was reported, included randomized trials. The only relevant systematic review (Crocetta, 2019) did not find any randomized studies up to their search date on the 30th of April in 2019. To update this

search, we selected all studies (n=25) published between the 1st of January 2019 and the 15th of July 2020 from our initial search. Thirteen of these 25 studies were initially selected based on title and abstract screening, using the following criteria: concerns patients with a cT1-2N0 oral cavity carcinoma, sentinel lymph node biopsy was compared to elective neck dissection, at least one outcome of interest was reported, and the study was a randomized trial. None of the 13 studies met the selection criteria.

On the 1st of July 2021 the search was updated and the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms, resulting in 25 new hits. Five studies were selected based on title and abstract. Studies were selected using the aforementioned criteria.

After reading the full text, three studies were excluded and two randomized trials were selected.

Results
Two randomized controlled trials were included. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Crocetta FM, Botti C, Pernice C, Murri D, Castellucci A, Menichetti M, Costantini M, Venturelli F, Bassi MC, Ghidini A. Sentinel node biopsy versus elective neck dissection in early-stage oral cancer: a systematic review. Eur Arch Otorhinolaryngol. 2020 Dec;277(12):3247-3260. doi: 10.1007/s00405-020-06090-9. Epub 2020 May 30. PMID: 32474648.
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Orofarynxcarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Behandeling T1-2N0-1 orofarynxcarcinomen

Uitgangsvraag

Hoe worden patiënten met T1-2N0-1 orofaryngeale tumoren behandeld?

Aanbeveling

Aanbeveling-1
Ondersteun de patiënt bij het maken van een behandelkeuze tussen chirurgische behandeling (TORS) en radiotherapie, waarbij de individuele patiëntkarakteristieken dienen te worden afgewogen.

En bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- **Behandelduur:**
  De duur van de behandelingen zonder complicaties bij TORS is één ingreep met een opnameduur van één tot enkele dagen. Voor RT is de behandelduur tot zeven weken.

- **Procedures:**
  TORS wordt onder narcose verricht, RT niet. RT zal volgens een behandelschema verlopen.

- **Korte en lange termijn complicaties en toxiciteit:**
  Bij TORS kunnen bloedingen, pijnklachten en ontstekingen optreden. Bij RT kan smaakverlies, een droge mond en slikklachten optreden. Ook kunnen hypothyroïdie, versnelling van artherosclerose en, met een zeer gering risico, secundaire tumoren ontstaan ten gevolge van RT. De kans op radiatiecariës en radionecrose neemt toe naar mate de tumor dicht bij de mandibula ligt of de manibula invalideert.
- **Kans op adjuvante behandeling:**
  Voor TORS bestaat er een aanzienlijke kans op een adjuvante behandeling met (chemo)radiatie.

Aanbeveling-2
Geef radiotherapie bij patiënten met primaire T1-2N0-1 orofarynxcarcinomen, tenzij er patiëntvoorkeuren voor een chirurgische behandeling zijn.

Overwegingen

Er werd één gerandomiseerde trial gevonden over Transoral Robotic Surgery (TORS) versus radtiotherapie (RT) die alle uitkomstmaten van interesse rapporteerde, behalve lokale controle (Nichols, 2019). Er was een zeer laag vertrouwen in de gerapporteerde 5-jaars overleving (log-rank p=0,89; HR=0,83 met 95%BHI: 0,21 tot 8,35). Het gerapporteerde verschil in overleving werd niet als klinisch relevant beschouwd, want hiervoor behoorde de hazard ratio kleiner dan 0,7 te zijn. Het is enigszins onduidelijk hoe de gerapporteerde hazard ratio tot stand is gekomen en welke groep als referentiegroep is gekozen in de calculatie hiervan. Ook werd er geen reden aangedragen waarom er een groot aantal deelnemers uit beide interventiegroepen gecensureerd werden in de analyse. Vermoedelijk verlieten deelnemers het onderzoek (de mediane follow-up was 27 maanden), maar het gerapporteerde verlies in de follow-up in de studie-doorstroom was slechts 2 personen in de primaire radiotherapie groep. Eén patiënt in de studie overleed ten gevolge van een Transoral

Robotic Surgery (TORS)-ingreep gerelateerde bloeding. Er was verder een zeer laag vertrouwen in de gerapporteerde ziektevrije overleving (HR=1,07 met 95%BHI: 0,28 tot 4,01), slikklachten (RR=1,11 met 95%BHI: 0.90 tot 1.37; Eén persoon in de studie (radiotherapie-groep) had een percutane voedingssonde) en kwaliteit van leven (MDADI totale score: 80,1 (TORS) versus 86,9 (RT), p=0,042; MDADI composietscore: 80,2 (TORS) versus 86,7 (RT), p=0,049). Er werden significante verschillen in (slik-gerelateerde) kwaliteit van leven met het MDADI-instrument gemeten, maar deze konden niet worden gezien als een klinisch relevant verschil (dat wil zeggen >10 punten verschil). Kwaliteit van leven werd tevens met meerdere vragenlijsten beoordeeld. Zie Tabel 1 in de resultaten onder het tabblad 'Onderbouwing' voor de door Nichols (2019) gerapporteerde scores. Het zeer lage vertrouwen werd veroorzaakt door het geringe aantal deelnemers in de studie en het gebrek aan blindering van patiënten, zorgverleners en uitkomstbeoordelaars bij 'zachte' uitkomstmaten. Er werden geen resultaten gevonden voor lokale controle. Ook in de gevonden resultaten over de belangrijke uitkomstmaten is er op dit moment een zeer laag vertrouwen door het geringe aantal deelnemers in de studie en het gebrek aan blindering van patiënten, zorgverleners en uitkomstbeoordelaars.

Nichols (2019) berekende het benodigde aantal deelnemers aan de hand van het klinisch relevante verschil op de MDADI (gemiddeld verschil: 10 punten; gepoolde SD: 12; alfa=0,05, bèta=0,1, 10% verwachte drop-out). Het aantal deelnemers in de studie voldeed aan deze berekening, maar er werd geen klinisch relevant verschil gevonden. Aan de hand van het daadwerkelijk gevonden verschil kon worden berekend dat de behaalde 'power' 0,57 was bij een gemiddeld verschil van 6,8 punten, een gepoolde SD van 12,3, een alfa van 0,05, een bèta van 0,9, en met n=30 per arm (er waren 30 (TORS) en 27 (RT) ingevulde vragenlijsten op het 1-jaars tijdpunt). Omdat er een zeer beperkt aantal patiënten aan deze studie deelnamen is de imprecisie van de effectschatters groot. In de toekomst zullen resultaten van andere gerandomiseerde studies meer informatie toevoegen over het eventuele (on)gunstige effect van transorale robotische chirurgie ten opzichte van primaire radiotherapie. Via het zoekportaal in het International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) van de World Health Organization werd er naar geregistreerde gerandomiseerde studies gezocht die transorale robotische chirurgie vergeleken met een vorm van primaire radiotherapie. Er werden vijf gerandomiseerde trials gevonden (zie Tabel 2), waarvan er 1 reeds werd beëindigd, 2 actief zijn maar niet rekruteren en 2 op dit moment rekruteren. Naar verwachting zullen de laatste metingen van patiënten in de trials plaats vinden tussen 2021 en 2029.

Tabel 2 Geïdentificeerde trials naar transorale robotische chirurgie versus radiotherapie voor orofarynx carcinomen; uit het International Clinical Trials Registy Platform van de World Health Organization

Randomized trial	Trial ID	Status	Intervention A	Intervention B	Inclusion TNM	Primary completion date (last participant recruitment)	Study completion date (last measurement of intervention treatment)

EORTC-1420-HNCG-ROG ("Best of" trial)	NCT02984410 (Clinicaltrials.gov)	Recruiting	Any transoral surgery approach (e.g. transoral laser micro-surgery, conventional transoral surgery, transoral robotic surgery)	Intensity modulated radiotherapy with simultaneous integrated boost		June 2021	Janua
QoLATI	NCT04124198 (Clinicaltrials.gov)	Recruiting	Transoral robotic surgery + neck dissection	Intensity-modulated radiation therapy	cT1-2 cN0-1 Distant metastases will be excluded	January 2024	Janua

ECOG 3311	NCT01898494 (Clinicaltrials.gov)	Active, not recruiting	Transoral surgery	Transoral surgery + low-dose intensity-modulated radiation therapy Transoral surgery + standard-dose intensity-modulated radiation therapy Transoral surgery + standard-dose intensity-modulated radiation therapy + chemotherapy	Stage III Stage IVa Stage IVb No evidence of distant metastases	February 2020	Febru 2023
ORATOR	NCT01590355 (Clinicaltrials.gov)	Active, not recruiting	Transoral robotic surgery + neck dissection	Radiotherapy with or without chemotherapy	T1-2 N0-2 Without extranodal extension	June 2021	June
NRG/RTOG 1221	NCT01953952 (Clinicaltrials.gov)	Withdrawn (Slow accrual)	-	-	-	-	-

In 2009 werd TORS goedgekeurd voor de behandeling T1-2 orofarynxcarcinomen door de Amerikaanse Food and Drug Administration (FDA) op basis van korte termijn uitkomsten (30-dagen). De volgende studies hebben destijds tot de goedkeuring geleid en zijn samengevat in Tabel 3. (Weinstein, 2007; Weinstein, 2007). Zowel TORS als radiotherapie hebben een curatief doel. Beide behandelingen hebben echter een verschillend patroon van complicaties en toxiciteit door de aard van de interventie. De voorkeur van een patiënt voor één van beide interventies kan hiervan afhangen. Het is daarom belangrijk om de voor- en nadelen van beide interventies met de patiënt te bespreken.

Tabel 3 Uitkomsten van studies die tot de FDA goedkeuring hebben geleid

Author (year)	Intervention	Sample size	Patient characteristics	Outcomes

Weinstein (2007)	Radical tonsillectomy	n=27 (1 patient lost to follow-up)	Sex: 25 males / 2 females	*During TORS procedure:* Mean blood loss, ml (range): 189 (0-500)
			T-stage, n: T1: 5 T2: 16 T3: 6	*30-day postoperative complications:* Mucosal bleeding, n: 1/27 (4%)
			N-stage, n: N0: 4 N1: 13 N2: 10 N3: 0	Tracheotomy (for exacerbation of sleep apnea), n: 1/27 (4%)
			Differentiation, n: Well: 2 Moderate to well: 2 Moderate: 11 Moderate to poor: 6 Poor: 6	Moderate trismus, n: 2/27 (7%) Hypernasality, n: 1/27 (4%) Delirium tremens, n: 1/27 (4%) Mortality, n: 0/27 (0%) *Follow-up:* Local or regional recurrences, n: 0/26 (0%)
			Karnofsky score, n: 0-60: 0 70: 1 80: 3 90: 15 100: 8	Intubation period: 1 patient had a tracheotomy during the TORS procedure 20 patients were extubated at the end of the TORS procedure 6 patients remained intubated for 2.7 days postoperatively (range: 2-3 days)
			Charlson Comorbidity Index, n: 0: 11 1: 12 2: 2 3: 3	Swallowing without the use of gastrostomy, n: 26/27 (96%) Adjuvant therapy, n: Postoperative radiation without chemotherapy: 9 Postoperative irradiation with chemotherapy: 15 Postoperative chemotherapy: 1

Weinstein (2007)	Supraglottic partial laryngectomy	n=3	Sex: 2 males / 1 female	Surgical time, hours:minutes:seconds: Patient 1: 2:58:18 Patient 2: 1:35:01 Patient 3: 1:32:48
			Median age, years: 62.3	Hospitalization, days: Patient 1: 3 Patient 2: 8 Patient 3: 5
			TNM-stage, n: T2N0M0: 2 T3N0M0: 1	Return to swallowing, week: Patient 1: 6 Patient 2: 5 Patient 3: 5
				Mean blood loss, ml (range): 200 (100-400)
				Complications: No complications
				Conversions: No conversions
				Adjuvant therapy: The patient with the T3N0M0 carcinoma received chemoradiation after positive lymph nodes were found from neck dissection

TORS heeft als voordeel dat het één enkele ingreep betreft en, wanneer er geen complicaties optreden, de opnameduur één nacht is. Wanneer bij histopathologisch onderzoek van het resectiepreparaat na TORS geen indicaties voor adjuvante radiotherapie bestaat kan radiotherapie achter de hand worden gehouden voor het geval er recidief of tweede primaire tumor optreedt. Echter, een nadeel van TORS is dat de patiënt onder narcose moet om de operatie te ondergaan. Er kunnen bloedingen, pijn en ontstekingen ontstaan. Na de ingreep kan tevens blijken dat TORS niet afdoende is geweest en zal een nabehandeling met (chemo)radiatie noodzakelijk zijn. Wanneer er gekozen wordt voor een behandeling met TORS bestaat er een kans dat adjuvante behandeling noodzakelijk blijkt. In de RCT van Nichols (2019), waarin de helft (51%) van de deelnemers N2 status hadden, kregen 70,6% van de deelnemers die TORS ondergingen óók postoperatieve radiotherapie (n=16; 47,1%) of chemoradiotherapie (n=8; 23,5%). De kans op adjuvante chemoradiotherapie zou hoogstwaarschijnlijk lager zijn wanneer er geen patiënten met N2 status waren gerekruteerd. Voor radiotherapie hoeven patiënten niet onder narcose. Door de aard van deze interventie levert radiotherapie géén chirurgie-gerelateerde complicaties op, zoals bloedingen en ontstekingen. Bij het verstrekken van radiotherapie is de duur van de behandeling langer dan de chirurgische interventie. Een radiotherapeutische

behandeling kan tot zeven weken duren. Radiotherapie kan daarnaast acute toxiciteit veroorzaken met slikklachten, smaakverlies en een droge mond als gevolg. Ook kunnen lange termijn bijwerkingen optreden zoals, eveneens, slikklachten en een droge mond, maar ook hypothyroïdie, radiatiecariës, radionecrose en/of versnelling van de atherosclerose. Als gevolg van de radiotherapie kunnen met zeer geringe kans op langere termijn secundaire tumoren ontstaan in het hoofd-halsgebied. Van de patiënten die in de RCT van Nichols (2019) radiotherapie ondergingen, in plaats van TORS, ontving 71,9% (n=23) óók concomitante chemotherapie.

De kosteneffectiviteit van deze therapieën zouden een verdere afweging kunnen zijn. De Almeida (2015) beschreef dat TORS kosteneffectief is bij patiënten met vroege T-stadium tumoren ongeacht het N-stadium, maar dat de kosteneffectiviteit afneemt naarmate er vaker adjuvante therapie na TORS gegeven moet worden. De auteurs stellen dat een goede patiëntenselectie hierbij belangrijk is om de waarschijnlijkheid op een adjuvante behandeling te verminderen. Rudmik (2015) rapporteert dat intensiteitsgemoduleerde radiotherapie een grotere waarschijnlijkheid heeft om kosteneffectief te zijn dan TORS bij patiënten met T1-2N0M0 tumoren bij afkapwaarden van de bereidheid tot betalen tussen $50.000 en $150.000 per quality-adjusted life-year (QALY). De auteurs dragen aan dat hoog-volume centra wellicht de waarde van zorg (zgn. value of care) van TORS zou kunnen verhogen. Rodin (2016) beschrijft dat de kosteneffectiviteit van zowel TORS als RT afhankelijk waren van specifieke klinische situaties bij niet eerder behandelde patiënten met cT1-2cN0-1 tumoren. De auteurs rapporteren door middel van een probabilistische analyse dat RT een grotere waarschijnlijkheid heeft om kosteneffectief te zijn bij afkapwaarden van de bereidheid tot betalen tussen $50.000 en $150.000 per QALY. Sher (2016) beschreef dat RT een kosteneffectieve behandeling met hoge waarde was voor de niet-rokende, 65 jaar oude man met een HPV-positieve T1-2N2a-b tumor. De auteurs gaven aan dat TORS wellicht een kosteneffectieve interventie zou kunnen worden wanneer het tot een betekenisvolle relatieve verbetering van locoregionale controle zou leiden ten opzichte van primaire chemoradiotherapie, maar dat er nog geen literatuur bekend was die dit aan zou tonen. Kosteneffectiviteitsanalyses zijn afhankelijk van de gebruikte parameters in het model en de eventuele aannames in de analyses. De hier besproken kosteneffectiviteitsanalyses zijn daarom wellicht niet direct één-op-één over te nemen voor de Nederlandse situatie.

In Nederland wordt TORS uitgevoerd in een beperkt aantal geselecteeerde centra voor beperkte indicaties. Er zijn geen algemeen geaccepteerde indicaties maar vaak uitgeoefende selectiecriteria zijn de volgende: de tumor is goed bereikbaar, een excisie met chirurgische marges (1cm) is haalbaar en er is geen of één kleine lymfekliermetastase in de hals. De overweging is om adjuvante RT na TORS te voorkomen.

Op dit moment is radiotherapie de standaardbehandeling in Nederland. Het is van belang dat de patiënt hiervan op de hoogte wordt gebracht, maar ook dat er eventueel een alternatieve chirurgische optie mogelijk is middels TORS. Door de voor- en nadelen van beide interventies te bespreken in combinatie met de professionele opinie van de medisch-specialist zal gezamenlijk (middels gedeelde besluitvorming) moeten worden afgewogen welke behandeling zal worden ingezet.

De werkgroep is echter van mening dat radiotherapie op dit moment de standaard zorg blijft, omdat er onvoldoende bewijs werd gevonden wat met hogere zekerheid het afwijken van de huidige standaardbehandeling ten faveure van TORS in voldoende mate ondersteunt. Er zijn een aantal lopende

gerandomiseerde studies geïdentificeerd (Tabel 2). Resultaten van die studies zullen meer wetenschappelijke data toevoegen zodat er in de toekomst mogelijk met hogere zekerheid aanbevelingen kunnen worden gemaakt met betrekking tot de (on)gunstige effecten van beide interventies.

Door een sterke voorkeur van de patiënt voor een chirurgische behandeling zou TORS als alternatieve interventie eventueel ingezet kunnen worden wanneer TORS in dat geval óók door de medisch specialist als adequaat voor de betreffende situatie wordt beschouwd. De chirurgische optie vervalt vanzelfsprekend indien er contra-indicaties voor TORS aanwezig zijn. Om de chirurgische interventie (dat wil zeggen TORS) te kunnen uitvoeren moet de betreffende chirurg de benodigde certificering hebben. Daarnaast moet de chirurg ook ervaring met deze operatie hebben en de operatie op regelmatige basis uitvoeren om TORS te kunnen aanbieden.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Aanbeveling-1
De werkgroep is van mening dat patiënten door de verschillende complicatie- en toxiciteitspatronen die ontstaan wegens de aard van beide interventies een sterke voorkeur voor één van beide interventies kan hebben. De werkgroep acht het daarom belangrijk dat de voor- en nadelen van beide interventies besproken moeten worden, maar ook dat aangegeven wordt dat radiotherapie vooralsnog de huidige standaardzorg is.

Aanbeveling-2
De werkgroep is van mening dat radiotherapie de standaardbehandeling van patiënten met T1-2N0-1 orofarynxcarcinomen blijft. Op dit moment is de huidige behandeling radiotherapie en geeft de lage zekerheid in het gevonden bewijs vooralsnog geen richting om TORS boven radiotherapie te verkiezen, maar behandel patiënten zo veel mogelijk met één behandelingsmodaliteit. Bij patiënten met N1 ziekte die behandeld worden met TORS zal er een halsklierdissectie verricht moeten worden. De resultaten van de lopende gerandomiseerde studies dienen afgewacht te worden.

Deze aanbeveling is daarom gebaseerd op het ontbreken van een hoge(re) zekerheid in alle eindpunten die in de PICO gedefinieerd zijn. Er is maar één RCT beschikbaar. Vanuit deze studie zijn er met lage zekerheid aanwijzingen dat beide behandelingen (TORS en RT) mogelijk een vergelijkbare 5-jaars overleving hebben. Er is geen data over de impact van beide modaliteiten wat betreft de lokale controle in deze studie. Tevens is het effect van TORS ten opzichte van RT op alle toxiciteit eindpunten onduidelijk vanuit deze studie.

Onderbouwing

Achtergrond

De standaardbehandeling van patiënten met T1-2N0-1 orofarynxcarcinomen is radiotherapie. Transorale robotische chirurgie (Transoral Robotic Surgery, TORS) wordt in aantal ziekenhuizen aangeboden als alternatief. In de Verenigde Staten is TORS geregistreerd voor deze indicatie door de Food and Drugs Administration (FDA). Gezien het feit dat deze aandoening bij een steeds jongere patientenpopulatie vastgesteld wordt door de toename van HPV+ tumoren en gelet de toxiciteit van de radiotherapie, zeker op lange termijn, wordt de behandeling middels TORS al dan niet in combinatie met (een eventueel lagere dosis) radiotherapie intensief onderzocht.

Conclusies

Conclusions
<u>Transoral robotic surgery (TORS, including patients that received adjuvant (chemo)radiotherapy) versus primary radiotherapy (RT, including patients that reveived concurrent chemotherapy and salvage surgery)</u>

Very low GRADE	We are unsure about the differences between TORS and RT in the 5-year overall survival. *Sources: (Nichols, 2019)*

Very low GRADE	We are unsure about the effect of TORS on the disease-free survival when compared to RT. *Sources: (Nichols, 2019)*

Very low GRADE	We are unsure about the effect of TORS on swallowing complaints when compared to RT. *Sources: (Nichols, 2019)*

- GRADE	No studies were included that assessed and reported the local control.

Very low GRADE	We are unsure about the effect of TORS on the quality of life when compared to RT. *Sources: (Nichols, 2019)*

Very low GRADE	We are unsure about the effect of TORS on trismus when compared to RT. *Sources: (Nichols, 2019)*

Very low GRADE	We are unsure about the effect of TORS on taste alterations when compared to RT. *Sources: (Nichols, 2019)*

Very low GRADE	We are unsure about the effect of TORS on the dryness of the mouth when compared to RT. *Sources: (Nichols, 2019)*

Very low GRADE	We are unsure about the effect of TORS on oral mucositis when compared to RT. *Sources: (Nichols, 2019)*

Samenvatting literatuur

<u>Description of studies</u>
<u>*Transoral robotic surgery (TORS) versus primary radiotherapy (RT) in Nichols (2019)*</u>
Nichols (2019) reported on a multicenter randomized controlled trial with centers recruiting in Canada and Australia to compare TORS with neck dissection (on indication) with primary radiotherapy (RT) as part of the ORATOR-trial. Data and procedures were extracted from the study protocol (Nichols, 2013) and the study report with appendices (Nichols, 2019).

Nichols (2019) included patients who were over 18 years old, had an ECOG-status of 0 to 2, had a histologically confirmed squamous cell carcinoma where the primary site was the oropharynx, had a T1-2 carcinoma and were likely to have negative resection margins at surgery, had N0-2 without extranodal extension (on pre-randomization imaging), the complete blood count/differential was obtained 4 week prior to randomization (with adequate bone marrow, hepatic, and renal function), and the patient was assessed at a multidisciplinary head and neck clinic and presented at a multidisciplinary tumor board prior to randomization. Patients were excluded when there were serious medical comorbidities, there were contraindications to therapy (radiotherapy, chemotherapy, surgery), there was prior history of head and neck cancer within 5 years, the patient had prior head or neck radiation, the patient had metastases, the patient was unable to attend full-course radiotherapy or follow-up visits, the patient had prior malignant disease (unless 5-year disease-free) with the exception of non-melanoma skin cancer, the patient was pregnant or lactating, or when the patient was unwilling or unable to complete the quality of life questionnaires.

A total of 68 patients were recruited and randomly allocated (1:1 allocation, block size 4). Patients in the TORS-group (n=34, 28 males) had a median age of 58.2 years (IQR: 52.6 to 64.5) and the primary tumor located at the tonsil / tonsillar fossa (n=24) or at the base of the tongue (n=10). Patients had an ECOG score of either 0 (n=30) or 1 (n=4), while 6 out of 22 (27%) who were asked drank over 21 drinks per week. Twenty-one (62%) patients undergoing TORS had a smoking history. Clinical T-stage was either T1 (n=17) or T2 (n=17), while clinical N-stage was N0 (n=9), N1 (n=7), or N2 (n=18). There were 30 HPV-positive patients in the TORS-group, as measured with p16 staining. Patients in the radiotherapy-group (n=34, 31 males) had a median age of 60 years (IQR: 53.2 to 65.2) and the primary tumor located at the tonsil / tonsillar fossa (n=26) or at the base of the tongue (n=8). Patients had an ECOG score of 0 (n=30) or 1 (n=4). Eighteen persons were asked about the alcohol-intake, resulting in 1 person (6%) having more than 21 drinks per week. Twenty-eight (82%) patients had a smoking history. In the RT group, the clinical T-stage was T1 (n=13) or T2 (n=21), while the clinical N-stage was N0 (n=12), N1 (n=5), or N2 (n=17). There were 30 HPV-positive patients by p16 staining in the RT-group as well.

In the TORS-group, a surgical robot was used to excise the primary oropharyngeal tumor with the spatula caultry (1cm resection margin). Selective neck dissection was performed at the discretion of the surgeon during surgery or within 2 weeks after surgery. Surgeons had to perform at least 10 TORS excisions prior to enrolling patients in the study. The surgical specimen was sent for frozen section analysis and the excision continued until negative margins were obtained. Adjuvant radiotherapy was given, however could be omitted when there was no extranodal extension, positive margins, pT3-4, nodal disease, or lymphovascular invasion. Thus, radiotherapy was given in the region of positive margins (64 Gy, 30 fractions, 6 weeks), in high risk

nodal areas (60 Gy, 30 fractions, 6 weeks), or in low risk nodal areas (54 Gy, 30 fractions, 6 weeks). Concurrent chemotherapy with cisplatin (100mg/m^2 every 3 weeks in a 3 week cycle) could be administered when there were positive margins or extracapsular extensions. When patients were deemed unfit for cisplatin chemotherapy the doses and schedules could be modified, or cetuximab or weekly carboplatin (AUC 1.5) could be administered at the discretion of the medical oncologist. Out of the 34 patients in the TORS-group, 24 (71%) patients received radiotherapy and 8 (24%) patients received chemotherapy (cisplatin: n=5, carboplatin: n=3). Patients received chemotherapy in a median number of cycles of 6 (IQR: 4.5 to 6). It was unclear whether there were any deviations from the cisplatin schedule (100mg/m^2 every 3 weeks in a 3 week cycle) at the medical oncologist's discretion.

In the RT-group, primary radiotherapy was given to the gross tumor and nodes (70 Gy, 35 fractions, 7 weeks). Radiotherapy was further administered in high risk nodal areas (63 Gy, 35 fractions, 7 weeks) and in low risk nodal areas (56 Gy, 35 fractions, 7 weeks). At the treating radiation oncologist's discretion the radiotherapy regimen could be accelerated or hyperfractionated, where the same dose could be provided in 6 weeks. Concurrent chemotherapy was administered with positive nodes (i.e. N1-2) and omitted when N0. Chemotherapy doses and schedules could be modified for patients who were deemed unfit for cisplatin, or cetuximab or weekly carboplatin (AUC 1.5) could be administered at the discretion of the medical oncologist. Twenty-three (68%) patients received chemotherapy (cisplatin: n=19, carboplatin: n=3, cetuximab: n=1). Patients received chemotherapy in a median number of cycles of 3 (IQR: 2-6). It was unclear whether there were any deviations from the cisplatin schedule (100mg/m2 every 3 weeks in a 3 week cycle) at the medical oncologist's discretion.Treatment response was evaluated by CT or PET-CT 8 to 12 weeks after completion of radiotherapy. When the CT showed residual nodes over 1 centimeter, patients were recommended salvage surgery. For PET-CT evaluation, residual nodes had to be over 1 centimeter and FDG-avid. Patients were offered surgical salvage when feasible for relapse or progressive disease. Four (12%) patients received salvage surgery, however it was unclear whether nodes were examined by a pathologist to confirm metastases.

Patients were followed-up every 3 months in the first two years and every 6 months in year 3 to 5. Physical examination and adverse event monitoring took place at every visit. Quality of life measurements and a chest x-ray was performed every 6 months, with the exception of the 1-year time point where a CT-scan was taken instead of an x-ray. The RT-group had an additional assessment at 8 to 12 weeks post-radiotherapy to assess the treatment response and the need for salvage surgery. The median follow-up in de study was 27 months (IQR: 20 to 48). Two patients in the RT-group withdrew consent after randomization (no reasons provided).

Nichols (2019) measured quality of life (QoL) with several validated questionnaires: MD Anderson Dysphagia Index (MDADI, score range: 20 to 100, higher indicates a better QoL), European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients general (EORTC QLQ-C30, score range: 0 to 100, higher score indicates a worse QoL), Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients Head and Neck (EORTC H&N35, score range: 0 to 100, higher score indicates a worse QoL), Voice Handicap Index (VHI-10, score range: 0 to 40, higher score indicates a better QoL), Neck Dissection Impairment Index (NDII, score range: 0 to 100, higher score indicates a better QoL), Patient Neurotoxicity Questionnaire (PNQ, 2 items on a 5-point Likert scale), and Functional Oral Intake Scale (FOIS, 7-point Likert scale, higher scores indicate a better QoL).

Results

Transoral robotic surgery (TORS) versus primary radiotherapy (RT)

Overall survival

Nichols (2019) reported the 5-year overall survival of both groups, each containing 34 patients (reference group=TORS; log-rank p=0.89; HR=0.83, 95%CI: 0.21 to 8.35). Over the course of 5 years, there were 4 observed deaths in the RT-group (n=3 metastatic disease, n=1 cardiac event outside the hospital) and 5 observed deaths in the TORS group (n=3 metastatic disease, n=1 TORS-related bleeding, n=1 cardiac arrest after alcohol overdose and hypoglycaemia). A total of 27 persons in the TORS-group and 28 persons in the RT-group were censored over the course of 5 years. No reasons for censoring were provided.

Disease-free survival

Nichols (2019) defined the 5-year 'progression-free survival' as the time from randomization to either death or recurrence, whichever occurred first. A hazard ratio of 1.07 (95%CI: 0.28 to 4.01; reference group=TORS) and a log-rank p of 0.63 were reported. A total of 26 persons in the TORS-group and 28 persons in the RT-group were censored over the course of 5 years. No reasons for censoring were provided. There were 4 recurrences observed in each group.

Swallowing

Nichols (2019) reported swallowing complications per grade. The relative risk (RR) was not reported, however from these data the RR could be calculated. For grade 1 to 2 dysphagia an RR of 1.00 (95%CI: 0.69 to 1.45, reference group=RT) was reported. Both in the TORS and RT-group 21 grade 1-2 events were observed. Grade 3 dysphagia had 9 events in the TORS-group and 6 events in the RT-group. Here, an RR of 1.50 (95%CI: 0.60 to 3.75) was calculated. When all observed events were combined (TORS: 30 events, RT: 27 events) the RR was 1.11 (95%CI: 0.90 to 1.37). One person in the RT-group used a percutaneous feeding tube at the 1 year time point, compared to none in the TORS-group.

Local control

No studies were included that reported the local control.

Quality of life

Nichols (2019) assessed the 1-year quality of life with several questionnaires, however the quality of life as measured with the MDADI was the primary outcome measure. The MDADI total score differed significantly between groups at 1 year (TORS: 80.1 (SD: 13), RT: 86.9 (SD: 11.4), p=0.042), indicating the RT-group had a better swallowing-related quality of life. Similarly, a statistically significant difference was reported for the MDADI composite score (TORS: 80.2 (SD: 13.1), RT: 86.7 (SD: 11.4), p=0.049), indicating a better swallowing-related quality of life for the RT-group. The total score on the VHI-10 (TORS: 4.5 (SD: 4.3), RT: 4.4 (SD: 4.6), p=0.89) and NDII (TORS: 81.5 (SD: 28.7), RT: 92.3 (SD: 10), p=0.072) showed no significant difference. Summary scores for the EORTC QLQ-C30 and the EORTC H&N35 were not reported. For scores on sub-scales of the questionnaires we refer to Table 1.

Table 1 Overview of the 1-year quality of Life measurements per questionnaire as measured by Nichols (2019)

Quality of life instrument	Outcome

MD Anderson Dysphagia Index (MDADI, score range: 20-100, higher indicates a better QoL), completed surveys at the 1-year time point: 30 for TORS, 27 for RT.	MDADI total score, mean score (SD): TORS: 80.1 (13) RT: 86.9 (11.4) Mean difference: 6.7 (95%CI: 0.2 to 13.2) Statistically significant difference between groups: p=0.042 MDADI global sub-scale score, mean score (SD): TORS: 79.3 (22.6) RT: 89.6 (15.1) Mean difference: 10.3 (95%CI: 0.2 to 20.4) Statistically significant difference between groups: p=0.046 MDADI emotional sub-scale score, mean score (SD): TORS: 81.3 (12.5) RT: 88.8 (12) Mean difference: 7.4 (95%CI: 0.9 to 14) Statistically significant difference between groups: p=0.027 MDADI functional sub-scale score, mean score (SD): TORS: 86.5 (12) RT: 89.9 (11.5) Mean difference: 3.4 (95%CI: -2.9 to 9.6) No statistically significant difference between groups: p=0.28 MDADI physical sub-scale score, mean score (SD): TORS: 75.3 (16.5) RT: 83.1 (14.1) Mean difference: 7.9 (95%CI: -0.3 to 16) No statistically significant difference between groups: p=0.058 MDADI composite score, mean score (SD): TORS: 80.2 (13.1) RT: 86.7 (11.4) Mean difference: 6.5 (95%CI: 0.0 to 13.1) Statistically significant difference between groups: p=0.049
European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients General (EORTC QLQ-C30, score range: 0-100, higher score indicates a worse QoL on symptom scales, a high score on functional and global health scales represent higher functioning/QoL), unclear number of	EORTC-C30 Global health status sub-scale score, mean score (SD): TORS: 77.9 (19.5) RT: 76.2 (20.9) No statistically significant difference between groups: p= 0.76 EORTC-C30 Physical functioning sub-scale score, mean score (SD): TORS: 9.4 (16.1) RT: 5.9 (7.2)

completed surveys at the 1-year time point.	No statistically significant difference between groups: p= 0.29 <u>EORTC-C30 Role functioning sub-scale score, mean score (SD):</u> TORS: 18.3 (30.1) RT: 11.1 (17.9) No statistically significant difference between groups: p= 0.27 <u>EORTC-C30 Emotional functioning sub-scale score, mean score (SD):</u> TORS: 14.9 (19.5) RT: 12.0 (15.9) No statistically significant difference between groups: p= 0.54 <u>EORTC-C30 Cognitive functioning sub-scale score, mean score (SD):</u> TORS: 13.8 (18.9) RT: 11.7 (15.9) No statistically significant difference between groups: p=0.66 <u>EORTC-C30 Social functioning status sub-scale score, mean score (SD):</u> TORS: 13.2 (20.1) RT: 6.4 (13.4) No statistically significant difference between groups: p= 0.14 <u>EORTC-C30 Fatigue sub-scale score, mean score (SD):</u> TORS: 18.1 (20.5) RT: 15.6 (13.5) No statistically significant difference between groups: p= 0.59 <u>EORTC-C30 Nausea/ vomiting sub-scale score, mean score (SD):</u> TORS: 5.0 (9.9) RT: 4.3 (10.9) No statistically significant difference between groups: p= 0.81 <u>EORTC-C30 Pain sub-scale score, mean score (SD):</u> TORS: 21.8 (25.2) RT: 8.0 (16.3) Statistically significant difference between groups: p= 0.018 <u>EORTC-C30 Dyspnea sub-scale score, mean score (SD):</u> TORS: 7.8 (14.3) RT: 4.9 (12.1)

	No statistically significant difference between groups: p= 0.42
	EORTC-C30 Insomnia sub-scale score, mean score (SD): TORS: 17.8 (27.3) RT: 28.4 (28.8) No statistically significant difference between groups: p= 0.16
	EORTC-C30 Appetite loss sub-scale score, mean score (SD): TORS: 13.3 (27.1) RT: 16.0 (25.1) No statistically significant difference between groups: p= 0.70
	EORTC-C30 Constipation sub-scale score, mean score (SD): TORS: 4.4 (14.5) RT: 8.6 (14.9) No statistically significant difference between groups: p= 0.29
	EORTC-C30 Diarrhea sub-scale score, mean score (SD): TORS: 5.7 (15.6) RT: 2.5 (8.9) No statistically significant difference between groups: p= 0.34
	EORTC-C30 Financial difficulties sub-scale score, mean score (SD): TORS: 14.9 (29.0) RT: 11.1 (24.5) No statistically significant difference between groups: p= 0.59
Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients Head and Neck (EORTC H&N35, score range: 0-100, higher score indicates a worse QoL on symptom scales, a high score on functional scales represent higher functioning/QoL), unclear number of completed surveys at the 1-year time point.	EORTC QLQ-HN35 Pain sub-scale score, mean score (SD): TORS: 13.3 (14.9) RT: 9.0 (12.4) No statistically significant difference between groups: p= 0.23 EORTC QLQ-HN35 Swallowing sub-scale score, mean score (SD): TORS: 12.7 (16.1) RT: 7.4 (7.4) No statistically significant difference between groups: p= 0.11 EORTC QLQ -HN35 Senses sub-scale score, mean score (SD): TORS: 20.6 (21.3) RT: 20.5 (22.8) No statistically significant difference between groups: p > 0.99 EORTC QLQ -HN35 Speech sub-scale score, mean score (SD): TORS: 7.7 (9.9)

RT: 5.8 (9.9)

No statistically significant difference between groups: p= 0.48

EORTC QLQ -HN35 Social eating sub-scale score, mean score (SD):

TORS: 11.8 (14.4)

RT: 7.1 (10.3)

No statistically significant difference between groups: p= 0.16

EORTC QLQ -HN35 Social contact sub-scale score, mean score (SD):

TORS: 4.6 (10.1)

RT: 1.5 (6.5)

No statistically significant difference between groups: p= 0.17

EORTC QLQ -HN35 Less sexuality sub-scale score, mean score (SD):

TORS: 22.0 (27.6)

RT: 17.3 (25.2)

No statistically significant difference between groups: p= 0.51

EORTC QLQ -HN35 Teeth sub-scale score, mean score (SD):

TORS: 12.2 (22.3)

RT: 1.2 (6.4)

Statistically significant difference between groups: p= 0.014

EORTC QLQ -HN35 Opening mouth sub-scale score, mean score (SD):

TORS: 11.1 (22.0)

RT: 6.4 (13.4)

No statistically significant difference between groups: p= 0.33

EORTC QLQ -HN35 Dry mouth sub-scale score, mean score (SD):

TORS: 44.4 (30.7)

RT: 53.1 (31.0)

No statistically significant difference between groups: p= 0.30

EORTC QLQ -HN35 Sticky saliva sub-scale score, mean score (SD):

TORS: 31.1 (34.9)

RT: 32.1 (28.5)

No statistically significant difference between groups: p= 0.91

EORTC QLQ -HN35 Coughing sub-scale score, mean score (SD):

	TORS: 22.2 (23.7) RT: 24.7 (25.5) No statistically significant difference between groups: p= 0.71 EORTC QLQ -HN35 Felt ill sub-scale score, mean score (SD): TORS: 6.7 (13.6) RT: 3.7 (10.7) No statistically significant difference between groups: p= 0.36 EORTC QLQ -HN35 Pain killers sub-scale score, mean score (SD): TORS: 44.8 (50.6) RT: 14.8 (36.2) Statistically significant difference between groups: p= 0.013 EORTC QLQ -HN35 Nutritional supplements sub-scale score, mean score (SD): TORS: 24.1 (43.5) RT: 29.6 (46.5) No statistically significant difference between groups: p= 0.65 EORTC QLQ -HN35 feeding tube sub-scale score, mean score (SD): TORS: 0.0 (0) RT: 3.7 (19.2) No statistically significant difference between groups: p= 0.33 EORTC QLQ -HN35 weight loss sub-scale score, mean score (SD): TORS: 20.7 (41.2) RT: 3.7 (19.2) No statistically significant difference between groups: p= 0.053 EORTC QLQ -HN35 weight gain sub-scale score, mean score (SD): TORS: 37.9 (49.4) RT: 40.7 (50.1) No statistically significant difference between groups: p= 0.83
Voice Handicap Index (VHI-10, score range: 0-40, higher score indicates a better QoL), unclear number of completed surveys at the 1-year time point.	VHI-10 total score, mean score (SD): TORS: 4.5 (4.3) RT: 4.4 (4.6) No statistically significant difference between groups: p= 0.89

Neck Dissection Impairment Index (NDII, score range: 0-100, higher score indicates a better QoL), unclear number of completed surveys at the 1-year time point.	NDII total score, mean score (SD): TORS: 81.5 (28.7) RT: 92.3 (10.0) No statistically significant difference between groups: p= 0.072
Patient Neurotoxicity Questionnaire (PNQ, 2 items on a 5-point Likert scale), unclear number of completed surveys at the 1-year time point.	PNQ Numbness sub-scale score, mean score (SD): TORS: 0.5 (0.8) RT: 0.3 (0.6) No statistically significant difference between groups: p= 0.57 PNQ Weakness sub-scale score, mean score (SD): TORS: 0.5 (1.0) RT: 0.2 (0.5) No statistically significant difference between groups: p= 0.14
Functional Oral Intake Scale (FOIS, 7-point Likert scale, higher scores indicate a better QoL), unclear number of completed surveys at the 1-year time point.	FOIS, level 7 "expansion of oral diet" reached at 1 year, n(%): TORS: 26/31 (84%) RT: 27/27 (100%) No statistically significant difference between groups: p= 0.055
QoL: Quality of Life RT: Radiotherapy-group TORS: Transoral robotic surgery-group	

Trismus
Nichols (2019) reported grade 1-2 trismus in 8 of the 34 patients (23.5%) in the TORS-group and in 1 of the 34 patients (2.9%) in the RT-group. The RR was not reported, however from these data the RR could be calculated. Based on the data an RR of 8.00 (95%CI: 1.06 to 60.5) was calculated. One patient in the TORS-group had a grade 3 trismus complication, therefore the overall RR was 9.00 (95%CI: 1.21 to 67.21).

Taste
Grade 1 to 2 taste alterations were observed by Nichols (2019) in 17 patients (50%) in the TORS-group, compared to 19 patients (55.9%) in the RT group. The RR was not reported, however from these data the RR could be calculated. An RR of 0.89 (95%CI: 0.57 to 1.40) was calculated. Taste alterations in grade 3 or higher were not prevalent in both groups.

Dryness of the mouth
Grade 1 to 2 dryness of the mouth was reported in 18 of the 34 patients (52.9%) in the TORS-group, compared to 24 out of 34 patients (70.6%) in the RT-group. The RR was not reported, however from these data the RR could be calculated. The calculated RR was 0.75 (95%CI: 0.51 to 1.10). One patient in the RT-group had a grade 3 dryness of the mouth. The RR of all observed events was 0.72 (95%CI: 0.49 to 1.05, TORS: 18 events, RT: 25 events).

Mucositis
Nichols (2019) reported oral mucositis in 8 (23.5%) patients in the TORS-group, compared to 11 (32.4%) patients in the RT-group. The RR was not reported, however from these data the RR could be calculated. From the data, the calculated RR was 0.73 (95%CI: 0.33 to 1.58). Four patients in the RT-group had a grade 3 oral mucositis. The overall RR for oral mucositis was 0.53 (95%CI: 0.26 to 1.09, TORS: 8 events, RT: 15 events).

<u>Level of evidence of the literature</u>
Transoral robotic surgery (TORS) versus primary radiotherapy (RT)
The level of evidence regarding the outcome measure overall survival (crucial) was downgraded by 3 levels because of the number of included patients (imprecision: only 34 patients were included in each study arm. The number of censored participants was large in both arms, providing limited data to the 5-year overall survival); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed. We did not downgrade for a lack of blinding (risk of bias), because overall survival was considered as a 'hard' outcome measure.

The level of evidence regarding the outcome measure disease-free survival (crucial) was downgraded by 4 levels because of study limitations (1 level for risk of bias: care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34 patients were included in each study arm. The number of censored participants was large in both arms, providing limited data to the 5-year disease-free survival); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

The level of evidence regarding the outcome measure swallowing (crucial) was downgraded by 4 levels because of study limitations (1 level for risk of bias: patients, care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34 patients were included in each study arm); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

The level of evidence regarding the outcome measure local control (crucial) was not graded, since there were no studies included that reported this outcome measure.

The level of evidence regarding the outcome quality of life (crucial) was downgraded by 4 levels because of study limitations (1 level for risk of bias: patients, care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34 patients were included in each study arm. Power calculation (using the reported mean difference of 6.8 on de MDADI, SD=12.2, alpha=0.05, beta=0.1, +10% assumed dropout) revealed that 75 participants per arm were needed); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

The level of evidence regarding the outcome measure trismus (important) was downgraded by 4 levels because of study limitations (1 level for risk of bias: patients, care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34

patients were included in each study arm); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

The level of evidence regarding the outcome measure taste (important) was downgraded by 4 levels because of study limitations (1 level for risk of bias: patients, care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34 patients were included in each study arm); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

The level of evidence regarding the outcome measure dryness of the mouth (important) was downgraded by 4 levels because of study limitations (1 level for risk of bias: patients, care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34 patients were included in each study arm); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

The level of evidence regarding the outcome measure mucositis (important) was downgraded by 4 levels because of study limitations (1 level for risk of bias: patients, care providers and outcome assessors were not blinded for the treatment allocation); and the number of included patients (2 levels for imprecision: only 34 patients were included in each study arm); indirectness (1 level for indirectness: about half of the recruited patients had an N2 carcinoma); publication bias could not be assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of TORS (with or without transoral microsurgery, and with or without adjuvant radiotherapy) on overall survival, disease-free survival, local control and quality of life, e.g. swallowing, trismus, taste, dryness of the mouth, and mucositis in patients with a T1-2N0-1 oropharyngeal carcinoma, when compared to primary radiotherapy.

P: patients with a T1-2N0-1 oropharyngeal carcinoma;
I: transoral robotic surgery with or without transoral microsurgery and with or without adjuvant radiotherapy;
C: primary radiotherapy;
O: overall survival, disease-free survival, local control, swallowing (complaints), trismus, taste, dryness of the mouth, mucositis, quality of life.

Relevant outcome measures
The guideline development group considered overall survival, disease-free survival, local control, swallowing, and quality of life (as measured with the MD Anderson Dysphagia Index (MDADI)) as a critical outcome measure for decision making; and trismus, dryness of the mouth, and mucositis as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")*:

- > 5% difference or more >3% and HR <0.7 in overall survival.
- HR< 0.7 for progression free survival.

And, in case of absence of a clinically relevant difference in overall survival or progression free survival:

- A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 (in line with Mehanna, 2019) or a difference of a similar magnitude on other quality of life instruments.
- Statistically significant less complications/adverse events.
- Statistically significant better functional outcomes, work participation.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 6th of January 2019 for systematic reviews and randomized controlled trials. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 106 hits. Studies or systematic reviews were selected based on the following criteria: patients had a T1-2N0-1 oropharyngeal carcinoma, transoral robotic surgery was compared with primary radiotherapy, at least one of the outcomes of interest was reported (overall survival, disease-free survival, local control, swallowing (complaints), trismus, dryness of the mouth, mucositis, quality of life), the study design was a randomized controlled trial or the systematic review contained randomized controlled trials, reports had to be written in English or Dutch. Twenty-one studies were initially selected based on title and abstract screening. After reading the full text, 20 studies were excluded (see the table with reasons for exclusion under the tab Evidence tables) and 1 randomized controlled trial was included.

Results

One randomized controlled trial (Nichols, 2019) was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab Evidence tables).

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Behandeling HPV-positieve orofarynx tumoren

Uitgangsvraag

Dienen HPV-positieve orofarynx tumoren op een andere wijze behandeld te worden dan HPV-negatieve orofarynx tumoren? Is er plaats voor de-escalatie?

Aanbeveling

De-escaleer de behandeling van patiënten met een HPV-positief orofarynxcarcinoom alleen in studieverband.

Overwegingen

De werkgroep is van mening dat, op basis van het anno 2019 beschikbare bewijs over de-escalatie strategieën, er geen reden is om HPV-positieve tumoren op een andere wijze te behandelen dan HPV-negatieve tumoren. Studies met zeer lage bewijskracht laten een lagere overleving zien in de de-escalatie groep. Volgens de werkgroep is er alleen binnen studieverband plaats voor de-escalatie van de behandeling.

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Alhoewel de-escalatie van de behandeling van HPV positieve orofarynxtumoren in meerdere studies is onderzocht, zijn er op dit moment slechts twee volledig uitgevoerde, gerandomiseerde studies beschikbaar. In deze studies werd concurrente radiotherapie met cetuximab vergeleken met concurrente radiotherapie met cisplatin. Van slechts één studie is op dit moment de lange-termijn follow-up data (> 3 jaar) beschikbaar (Gillison, 2019). De bewijskracht van deze ene studie is zeer laag. We zijn daarom onzeker of behandeling met cetuximab daadwerkelijk leidt tot een lagere overleving (6%-punt lager) en lagere "progression-free survival" (11%-punt lager).

Alhoewel de 2-jaars follow-up data van Mehanna (2019) niet voldoet aan de definitie van "lange-termijn follow-up", laat ook deze data een lagere overleving zien in de cetuximabgroep (20/168, 11.9%) vergeleken met de cisplatingroep (6/166, 3.6%).

De anno 2019 beschikbare data laat geen verschil zien in complicaties, toxiciteit, kwaliteit van leven of functionele uitkomsten, zoals slikproblemen. De bewijskracht is zeer laag. We kunnen daarom niet met zekerheid stellen dat er daadwerkelijk geen verschil is.

De werkgroep is van mening dat, op basis van het anno 2019 beschikbare bewijs over chemoradiotherapie met cetuximab vergeleken met chemoradiotherapie met cisplatin, er geen reden is om HPV-positieve tumoren op een andere wijze te behandelen dan HPV-negatieve tumoren.

Na de zoekdatum in deze richtlijnmodule werden er nog twee RCTs geïdentificeerd (Gebre-Medhin, 2020; Yom, 2021).

Gebre-Medhin (2020) rekruteerde patiënten met stadium III-IV (volgens de UICC TNM7-classificering) orofarynx-, hypofarynx-, mondholte of larynxcarcinomen zonder metastasen op afstand die in aanmerking kwamen voor een curatieve behandeling met radiotherapie. Patiënten werden gerandomiseerd en ontvingen

400 mg/m^2 intraveneuze cetuximab een week voor aanvang van de radiotherapie en vervolgens 250 mg/m^2 per week (n=149) óf ontvingen wekelijks 40 mg/m^2 intaveneuze cisplatin tijdens radiotherapie (n=149). In beide behandelgroepen werden patiënten geëxcludeerd (door middel van screening vóór het verstrekken van de behandeling) of vielen patiënten uit (vanwege sterfte of het stoppen van de behandeling) waardoor er bij n=144 patiënten een tumor respons evaluatie kon plaats vinden in de cetuximab-groep, tegenover n=143 in de cisplatin-groep. De tumorlocatie in de cetuximab-groep (n=125 orofarynx, n=8 mondholte, n=6 larynx, n=7 hypofarynx) en in de cisplatin-groep (n=123 orofarynx, n=7 mondholte, n=6 larynx, n=9 hypofarynx) leken gelijk tussen de groepen te zijn verdeeld. De radiotherapie had conventionele fractionering, maar patiënten met een T3-4-stadium carcinoom werden verder gerandomiseerd en ontvingen een radiotherapie dosis van 68Gy óf 73,1Gy. De patiënten werden aan de hand van p16 getest op de HPV-status. In de cetuximab-groep waren 108 patiënten (72,5%, n=14 negatief, n=1 missing) HPV-positief volgens p16 analyse, tegenover 113 patiënten (75,9%, n=11 negatief, n=1 missing) in de cisplatin groep. De auteurs vonden een niet-significant verschil in de algehele overleving op drie jaar follow-up in het voordeel van cisplatin. Daarnaast vonden de auteurs een statistisch significant verschil op de cumulatieve incidentie van het locoregionale falen op drie jaar in het voordeel van cisplatin. De auteurs rapporteerden ook dat de cumulatieve incidentie van het falen op afstand niet verschilde tussen de groepen. De dosisescalatie van radiotherapie bij T3-4-stadium carcinomen zorgde niet voor een verbeterde lokale controle. De auteurs concludeerden dat cetuximab als concomitante behandeling met radiotherapie inferieur is aan cisplatin voor locoregionale controle en dat wellicht nieuwe studies nodig zijn om subgroepen te kunnen identificeren die mogelijk baat zouden hebben bij cetuximab als concomitante behandeling (Gebre-Medhin, 2020).

Yom (2021) rekruteerde patiënten met histologisch aangetoonde orofaryngeale plaveiselcelcarcinomen en een Zubrod-status van 0 of 1. Deelnemers hadden HPV-positieve T1-2N1-2bM0 of T3N0-2bM0 tumoren volgens de 7^e editie van het TNM-stadiëringssysteem en een rookgeschiedenis van ≤10 pakjesjaren. Hematologische en nier- en leverfuncties moesten adequaat zijn voor het toedienen van cisplatin. Patiënten werden gerandomiseerd en 152 deelnemers ontvingen intensiteitsgemoduleerde radiotherapie met concurrente cisplatin (60Gy in 30 fracties, 5 fracties per week, wekelijks 40 mg/m^2 cisplatin) tegenover 147 deelnemers die alléén intensiteitsgemoduleerde radiotherapie ontvingen (60Gy, 6 fracties per week). Voor een intermediair risico volume rond de primaire locatie, de betrokken halsniveaus en de direct naastgelegen niet-betrokken halsniveaus werd 54Gy voorgeschreven. Voor de overige electief behandelde halsniveaus werd 48Gy voorgeschreven. In de cisplatin groep zaten 133 mannen en 25 vrouwen met tumoren op de volgende locaties: orofarynx (n=5, waarvan n=1 faryngeale orofarynx), tonsil of fossa tonsilaris (n=83), basis van de tong (n=68), en de posterieure faryngeale wand (n=1). Het T-stadium in deze groep was T1 (n-64), T2 (n=67) of T3 (n=26) en het N-stadium was N0 (n=6), N1 (n=28), N2a (n=24) of N2b (n=99). In de groep die alléén radiotherapie ontving zaten 124 mannen en 25 vrouwen met tumoren op de volgende locaties: orofarynx (n=13), tonsil of fossa tonsilaris (n=78) of de basis van de tong (n=58). Het T-stadium was T1 (n=51), T2 (n=80) of T3 (n=18). Het N-stadium was N0 (n=7), N1 (n=34), N2a (n=19) of N2b (n=89). Er werden geen significante verschillen gevonden tussen de groepen voor algehele overleving, progressievrije overleving, het ontstaan van afstandsmetastasen en voor de verschilscore tussen baseline en een jaar later van de MDADI composietscore. Er werd een significant verschil gevonden voor het lokaal-regionaal falen, in het voordeel van de cisplatin-groep. Ook werden er meer graad 3-4 complicaties geobserveerd in de cisplatin-groep. De

auteurs vermeldden dat de hoeveelheid late complicaties niet significant verschillen tussen de groepen. Er werd door de auteurs geconcludeerd dat de resultaten voldoende rechtvaardiging geven voor verder onderzoek in een fase III trial.

Andere de-escalatie strategieën, zoals behandeling met alleen radiotherapie of het verlagen van de radiotherapie of chemotherapie dosis, zijn niet in gerandomiseerd onderzoek onderzocht.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Windon (2019) onderzocht in een prospectieve studie de behandelingsdoelen van patiënten met HPV-positieve orofarynxtumoren voorafgaand aan hun behandeling en na hun behandeling. Patiënten (n=37) vulden tweemaal (bij diagnosestelling en gemiddeld 10 maanden later) een vragenlijst in over hun behandelingsdoelen en zorgen. Uit deze studie bleken behandelingsdoelen voor het grootste deel onveranderd. Patiënten vonden genezing van de kanker, overleving en slikken zowel voor als na de behandeling het belangrijkst. De enige significante verandering was dat na de behandeling patiënten "een vochtige mond hebben" belangrijker vonden dan voorafgaand aan de behandeling.

Op basis van de bevindingen van Windon (2019) stelt de werkgroep dat zij het gerechtvaardigd vinden om bij het formuleren van de aanbeveling ervan uit te gaan dat in het algemeen patiënten de behandelingsoptie met de beste kans op genezing en overleving zullen prefereren.

Kosten (middelenbeslag)
De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van de-escalatie strategieën. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht geen relevante impact op de zorgkosten door de aanbeveling.

Aanvaardbaarheid, haalbaarheid en implementatie
De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar is en implementeerbaar. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

Onderbouwing

Achtergrond

Standard treatment with cisplatin-based chemoradiotherapy for stage III-IV human papillomavirus (HPV)-positive oropharyngeal cancer results in considerable acute and long-term toxicity. Wide consensus exists about the need for de-escalation treatments with decreased toxicity and similar survival. Forms of de-escalation in this setting are cetuximab-based bioradiotherapy, radiotherapy alone, lowering the dose of the radiotherapy, low dose cisplatin and minimally invasive transoral surgery followed by de-intensified adjuvant therapy compared to standard dose cisplatin based concurrent chemoradiotherapy.

Conclusies

What are the effects of a de-escalating strategy in the treatment of human papilloma virus (HPV)-associated oropharyngeal cancer (OPC) compared to care-as-usual?

Radiotherapy alone or lowering the dose of the radiotherapy

- GRADE	We found no credible literature on de-escalating strategies, such as radiotherapy alone or lowering the dose of the radiotherapy.

Cetuximab-based bioradiotherapy versus cisplatin-based chemoradiotherapy

Very low GRADE	**Overall survival** may be lower after treatment with the de-escalating strategy "cetuximab-based bioradiotherapy", but the evidence is very uncertain. *Sources: (Gillison, 2019)*

Very low GRADE	**Progression free survival** may be lower after treatment with the de-escalating strategy "cetuximab-based bioradiotherapy", but the evidence is very uncertain. *Sources: (Gillison, 2019)*

Very low GRADE	There may be no difference in **complications/adverse events and toxicity,** but the evidence is very uncertain. *Sources: (Gillison, 2019, Mehanna, 2019)*

Very low GRADE	The evidence is very uncertain about the effect of the de-escalating strategy "cetuximab-based bioradiotherapy" on **quality of life**. *Sources: (Mehanna, 2019)*

Very low GRADE	The evidence is very uncertain about the effect of the de-escalating strategy "cetuximab-based bioradiotherapy" **on swallowing problems**. Other functional outcomes or work participation were not reported in the studies. *Sources: (Gillison, 2019; Mehanna, 2019)*

Samenvatting literatuur

Cetuximab-based bioradiotherapy versus cisplatin
Two RCTs (RTOG 1016 and De-ESCALaTE) directly compared the efficacy of cisplatin (CDDP) versus cetuximab (C225) given concurrently with RT as definitive treatment of p16-positive, non-metastatic, and locally advanced/unresectable OPC. In both studies p16-positive immunohistochemical staining was used as surrogate marker for HPV-positivity and both studies included patients with advanced stage tumors. Gillison 2019 published the results after a median follow-up duration of 4.5 years of the RTOG 1016 non-inferiority trial. The sample consisted of T1 (n=175), T2 (n=325), T3 (n=208), and T4 (n=97) tumors, and N0 (n=34), N1 (n=45), N2a (n=115), N2b (n=417), N2c (n=165), and N3 (n=29) lymph node metastases. Mehanna (2019)

published the results of the De-ESCALaTE trial at 24 months. The sample consisted of T1-2 (n=216) and T3-4 (n=118) tumors, and N0-1 (n=81) and N2-3 (n=253) lymph node metastases. Details about these two trials are presented in Table 2b.

Table 2b. Details of the trials that compared cetuximab-based bioradiotherapy versus cisplatin

Trial	Intervention (n, treatment)	Control (n, treatment)	Outcomes
RTOG 1016 (Gillison, 2019)	n=399 Intravenous cetuximab at a loading dose of 400 mg/m² 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m² weekly for seven doses (total 2150 mg/m²). All patients received accelerated intensitymodulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart).	n=406 Cisplatin (commercially available and obtained by each individual institution) 100 mg/m² on days 1 and 22 of radiotherapy (total 200 mg/m²) All patients received accelerated intensitymodulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart).	• 5-yr overall survival • 5-yr progression-free survival • Toxicity • Swallowing • Dental health
De-ESCALaTE (Mehanna, 2019)	N=168 Intravenous **cetuximab** 400 mg/m² loading dose 1 week before followed by seven weekly infusions of 250 mg/m² during radiotherapy All patients received accelerated intensitymodulated radiotherapy delivered at 70 Gy in 35 fractions over 7 weeks at five fractions per week.	N=166 Three doses of intravenous **cisplatin** 100 mg/m² on days 1, 22, and 43 of radiotherapy. All patients received accelerated intensitymodulated radiotherapy delivered at 70 Gy in 35 fractions over 7 weeks at five fractions per week. NB: only 38% of the patients in the cisplatinum group were able to get all three courses.	• 2-yr overall survival • Toxicity • Quality of life • Swallowing

Important remarks and differences between the studies

The studies differed in some aspects: low risk HPV-positive oropharyngeal cancer (Mehanna, 2019) versus low and moderate risk HPV-positive oropharyngeal cancer (Gillison, 2019), conventional (Mehanna 2019) versus accelerated radiotherapy (Gillison, 2019), three (Mehanna, 2019) versus two courses of cisplatin (Gillison, 2019) and toxicity (Mehanna 2019) versus survival (Gillison, 2019) as a primary outcome measure.

In the De-ESCALaTe study, 6% of the p16 positive tumors in HPV DNA in situ hybridization were negative, so that the difference between the two groups could be even greater. For a more in-depth discussion of the two studies, we refer to De Bree and Devriese 2019.

<u>Results</u>

Overall survival (follow-up ≥ 3 years)
In November 2019 only long-term follow-up data of the RTOG 1016 trial (Gillison, 2019) were available. In this trial 133 patients died after a median followup duration of 4.5 years: 78 (78/399, 19.5%) in the cetuximab group and 55 (55/406, 13.5%) in the cisplatin group (HR 1.45, onesided 95% upper CI 1.94; p=0.5056 for non-inferiority; RR 1.44, 95% CI 1.05 to 1.98). The boundary for clinical relevance (>5% difference) was exceeded, indicating worse overall survival after treatment with cetuximab.

Progression free survival
Fiveyear progression freesurvival was 67.3% (95% CI 62.4 to 72.2) in the cetuximab group and 78.4% (73.8 to 83.0) in the cisplatin group (HR 1.72, 95% CI 1.29 to 2.29; p=0.0002) (Gillison, 2019). The boundary for clinical relevance was exceeded, indicating better progression free survival after treatment with cisplatin.

Mehanna (2019) did not report progression free survival as such, but reported that they observed:

- "Significantly fewer recurrences with cisplatin than with cetuximab (ten (6%) versus 29 (18%); log-rank p=0.0007).
- Significantly fewer locoregional recurrences with cisplatin than with cetuximab (3% versus 12%, log-rank p=0.0026).
- Significantly fewer distant metastases with cisplatin than with cetuximab (3% versus 9%, log-rank p=0.0092).
- Five (3%) patients in each group developed second primaries."

Toxicity
Mehanna (2019) reported the mean number of acute, late, and overall toxicity events per patient. No statically significant differences were found. Details are presented in Table 3.

Table 3 Mean number of acute, late, and overall toxicity events per patient, by treatment group (Mehanna, 2019)

	mean number of events per patient in cisplatin group	mean number of events per patient in cetuximab group
Severe short-term toxicities	4.4 (95% CI 3.9–4.97)	4.4 (3.8–4.9)
All-grade short-term toxicity	20.0 (95% CI 18.8–21.1	20.4 (19.2–21.5)
Severe late toxicity events	0.4 (95% CI 0.29-0.54)	0.5 (0.030-0.67)
All-grade late toxicity events	9.4 (95% CI 8.53–10.34)	9.9 (95% CI 9.02-10.72)

Similar to Mehanna (2019), Gillison (2019) found that with regard to late toxicity in the cetuximab versus cisplatin groups, no statistically significant differences were found. Gillison (2019) found, however, that patients in the cetuximab group had a significantly lower mean number of grade 3 to 4 acute toxicity events per patient than did those in the cisplatin group (raw Tscore 2.35 versus 3.19; p<0·0001), corresponding to a 40% lower acute toxicity burden.

Adverse events
Mehanna (2019) found that there were significantly more serious adverse events with cisplatin than with cetuximab. 162 adverse events (mean rate of one event per patient) occurred in patients receiving cisplatin and 95 events (mean rate of 0.6 events per patient) occurred in patients receiving cetuximab (p<0.0001).

Gillison (2019) reported that the proportion of one or more grade 3 to 4 acute adverse events was similar in the cetuximab and cisplatin groups (305 of 394 patients, 77.4%, 95% CI 73.0 to 81.5 versus 325 of 398 patients, 81.7%, 77.5 to 85.3; p=0.16).

Next to this, Gillison (2019) reported that the number of early deaths (death due to adverse event or within 30 days of treatment completion) was the same in the cetuximab and cisplatin groups (6 of 394 patients in the cetuximab group; 6 of 398 in the cisplatin group; 1.5%, 95% CI 0.6 to 3.3; p=1.0).

Quality of life
Mehanna (2019) did not find statistically significant differences in the mean global quality-of-life score on EORTC QLQ-C30 between treatment groups at any of the timepoints. A statistically significant difference in social functioning was observed in favour of cetuximab at the end of treatment (mean difference of 8.67 points, p=0.0374), but this difference disappeared 6 months later. At 12 months and 24 months, a significant difference in role functioning was observed in favour of cisplatin (difference in mean scores of 8.32 points, p=0.0173. None of the differences reached the minimal clinically important difference of 10 points.

Gillison (2019) reported only the EORTC QLQH&N35 swallowing domain (see below: Functional outcomes). Additional quality of life endpoints will be reported in future publications.

Functional outcomes, work participation.
Gillison (2019) found that patientreported severity of swallowing problems, as measured with the EORTC QLQ-H&N35 subscale, increased in both the cetuximab and cisplatin groups from pretreatment to end of treatment, but no difference was observed between groups in change scores from baseline (mean 47.4 versus 48.0; p=0.86). At 1 year, the cetuximab group had a statistically significant increase in symptoms from pretreatment compared with the cisplatin group (7.6 versus 2.5; p=0.04), but this difference was below the, by the authors of the study, estimated clinically important difference.

None of the studies reported on (work) participation.

<u>Level of evidence of the literature</u>
The levels of evidence regarding the outcome measures overall survival, progression free survival, quality of life and functional outcomes were downgraded by one level because of study limitations (risk of bias in only

one study) and two levels because of the number of events in only one study (very serious imprecision, two levels). The level of evidence regarding the outcome measures complications/adverse events and toxicity were downgraded by one level because of study limitations (risk of bias), one level because of the low number of events (serious imprecision) and one level because of inconsistency (conflicting results).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of a de-escalating strategy in the treatment of advanced human papilloma virus (HPV)-associated oropharyngeal cancer (OPC) compared to care-as-usual for OPC?

P: patients with HPV-positive oropharyngeal cancer;
I: de-escalating strategy, such as cetuximab-based bioradiotherapy, radiotherapy alone or lowering the dose of the radiotherapy;
C: care-as-usual, such as cisplatin-based chemoradiotherapy;
O: overall survival, complications/adverse events, quality of life, head and neck cancer–specific functional outcomes.

Relevant outcome measures
The guideline development group considered overall survival and quality of life as critical outcome measures for decision making; and complications/adverse events, functional outcomes and (work) participation as important outcome measures for decision making.

The working group defined the outcome measures as follows:
Overall survival: Overall survival (defined as time from randomisation to death from any cause) after a minimum follow-up of 3 years.
Progression free survival: Progression free survival (time during and after the treatment of a disease that the patient lived with the disease but it did not get worse) after a minimum follow-up of 3 years.
Quality of life: Quality of life (overall or regarding a specific domain) as measured with a validated and reliable instrument such as the SF-36 or European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ).
Complications/adverse events: All negative effects related to the treatment (lethal, acute/serious, chronic).
Functional outcomes: Swallowing, oral pain, dry mouth, dental health, opening mouth/trismus, taste, excess/thick mucous/saliva, shoulder disability/ motion assessed by a validated and reliable instrument (Chera, 2014).
(Work) Participation: Participation in school, work and/or informal care.

The working group defined a minimal clinically relevant difference as *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")*:

- > 5% difference or more > 3% and HR<0.7 in overall survival.
- HR< 0.7 for progression free survival.

And, in case of absence of a clinically relevant difference in overall survival of progression free survival:

- A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 (in line with Mehanna, 2019) or a difference of a similar magnitude on other quality of life instruments.
- Statistically significant less complications/adverse events.
- Statistically significant better functional outcomes, work participation.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase were searched with relevant search terms until November 2019. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 409 hits (45 found with a filter for SRs, 364 found with a filter for RCTs). Only randomized controlled trials (whether or not included in systematic reviews) were considered for inclusion.

Systematic reviews
First, SRs were selected based on the following criteria: the population consists (mostly) of patients with HPV-positive oropharyngeal cancer, the study compares one or more de-escalating treatment modalities with care-as-usual, the study is a systematic review (SR) and describes one or more of the selected outcome measures.

Nineteen SRs were initially selected based on title and abstract screening. After reading the full text, 15 SRs were excluded (see the table with reasons for exclusion under the tab Evidence tables), and 4 SRs were included: Materson (2014) (comparing all de-escalation treatments); Suton 2019 (comparing cetuximab-based bioradiotherapy versus cisplatin); Szturz (2017) (comparing low dose versus high dose cisplatin) and Howard (2018) (comparing minimally invasive transoral surgery followed by de-intensified adjuvant therapy (either omission of chemotherapy or reduced-dose radiotherapy) versus minimally invasive transoral surgery followed by standard concurrent chemoradiotherapy or standard-dose radiotherapy).

Randomized controlled trials
Based on the SRs found, it was decided to select randomized controlled trials (RCTs) based on the following criteria: published after 2016, the population consists (mostly) of patients with HPV-positive oropharyngeal cancer, the study compares one or more de-escalating treatment modalities with care-as-usual, the study is a RCT and describes one or more of the selected outcome measures.

Ten articles were initially selected based on title and abstract screening. After reading the full text, 9 were excluded (see the table with reasons for exclusion under the tab Evidence tables), and 1 RCT was included: Misiukiewicz 2019 (comparing reduced dose chemoradiation with standard-dose chemoradiotherapy).

<u>Results</u>
Literature per type of de-escalating strategies
In 2014, Materson searched for all de-escalation treatment studies for HPV-associated, locally advanced (stage III-IV) oropharyngeal squamous cell carcinoma in their Cochrane literature review. They found no RCTs. In 2019, this review has not been updated yet. The most recent review on all de-escalation treatment strategies found in the present search for this guideline module was written by Stock in 2018. This was a narrative review, and not a systematic review, and was therefore not included.

We found the following literature on specific de-escalation strategies (Table 1):

1. Cetuximab-based bioradiotherapy versus cisplatin-based chemoradiotherapy (Suton, 2019 search up to December 2018).
2. Lowering the dose of the chemotherapy:
   a. Low dose versus high dose cisplatin (Szturz (2017) found no RCTs; search up to 2015).
3. Radiotherapy alone or lowering the dose of the radiotherapy:
   a. Radiotherapy alone (no recent SRs, Stock 2018 reported only retrospective analyses).
   b. Low dose cisplatin with concurrent lower dose radiotherapy (5600 cGy with weekly carboplatin) versus low dose cisplatin with concurrent standard-dose radiotherapy (7000 cGy with weekly carboplatin) after induction chemotherapy response (Misiukiewicz, 2019).
4. Minimally invasive transoral surgery followed by de-intensified adjuvant therapy (either omission of chemotherapy or reduced-dose radiotherapy) compared to minimally invasive transoral surgery followed by standard concurrent chemoradiotherapy or standard-dose radiotherapy (Howard 2018 found in their Cochrane review no RCTs, search up to April 2018).

Table 1 Literature on specific de-escalation strategies

De-escalation strategy	SR	Included RCTs
Cetuximab-based bioradiotherapy (versus cisplatin-based chemoradiotherapy)	Suton, 2019, search up to December 2018)	RTOG 1016 (Gillison, 2019) De-ESCALaTE (Mehanna, 2019)
Low dose cisplatin (versus high dose)	Szturz, 2017, search up to 2015	none
Radiotherapy alone	no recent SR	none
Reduced radiation dose chemoradiation (5600 cGy with weekly carboplatin) (versusstandard-dose chemoradiotherapy (7000 cGy with weekly carboplatin))		Quarterback trial (Misiukiewicz, 2019)
Minimally invasive transoral surgery followed by de-intensified adjuvant therapy	Howard, 2018, search up to April 2018	none

Reduced dose chemoradiation
The study of Misiukiewicz (2019) was terminated early due to lack of financial support for infrastructure to expand to multiple sites. Only 20 patients in total were included: 12 in the standard chemotherapy dose and reduced radiation dose group and 8 in the standard-dose chemoradiotherapy group. We decided that this very small sample size did not allow us to draw any useful conclusions for the purpose of developing a guideline. Details of the study are presented in Table 2a, but the study was excluded from the summary of the literature.

Table 2a. Details of the trial that compared reduced dose chemoradiation with standard-dose chemoradiotherapy

Trial	Intervention (n, treatment)	Control (n, treatment)	Outcomes
Quarterback trial (Misiukiewicz, 2019)	n=12 3 cycles of IC with docetaxel, cisplatin and fluorouracil (TPF) Clinical responders who were HPV positive by type-specific PCR received standard chemo and reduced dose radiotherapy (5600 cGy) with weekly carboplatin.	n=8 3 cycles of IC with docetaxel, cisplatin and fluorouracil (TPF) Clinical responders who were HPV positive by type-specific PCR received standard-dose chemoradiotherapy (7000 cGy) with weekly carboplatin.	• 3-yr overall survival • 3-yr progression-free survival • Toxicity

Cetuximab-based bioradiotherapy
Two trials were included in the summary of the literature (Gillison, 2019; Mehanna, 2019). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Dosering cisplatin lokaal gevorderde tumoren

Uitgangsvraag

Welke dosering van cisplatin heeft de voorkeur in combinatie met radiotherapie bij de definitieve behandeling van lokaal gevorderde hoofd-halstumoren?

Aanbeveling

Geef patiënten tot en met 70 jaar met een locoregionaal vergevorderd plaveiselcelcarcinoom van het hoofdhalsgebied (Stadium III-IV) die een indicatie hebben voor chemoradiatie bij voorkeur concomitante chemotherapie met cisplatin (100 mg/m2 op dag 1, 22 en 43) in combinatie met conventioneel gefractioneerde radiotherapie (voorbeeld 70 Gy in zeven weken).

Op basis van bijvoorbeeld ingeschat toxiciteitsrisico kan een wekelijks (40 mg/m^2) schema een te verdedigen alternatieve optie zijn.

Overwegingen

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>
Onze systematische zoekactie in Medline en Embase resulteerde in acht RCT's (Mashhour, 2020; Sahoo, 2017; Noronha, 2018; Rawat, 2016; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012). In vier van deze RCT's werden (ook) patiënten geïncludeerd die adjuvant behandeld werden (Mashhour, 2020; Noronha, 2018; Kiyota, 2022; Tsan, 2012).

Voor beide cruciale uitkomsten (overleving en terugkeer van de kanker) werden resultaten gerapporteerd. Overleving werd gerapporteerd in vijf studies, één studie rapporteerde een slechtere overleving in de groep die wekelijks 40 mg/m^2 cisplatin kreeg, vergeleken met driewekelijks cisplatin. Het ging hierbij echter om zeer kleine aantallen patiënten die waren overleden en een ongelijke grootte van de studiearmen (10/25 versus 9/31). Eén studie rapporteerde een betere overleving in de groep die wekelijks 40 mg/m2 cisplatin kreeg in de adjuvante setting, vergeleken met driewekelijks cisplatin.

Terugkeer van de kanker werd op twee verschillende manieren gerapporteerd: het wel of niet bereiken van een complete respons op de behandeling of locoregionale controle. Informatie over het bereiken van een complete respons was beschikbaar in vijf studies. Eén studie liet zien dat de frequentie van complete respons hoger was in de groep die wekelijks cisplatin kreeg (Nanda, 2020, 81% versus 75%; 40 mg/m^2, 100% definitieve behandeling).
Twee studies lieten geen verschil zien (Mashhour, 2020, 30 mg/m^2, 50% adjuvant behandeld en 50% definitief; Rawat, 2016, 35 mg/m2, 100% definitieve behandeling). Twee studies lieten zien dat de frequentie van complete respons lager was in de groep die wekelijks cisplatin kreeg (Sahoo, 2017, 72% versus 86%; 30 mg/m^2, 100% definitieve behandeling; Nair, 2017, 75% versus 90%, 40 mg/m2, 100% definitieve behandeling). Locoregionale controle werd gerapporteerd in zes studies. In drie studies was de frequentie van locoregionale controle lager in de groep die wekelijks cisplatin kreeg, waarbij het in twee studies ging om een zeer klein aantal patiënten waarbij de kanker terugkeerde (4/29 versus 2/31 en 13/30 versus 8/30). In één van deze studies werd een dosering van 40 mg/m^2 gebruikt in de definitieve setting en in de overige twee

studies werd in de definitieve of adjuvante setting een dosering van 30 mg/m^2 gebruikt. In één studie was de frequentie van locoregionale controle hoger in de groep die wekelijks 40 mg/m^2 cisplatin kreeg in de adjuvante setting, vergeleken met driewekelijks cisplatin.

Ook voor alle belangrijke uitkomsten (ziektevrije overleving, kwaliteit van leven en bijwerkingen) werden resultaten gerapporteerd. Ziektevrije overleving werd in vier studies gerapporteerd. Eén studie (40 mg/m^2) liet een slechtere 2-jaars overleving zien in de wekelijkse behandelgroep (53% versus 65%), twee studies (30 mg/m^2 en 40 mg/m^2) lieten geen verschil zien en in één studie (40 mg/m^2) was het niet mogelijk om te bepalen of het verschil klinisch relevant was, de mediane ziektevrije overleving was echter vrijwel gelijk tussen de groepen (26,4 maanden versus 27,4 maanden).

Bijwerkingen werden in alle studies gerapporteerd. De frequentie acute bijwerkingen van graad 3 of hoger lag in één studie (30 mg/m^2) lager in de wekelijkse behandelgroep (72% versus 85%; p=0.006), terwijl in een andere studie (40 mg/m2) geen verschil werd gevonden in de frequentie van bijwerkingen van graad 3 of hoger (81% versus 80%; p=0.87), maar wel in de frequentie van graad 4 bijwerkingen (8% versus 19%; p=0.017). Een andere studie analyseerde de frequentie van niet-hematologische bijwerkingen van graad 3 of hoger,
waarbij een lagere frequentie werd gerapporteerd in de wekelijkse behandelgroep (57% versus 77%). In sommige studies werd voor afzonderlijke niet-hematologische bijwerkingen van graad 3 of hoger een lagere frequentie in de wekelijkse groep gerapporteerd, bijvoorbeeld een verschil in de frequentie van dysfagie (63% versus 26%), maar dit werd niet consistent in alle studies teruggezien. Voor hematologische bijwerkingen werd in de meerderheid van de studies geen verschil in bijwerkingen van graad 3 of hoger tussen de groepen gerapporteerd.

Kwaliteit van leven werd in één studie gerapporteerd, waarbij zowel de scores voor de Trial Outcome Index (een combinatie van drie subschalen) als de scores voor vijf subschalen werden gerapporteerd. Scores op de Trial Outcome Index lagen op alle vier de meetmomenten wat lager (wat een lagere kwaliteit van leven inhoudt) in de wekelijkse behandelgroep. Alleen op het laatste meetmoment, drie maanden na het afronden van de behandeling, ging het om een klinisch relevant verschil tussen de groepen (9.7 punten verschil op een schaal van 0 tot 96). Voor de subschalen werd een wisselend beeld gezien.

De bewijskracht voor alle uitkomstmaten was zeer laag. Er werd afgewaardeerd wegens een risico op bias omdat de randomisatie en allocatie niet beschreven waren, omdat er niet geblindeerd was (voor de uitkomst kwaliteit van leven) en omdat één van de studies voortijdig stopgezet was wegens tegenvallende inclusie. Daarnaast werd in twee gevallen afgewaardeerd voor inconsistentie wegens verschillen in gerapporteerde effecten tussen de studies. Voor alle uitkomsten werd afgewaardeerd wegens indirectheid, omdat vier studies (ook) patiënten includeerden die in de adjuvante setting behandeling werden met chemoradiatie en omdat zeven van de acht studies waren uitgevoerd in Azië. Daarnaast ging het in zes van de acht studies om kleine patiëntaantallen (range 30 tot 71) wat leidde tot brede betrouwbaarheidsintervallen waardoor afgewaardeerd werd wegens imprecisie.

Uit de geïncludeerde studies bleek dat patiënten die wekelijks cisplatin kregen over het algemeen een lagere cumulatieve dosis ontvingen vergeleken met patiënten die driewekelijks cisplatin kregen. In twee

Nederlandse retrospectieve studies werd voor patiënten waarbij dosisbeperkende toxiciteit optrad een minder goede overleving gerapporteerd (Bril, 2022; Wendrich, 2017).

In de literatuursamenvatting zijn alleen RCT's geïncludeerd. De RCT's zijn over het algemeen relatief klein en hebben hun beperkingen. Er zijn diverse niet-gerandomiseerde studies verschenen die zich met name op een vergelijking van toxiciteit hebben gericht. Hieruit komen aanwijzingen naar voren dat het wekelijks toedienen van cisplatin (40 mg/m^2) tot minder (renale) toxiciteit zou kunnen leiden (Bauml, 2019; Driessen, 2016; Espeli, 2012; Ho, 2008). Daarnaast werd er één RCT geëxcludeerd omdat deze was uitgevoerd onder patiënten met een nasofarynxcarcinoom (Lee, 2016). Deze kleine RCT uit Korea suggereerde dat een wekelijkse dosis van 40 mg/m^2 niet inferieur zou zijn aan driewekelijkse toediening van cisplatin.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Het doel van het toedienen van cisplatin in een wekelijks schema in plaats van een driewekelijks schema is het verminderen van toxiciteit, zonder duidelijke afname van de effectiviteit. Er is geen onderzoek gedaan naar de waarden en voorkeuren van patiënten wat betreft deze twee doseringsschema's. Uit een meta-analyse van 107 RCT's naar de effecten van chemotherapie bij hoofd-halstumoren (Lacas, 2021) bleek dat met het toenemen van de leeftijd het effect van het toevoegen van cisplatin aan radiotherapie afneemt, waarbij er in de leeftijdsgroep boven de 70 jaar geen positief effect is op overleving en dit positieve effect in de leeftijdsgroep 60-69 ook aanzienlijk lager is dan in de groep jonger dan 50 jaar. Het is goed om te realiseren dat in de studies ook selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van het wekelijkse doseringsschema ten opzichte van het driewekelijkse schema. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht dat de aanbeveling geen relevante impact heeft op de zorgkosten.

Aanvaardbaarheid, haalbaarheid en implementatie
Patiënten bezoeken het ziekenhuis dagelijks voor de radiotherapie, daarom is de belasting van wekelijkse ten opzichte van driewekelijkse toediening wat minder groot. .

In Nederland is de hoofd-halsoncologie gecentreerd in 8 werkgroepen, waardoor een hoge mate van expertise is gewaarborgd. Voor sommige patiënten betekent dit langere reistijden wat een belasting kan zijn. Er zijn geen aanwijzingen dat dit de therapie trouw ten nadele beïnvloedt. In het algemeen is in de centra sprake van voldoende capaciteit, hoewel er binnen financiële kaders spanningen op kunnen treden. Gezien de zeer goede onderlinge samenwerking binnen een groot team, waarvan de samenstelling en benodigde expertise is vastgesteld in de SONCOS-normen, is de kwaliteit gewaarborgd. De centra worden regelmatig gevisiteerd. Alle patiënten worden besproken binnen het multidisciplinaire overleg (MDO), waarbij ook de behandelaar aanwezig is. Hierna vindt overleg plaats met de patiënt, waarbij op basis van de adviezen uit het MDO met aandacht voor de eigen voorkeur van de patiënt een beleid wordt vastgesteld.

De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Concomitante chemotherapie met cisplatin (100 mg/m^2 dag 1,22 en 43) in combinatie met conventioneel gefractioneerde radiotherapie (voorbeeld 70 Gy in zeven weken) wordt beschouwd als de standaard in de definitieve behandeling van het plaveiselcelcarcinoom van het hoofd-halsgebied. Op basis van de beschikbare literatuur is het onzeker of het wekelijkse schema tenminste net zo effectief is als het driewekelijkse schema met minder bijwerkingen.

Retrospectieve studies geven aanwijzingen dat de wekelijkse toediening gepaard zou kunnen gaan met minder (met name nefro-)toxiciteit. Een studie met dezelfde behandeling, maar voor een andere indicatie (nasofarynxcarcinoom) suggereerde dat wekelijkse toediening in een dosis van 40 mg/m^2 niet inferieur is aan driewekelijkse toediening. De weging van argumenten voor en tegen de ene dan wel de andere behandeling dient besproken te worden met patiënten.

Onderbouwing

Achtergrond

Bij de definitieve behandeling van lokaal gevorderde hoofdhals-tumoren leidt chemoradiatie met cisplatin tot betere uitkomsten dan radiotherapie alleen. Van oudsher wordt een driewekelijks schema gebruikt met een dosering van 100 mg/m^2 cisplatin op dag 1, 22 en 43 van de radiotherapie. Echter, dit gaat gepaard met aanzienlijke toxiciteit (in het bijzonder renale toxiciteit). In Nederland krijgt tegenwoordig ongeveer de helft van de patiënten cisplatin toegediend in een wekelijks schema, waarbij vaak een dosis van 40 mg/m^2 wordt gegeven. Er zijn ook studies gedaan met een lagere wekelijkse dosis van bijvoorbeeld 30 of 35 mg/m^2. De vraag is echter of een wekelijks doseringsschema even effectief is als het driewekelijkse schema en minder toxiciteit geeft.

Conclusies

Overall survival (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on overall survival when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Noronha, 2018; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Recurrence (complete tumour response) (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on recurrence (complete tumour response) when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Mashhour, 2020; Sahoo, 2017; Rawat, 2016; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Recurrence (locoregional control) (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on recurrence (locoregional control) when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Mashhour, 2020; Kiyota, 2022; Noronha, 2018; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Disease-free survival (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on disease-free survival when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Noronha, 2018; Kiyota, 2022; Nanda, 2019; Nair, 2017)*

Adverse events (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on adverse events when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Mashhour, 2020; Sahoo, 2017; Noronha, 2018; Rawat, 2016; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Quality of life (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on quality of life when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Tsan, 2012)*

Samenvatting literatuur

Samenvatting literatuur

<u>Description of studies</u>
Eight randomized controlled trials were included. Different doses of cisplatin (30, 35, or 40 mg/m^2) were used in the weekly treatment arms. Studies are grouped according to the dose provided. This clinical question is focused on patients treated with definitive chemoradiation. Four studies (also) included patients who received cisplatin in adjuvant setting (Mashhour, 2020; Noronha, 2018; Kiyota, 2022; Tsan, 2012). Most studies included patients with a carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, however the study of Nanda (2019) only included patients with an oropharyngeal carcinoma and Tsan (2012) only included patients with an oral cavity carcinoma. One study was performed in Egypt, the other seven studies were conducted in Asia.

30 mg/m^2
Mashhour (2020) conducted a randomized controlled trial in Egypt. Patients with a locally advanced head and neck squamous cell carcinoma, aged between 18 to 70 years, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were eligible. Patients were treated with adjuvant (52%) or definitive (48%) intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=30) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=30). Both groups received cisplatin concurrently with intensity modulated radiation therapy. Radiotherapy was given in a total dose of 70Gy in 33 fractions, delivered five days a week. Treatment compliance in terms of completing all planned cycles was higher in the weekly treatment group, where 70% of patients received at least six cycles of weekly chemotherapy with minor dose reductions because of toxicity. In the group receiving cisplatin every three weeks, 60% of patients completed three cycles of treatment and 40% received only two cycles. However, the median cumulative cisplatin dose was lower in the weekly treatment group (170 mg/m^2 versus 200 mg/m^2). In the weekly treatment group, 46% of patients received at least 200 mg/m^2, while in the three-weekly treatment group 75% received at least 200 mg/^{2}. Outcome measures included tumour response, locoregional control, and treatment toxicities. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

Sahoo (2017) conducted a randomized controlled trial at a regional cancer centre in India. Patients with advanced stage squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx, aged between 18 and 70 years, with an ECOG performance status ≤ 2 were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=15) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=15). External beam radiotherapy was delivered to a dose of 66 Gy in a conventional fractionation schedule. Treatment compliance in terms of completing all planned cycles was 67% in the weekly treatment arm (six cycles) and 47% in the three-weekly treatment arm (three cycles). Completion of 66 Gy radiotherapy was 87% in the weekly treatment group and 80% in the three-weekly treatment group. Outcome measures included tumour response, locoregional control, and acute and late toxicity. Toxicities were assessed using the Radiation Therapy Oncology Group Acute Radiation Morbidity Criteria.

Noronha (2018) conducted a randomized controlled trial at an academic oncology hospital in India. Patients with locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx or metastatic cervical lymphadenopathy of unknown primary, aged between 18 and 70 years, with an ECOG

performance status ≤ 2 were eligible. Patients were treated with adjuvant (93%) or definitive (7%) intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=150) or at a planned dose of 100 mg/m2 every three weeks (on days 1, 22, and 43) (n=150). External beam radiotherapy in a conventional fractionation schedule was delivered to a dose of 70 Gy in 35 fractions for patients receiving definitive treatment, and a dose of 60 Gy for patients receiving adjuvant treatment. Treatment compliance in terms of completing the planned chemoradiation was 89% in the weekly treatment arm and 94% in the three-weekly treatment arm. The chemotherapy dose was reduced in 9% of patients in the weekly treatment arm and 8% of patients in the three-weekly treatment arm, while dosing was delayed for 25% in the weekly arm and 28% in the three-weekly arm. The median cumulative cisplatin dose was 210 mg/m^2 in the weekly arm and 300 mg/m^2 in the three-weekly arm. Outcome measures included overall survival, tumour response, locoregional control, progression-free survival and acute and chronic toxicity. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (version 4.03).

35 mg/m^2
Rawat (2016) conducted a randomized controlled trial at a single centre in India. Patients with locally advanced (stage III – IV B) squamous cell carcinoma of the head and neck, aged between 18 and 65 years were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 35 mg/m2 weekly (n=30) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=30). Radiotherapy was given in a total dose of 70 Gy in 35 fractions. Treatment compliance in terms of completing all planned chemotherapy cycles was 90% in the weekly arm and 79% in the three-weekly arm. Mean cisplatin dose received was lower in the weekly arm as compared with the three-weekly arm (292 mg/m^2 versus 438 mg/m^2).
The mean dose of radiotherapy received was comparable between the arms (69.86 Gy versus 69.22 Gy). Radiotherapy had to be interrupted for 17% of patients in the weekly arm and 34% of patients in the three-weekly arm. Outcome measures included tumour response and toxicity. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Toxicity was assessed using the CTCAE version 4.03.
40 mg/m^2

Kiyota (2022) conducted a randomized controlled non-inferiority trial in 28 centres in Japan. Patients with postoperative high-risk locally advanced squamous cell carcinoma of the head and neck, aged between 20 and 75 years, with an ECOG performance score of 0 or 1 were eligible. All patients received treatment with adjuvant intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=129) or at a planned dose of 100 mg/m^2 every three weeks (n=132). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. The median number of chemotherapy cycles received was 6 (IQR 5 to 7) in the weekly arm and 3 (IQR 3 to 3) in the three-weekly arm. The median cumulative cisplatin dose was lower in the weekly treatment group (239 mg/m^2 [IQR 199 to 277] versus 280 mg/m^2 [IQR 250 to 299]). The median total radiotherapy dose was 66 Gy in both groups (IQR 66 to 66). Outcome measures included overall survival, relapse-free survival, local relapse-free survival, and adverse events. Toxicity was assessed using the CTACE version 4.0.

Nanda (2019) conducted a randomized controlled trial at a single centre in India. Patients with locally advanced oropharyngeal carcinoma, aged between 20 and 70 years, with a Karnofsky performance score > 70

were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=39) or at a planned dose of 100 mg/m^2 every three weeks (n=31). Radiotherapy was given in a total dose of 70 Gy in 35 fractions. The median number of chemotherapy cycles received was five in the weekly arm and two in the three-weekly arm. The median cumulative cisplatin dose was lower in the weekly treatment group (272 mg/m^2 versus 303 mg/m^2). Fewer patients in the weekly treatment group as compared with the three-weekly group received at least 200 mg/m^2 cisplatin (89% versus 97%). In the weekly arm, 54% of patients discontinued chemotherapy beyond four cycles, mostly because of toxicity. All patients received the planned radiation dose of 70 Gy. Outcome measures included overall survival, tumour response, locoregional control, disease-free survival, and toxicities. Tumour response was evaluated according to the WHO criteria. Toxicity was assessed using the Radiation Therapy Oncology Group criteria for radiotherapy-induced acute toxicities, and Common Toxicity Criteria for chemotherapy-induced toxicity.

Nair (2017) conducted a randomized controlled trial at a regional cancer centre in India. Patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx or larynx, aged between 18 and 70 years, with an ECOG performance status 0 or 1 were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=25) or at a planned dose of 100 mg/m^2 every three weeks (n=31). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. Treatment compliance in terms of completing all planned chemotherapy cycles was 63% in the weekly treatment group (six cycles) and 35% in the three-weekly treatment group (three cycles). The mean cumulative cisplatin dose was slightly lower in the weekly treatment group (339 mg/m^2 versus 357 mg/m^2). All patients completed radiation apart from one patient who died during treatment. Outcome measures included overall survival, locoregional control, tumour response, disease-free survival, and toxicities. Tumour response was evaluated using RECIST criteria. Toxicity was assessed using the Radiation Therapy Oncology Group criteria for radiotherapy-induced toxicities, and Common Terminology Criteria version 4 for chemotherapy-induced toxicity.

Tsan (2012) conducted a randomized controlled trial at a single centre in Taiwan. Patients with high-risk oral cavity squamous cell carcinoma, aged between 18-70 years, with an ECOG performance status 0 to 2 were eligible. All patients received treatment with adjuvant intent. The trial aimed to recruit 371 patients but the trial was stopped after recruiting only 55 patients (of which 50 were randomized) over 30 months. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=24) or at a planned dose of 100 mg/m^2 every three weeks (n=26). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. The mean cumulative doses of cisplatin and radiotherapy were comparable between the groups. However, fewer patients in the weekly treatment group received at least 200 mg/m^2 cisplatin (63% versus 89%). Outcome measures included (preliminary) overall survival, (preliminary) locoregional recurrence-free survival, quality of life (Chinese version of the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) questionnaire) and adverse events. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results

No meta-analysis was performed because of clinical and methodological heterogeneity, but the results for overall survival and locoregional recurrence are shown in Figures 13.9.1 and 13.9.2 to provide more insight in the effects found.

30 mg/m²
Overall survival
Noronha (2018) observed 60 deaths in the weekly treatment arm (40%) and 53 deaths in the three-weekly treatment arm (35%). Median overall survival was 39.5 months in the weekly treatment arm, while median overall survival was not reached in the three-weekly treatment arm (HR 1.14 (95%CI 0.79 to 1.65; p=0.48).

Recurrence (tumour response)
Mashhour reported tumour response, a complete response was seen in 77% of patients receiving weekly cisplatin and 76% of patients receiving three-weekly cisplatin. A partial response was seen in 13.2% of patients receiving weekly cisplatin and 12.6% of patients receiving three-weekly cisplatin. Two months after treatment, stable disease was observed in 4.6% of patients in the weekly treatment group and 4.1% of patients in the three-weekly treatment group.

Sahoo (2017) reported that after a median follow-up of seven months, complete response was achieved by 73% of patients in the weekly arm and 86% of patients in the three-weekly arm (not statistically significant).

Recurrence (locoregional control)
Mashhour (2020) reported that after a median follow-up of 24 months, locoregional control rates were 57.6% in the weekly treatment group and 72.8% in the three-weekly treatment group (HR 1.78; p=0.015).

Noronha (2018) reported that the 2-year locoregional control rate was 58.5% in the study arm receiving weekly cisplatin and 73.1% in the group receiving three-weekly cisplatin (HR 1.76 (95%CI 1.11 to 2.79; p=0.014).

Disease-free survival
In the trial by Noronha (2018), the estimated median progression-free survival was 17.7 months (95%CI 0.42 to 35.05) in the weekly treatment arm and 28.6 months (95%CI 15.9 to 41.3) in the three-weekly treatment arm (HR 1.24 (95%CI 0.89 to 1.73); p=0.21).

Quality of life
Quality of life was not reported in any of the RCTs using a dose of 30 mg/m².

Adverse events
Mashhour (2020) reported non-haematological and haematological adverse events. For non-haematological adverse events, acute toxicities grade ≥ 3 were observed less frequently in the weekly treatment group (56.6%) compared with the three-weekly treatment group (76.6%) (p=0.007). No statistically significant differences were found for individual grade ≥ 3 toxicities, including mucositis (53% in the weekly cisplatin

group versus 47% in the three-weekly cisplatin group), dysphagia (47% versus 67%) , nausea/vomiting (13% versus 20%), xerostomia (17% versus 20%), dermatitis (13% versus 10%), and laryngeal oedema (17% versus 17%).

For haematological adverse events, grade ≥ 3 leukopenia (20% versus 37%; p<0.05) and neutropenia (10% versus 20%; p<0.05) occurred less frequently in the weekly cisplatin group compared with the three-weekly cisplatin group. No differences were found between the frequency of grade ≥ 3 anemia (17% versus 30%) and thrombocytopenia (3% versus 10%) in the weekly and three-weekly treatment groups.

Sahoo (2017) reported that grade 3 mucositis and vomiting were less frequent in the weekly cisplatin arm compared with the three-weekly cisplatin arm (53% versus 40%; p=0.729) and (20% versus 7%; p=0.360). In contrast, grade 3 dermatitis was more frequent in the weekly arm compared with the three-weekly arm (27% versus 7%; p=0.360). The frequencies of grade 3 dysphagia, anemia, and leukopenia were (almost) similar between the arms (0% versus 7%, 7% versus 7%, 13% versus 7%). The frequency of late toxicities (xerostomia and skin fibrosis) was comparable between the study arms.

Noronha (2018) reported acute (within 90 days from the start of treatment) and chronic (more than 90 days from the start of treatment) toxicities. For acute toxicities, any acute toxicity grade ≥ 3 was observed in 72% of patients receiving weekly cisplatin and 85% of patients receiving three-weekly cisplatin (p=0.006). Toxicities that occurred less frequently in the weekly treatment group included vomiting (1% versus 7%; p=0.019), infection (21% versus 34%; p=0.015), deafness (5% versus 13%; p=0.013), hyponatremia (23% versus 52%; p<0.001), leukopenia (3% versus16%; p<0.001), neutropenia (1% versus 13%; p<0.001), febrile neutropenia (1% versus 6%; p=0.019), and lymphocytopenia (72% versus 89%; p=0.001). No differences between the weekly and three-weekly treatment group were observed in the frequency of mucositis, dysphagia, odynophagia, xerostomia, dysgeusia, dermatitis, diarrhoea, fatigue, weight loss, hoarseness, hypertension, hypokalemia, transaminase elevation, anemia and thrombocytopenia. There were no patients experiencing ≥ 3 neuropathy or renal dysfunction.

For chronic toxicities, any chronic toxicity grade ≥ 3 was observed in 10% of patients receiving weekly cisplatin and 14% of patients receiving three-weekly cisplatin (p=0.55). The only toxicity that occurred less frequency in the weekly treatment group was deafness (4% versus 16%; p=0.004). No differences between the weekly and three-weekly treatment group were observed in the frequency of mucositis, dysphagia, odynophagia, infection, xerostomia, subcutaneous, trismus, and hypertriglyceridemia. There were no patients experiencing ≥ 3 dysgeusia, skin toxicity, hypothyroidism, or thromboembolic events.

35 mg/m²
Overall survival
Rawat (2016) did not report on overall survival.

Recurrence (tumour response)
Rawat (2016) reported that three months after treatment completion, complete response was 67% in the group receiving weekly cisplatin and 62% in the group receiving three-weekly cisplatin. Partial responses were received in 33% of patients receiving weekly treatment and 38% of patients receiving three-weekly treatment. No statistically significant differences were found between the arms (p=0.20).

Recurrence (locoregional control)
Rawat (2016) did not report on locoregional control.

Disease-free survival
Rawat (2016) did not report on disease-free survival.

Quality of life
Rawat (2016) did not report on quality of life.

Adverse events
For non-haematological toxicities, Rawat (2016) reported that the frequency of grade 3 mucositis (70% versus 76%; p=0.20) was similar between the groups, while the frequency of grade 3 vomiting was lower in the group receiving weekly treatment (20% versus 35%; p=0.03). For haematological toxicities, no differences were found for grade 3 anemia (33% versus 31%; p=0.22) and thrombocytopenia (7% versus10%; p=0.32), while grade 3 neutropenia was less frequent in the group receiving weekly treatment (27% versus 55%; p=0.02). Rawat (2016) also reported on a number of other toxicities. For acute renal toxicity, only mild toxicity was observed, while for significant weight loss, hyponatremia and hypomagnesemia it was not clear whether the frequencies involved grade 3 toxicity.

<u>40 mg/m^2</u>
Overall survival

Kiyota (2022) reported estimated 2-year and 3-year survival rates of 77.7% and 71.6% in the weekly treatment arm and 74.5% and 59.1% in the three-weekly treatment arm. The hazard ratio was 0.69 (99.1%CI 0.37 to 1.27; one-sided p-value for non-inferiority=0.0027). Since the upper limit of the confidence interval was below the prespecified threshold of 1.32, the authors concluded that weekly treatment is non-inferior with regard to survival.

Nanda (2020) reported that median overall survival was 35.4 months in the weekly treatment group and 32.9 months in the three-weekly treatment group (p=0.303). The two-year and five-year survival rates were 55% and 42% in the weekly treatment group and 58% and 32% in the three-weekly treatment group (not statistically significant, no p-value provided).

Nair (2017) reported two-year survival rates of 61% in the weekly treatment arm and 71% in the three-weekly treatment arm (p=0.610).

Tsan (2012) reported preliminary overall survival after a median follow-up of 12 months. In each group, six patients had died. One-year overall survival rates were 72% in the weekly treatment group and 79% in the three-weekly treatment group (p=0.978).

Recurrence (tumour response)
Nanda (2020) reported that complete response was seen in 81% of patients receiving weekly treatment and

75% of patients receiving three-weekly treatment. Partial responses were seen in 14% of patients receiving weekly treatment and 13% of patients receiving three-weekly treatment. Eight weeks after completion of treatment, stable disease was 5% in the weekly treatment group and 4% in the three-weekly treatment group.

Nair (2017) reported that complete responses were observed in 75% of patients in the weekly treatment arm and 90% of patients in the three-weekly arm. Partial response rates were 12% and 6%. Twelve weeks after completion of treatment, two patients in each arm (8% versus 6%) had residual disease.

Recurrence (locoregional control)
Kiyota (2022) reported recurrences in 29% of patients receiving weekly treatment and 39% of patients received three-weekly treatment.

Nanda (2020) observed locoregional relapses in 14% of patients receiving weekly treatment and 6% of patients receiving three-weekly treatment. Three months after completion of treatment, stable or progressive disease was observed in 29% of patients in the weekly treatment group and 42% of patients in the three-weekly treatment group.

Nair (2017) reported that two patients in the weekly treatment group developed local recurrence and one patient developed lung metastasis (13%), while four patients in the three-weekly treatment group developed local recurrence (13%). In the weekly treatment group, three patients developed a second primary tumour (in the esophagus or tongue) (13%), while in the three-weekly group two patients developed a second primary tumour in the esophagus (6%). Two-year locoregional control rates were 63% in the weekly cisplatin arm and 61% in the three-weekly cisplatin arm.

Tsan (2012) reported preliminary locoregional recurrence-free survival after a median follow-up of 12 months. In the weekly arm, 9 patients had experienced a recurrence while in the three-weekly arm, 8 patients had experienced a recurrence. One-year locoregional recurrence-free survival rates were 60% in the weekly treatment group and 71% in the three-weekly treatment group (p=0.806).

Disease-free survival
Kiyota (2022) reported hazard ratios of 0.71 (95%CI 0.48 to 1.06) for relapse-free survival and 0.73 (95%CI 0.47 to 1.13) for local relapse-free survival.

Nanda (2020) reported that median progression-free survival was 26.4 months in the weekly treatment group and 27.4 months in the three-weekly treatment group (p=0.953).

Nair (2017) reported that two-year disease-free survival rates were 53% in the weekly arm and 65% in the three-weekly arm (p=0.674).

Adverse events

Kiyota (2022) reported no difference in the proportion of patients experiencing at least one grade ≥ 3 event (81.1% versus 79.8%; p=0.87), while fewer patients in the weekly group experienced a grade 4 event (8.2%

versus 18.6%; p=0.017). For haematological adverse events, there were no differences in the frequency of grade ≥ 3 events (64.8% versus 61.2%; p=0.06) and grade 4 events (7.4% versus 14.7%; p=0.07). Specific grade ≥ 3 adverse events that were reported to be lower in the weekly treatment group included neutropenia (35% versus 49%) and infection (7% versus 12%).

Nanda (2020) observed no statistically significant differences in the frequency of grade ≥ 3 radiation toxicities and haematological toxicities between the two groups. Radiation toxicities included mucositis (32% versus 29%; p=1.00), dysphagia (46% versus 32%; p=0.27), dermatitis (14% versus 19%; p=0.73), larynx (11% versus 10%; p=1.00), and nausea/vomiting (7% versus 0%; p=0.22). Haematological toxicities included anemia (0% versus 3%; p=1.00), leukopenia (25% versus 13%; p=0.32), neutropenia (18% versus 7%; p=0.24), and thrombocytopenia (0% versus 3%; p=1.00).

Nair (2017) reported a lower frequency of grade ≥ 3 dysphagia (63% versus 26%; p<0.05) in the weekly cisplatin group. No other statistically significant differences were reported in the frequency of grade ≥ 3 non-haematological and haematological toxicities between the two groups. Non-haematological toxicities included mucositis (54% versus 52%; p>0.05), and dermatitis (13% versus3%; p>0.05). Haematological toxicities included anemia (4% versus 0%; p>0.05), neutropenia (8% versus 3%; p>0.05), and thrombocytopenia (no grade 3 adverse events observed). No grade ≥ 3 renal toxicity was observed.

Tsan (2012) reported that overall, more grade ≥ 3 toxicities were observed in the weekly group (92%) compared with the three-weekly group (81%) (p=0.02). For non-haematological toxicities, mucositis was reported more frequency in the weekly treatment group (75%) compared with the three-weekly group (39%) (p=0.012). The frequencies of the following toxicities were comparable between the groups: pharyngitis (54% versus 54%; p=1.0), stomatitis (54% versus 54%; p=1.0), laryngeal edema (4% versus 12%; p=0.611), dermatitis (8% versus 8%; p=1.0), and nausea/vomiting (21% versus 12%; p=0.456).

For haematological toxicities, no differences were observed between the groups for anemia (4% versus 4%; p=1.0), leukopenia (13% versus 0%; p=0.103), neutropenia (4% versus 0%; p=0.480), and thrombocytopenia (0% versus 0%).

Quality of life
Tsan (2012) reported results for five subscales of the FACT H&N questionnaire and the Trial Outcome Index (TOI) which is a combined scale for the subscales physical well-being, functional well-being and the head and neck subscale. Higher scores represent better QoL. It was not reported how many patients completed the questionnaires at each time point.

For the physical well-being scale (range 0 to 28), lower scores were seen in the weekly treatment group at week 2 (difference of 4.5 points between the groups), week 4 (5.7 points), at the end of radiotherapy (7.8 points) and follow-up after three months (4.3 points). For the social well-being scale (range 0 to 28), higher scores were seen in the weekly treatment group at week 4 (difference of 2.9 points between the groups), at the end of radiotherapy (5.7 points), and follow-up after three months (5 points). Emotional well-being scores were comparable between the groups at all time points. Functional well-being scores (range 0 to 28) were only different between the groups at three months follow-up, with lower scores seen in the weekly treatment

group (3.3 points difference between the groups). Scores on the head and neck subscale were comparable between the groups at all time points. TOI scores (range 0 to 96) were only different between the groups at three months follow-up, with lower scores seen in the weekly treatment group (difference 9.7 points).

Level of evidence of the literature
All studies were RCTs, therefore the level of evidence started at 'high' for all outcome measures.

The level of evidence was downgraded for all outcomes because most (7/8) studies were conducted in Asia (India, Taiwan, and Japan), while it has been described that head and neck cancers in Asian countries have a different etiology and molecular biology. Publication bias was not assessed because of the low number of studies found.

The level of evidence regarding the outcome measure overall survival was downgraded by four levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one trial was stopped prematurely); applicability (-1; bias due to indirectness because three studies were conducted among patients who were treated (mainly) with adjuvant intent and all studies were conducted in Asia); and number of included patients (-2; imprecision because of wide confidence intervals including the possibility of a negative effect, no effect, and a positive effect). Publication bias was not assessed.

The level of evidence regarding the outcome measure recurrence (tumour response) was downgraded by five levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); conflicting results (-1; inconsistency because two studies showed worse tumour response rates, two studies showed no effect and one study showed better tumour response rates); applicability (-1; bias due to indirectness because in one study 52% of patients were treated with adjuvant intent and most studies were conducted in Asia); and number of included patients (-2; imprecision because of the low sample sizes). Publication bias was not assessed.

The level of evidence regarding the outcome measure recurrence (locoregional control) was downgraded by five levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one trial was stopped prematurely); conflicting results (-1; inconsistency because three studies showed worse locoregional control, two studies showed no effect, and one study showed better locoregional control); applicability (-1; bias due to indirectness because four studies were conducted among patients who were treated (mainly) with adjuvant intent and most studies were conducted in Asia); and number of included patients (-2; imprecision because of wide confidence intervals including the possibility of a negative effect, no effect, and a positive effect). Publication bias was not assessed.

The level of evidence regarding the outcome measure disease-free survival was downgraded by three levels because of conflicting results (-1; inconsistency because one study showed worse DFS and two showed no difference); applicability (-1; bias due to indirectness because two studies were conducted among patients who were treated (mainly) with adjuvant intent and all studies were conducted in Asia); and number of included patients (-1; imprecision because of confidence intervals including the possibility of a negative effect and no effect (and a positive effect)). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one study was stopped prematurely); applicability (-1; bias due to indirectness because four studies were conducted among patients who were treated (mainly) with adjuvant intent and most studies were conducted in Asia); and number of included patients (-1; imprecision because of the low number of patients included in individual studies). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>quality of life</u> was downgraded by five levels because of study limitations (-2 risk of bias because of incomplete reporting of study methodology, lack of blinding, and study stopped prematurely); applicability (-1; bias due to indirectness because the study was conducted among patients who were treated with adjuvant intent and was conducted in Asia); number of included patients (-2; imprecision because of the low sample size in a single study). Publication bias was not assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the benefits and risks of weekly versus three-weekly cisplatin concurrent with definitive radiotherapy for patients with locally advanced head and neck squamous cell carcinoma?

P: Patients with locally advanced head and neck squamous cell carcinoma.
I: Weekly cisplatin concurrent with definitive radiotherapy.
C: Three-weekly cisplatin concurrent with definitive radiotherapy.
O: Overall survival, recurrence (tumour response and locoregional control), disease-free survival, quality of life, adverse events.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and recurrence as critical outcome measures for decision making; and disease-free survival, adverse events, and quality of life as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically important difference as follows:

- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Tumour response: absolute difference > 5% in complete response rates
- Local recurrence: 0.8 or 1.25 as borders for risk or odds ratios.
- Locoregional control: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Progression-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Adverse events: statistically significant difference in grade ≥ 3 adverse event rate.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 12 November 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 534 hits (60 SRs and 474 RCTs). Studies were selected based on the following criteria: (1) patients with a locally advanced squamous cell carcinoma in the head and neck region; (2) comparison between radiotherapy combined with weekly or three-weekly cisplatin; (3) systematic review or randomized controlled trial; (4) full-text English language publication. Studies including only patients with nasopharyngeal cancer were excluded.

24 studies were initially selected based on title and abstract screening. After reading the full text, 17 studies were excluded (see the table with reasons for exclusion under the tab Methods) and seven studies were included. The working group identified an additional RCT that was published after the search date. This RCT was also included in the summary of literature. We cannot exclude the possibility that other relevant reviews or RCTs were published after the search date.

Results

Eight original studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Alternatief voor cisplatin bij chemoradiatie

Uitgangsvraag

Wat is de rol van systemische therapie in aanvulling op definitieve radiotherapie bij patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied bij wie cisplatin is gecontra-indiceerd?

Aanbeveling

Bespreek met patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied bij wie cisplatin gecontra-indiceerd is de alternatieven voor cisplatin in aanvulling op definitieve radiotherapie, te weten cetuximab, carboplatin of carboplatin in combinatie met 5-FU, en wijs daarbij op de voor- en nadelen van deze alternatieven.

Op basis van prospectief onderzoek kan geen aanbeveling worden gedaan voor patiënten boven de 70 jaar.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Onze systematische zoekactie in diverse databases resulteerde in 13 relevante studies die resultaten rapporteren van 9 verschillende RCT's.

1. RT + cetuximab
In totaal hadden 3 van de 13 studies betrekking op de vergelijking tussen radiotherapie en cetuximab enerzijds en alleen radiotherapie anderzijds (Bonner, 2006; Curran, 2007 en Bonner, 2010). Deze studies rapporteerden resultaten van een en dezelfde trial. Er werden klinisch relevante verschillen gevonden voor totale overleving (cruciale uitkomstmaat) op 3 en 5 jaar en progressievrije overleving (belangrijke uitkomstmaat) op 2 en 3 jaar, ten faveure van bioradiotherapie. Er werd geen klinisch relevant verschil gevonden voor kwaliteit van leven (belangrijke uitkomstmaat). Van de acute bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) traden een acné-achtige huiduitslag, infusiereacties en anemie statistisch significant vaker op bij patiënten die behandeld werden met radiotherapie en cetuximab, vergeleken met patiënten die alleen radiotherapie kregen. Het percentage patiënten met een late bijwerking van graad 3 of hoger verschilde niet tussen de behandelgroepen. Een subgroepanalyse liet zien dat voor totale overleving patiënten met een orofarynxtumor mogelijk het meeste baat hebben bij de toevoeging van cetuximab aan radiotherapie. Het percentage patiënten met een lokaal recidief (cruciale uitkomstmaat) werd niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege de actieve rol van de studiesponsor bij het verzamelen en analyseren van de data), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was) en imprecisie (vanwege het geringe aantal deelnemers en het feit dat de 3 studies betrekking hadden op slechts 1 RCT). Inconsistentie en publicatiebias konden niet beoordeeld worden.

2. RT + carboplatin
Eveneens 3 van de 13 studies hadden betrekking op de vergelijking tussen radiotherapie en carboplatin enerzijds en alleen radiotherapie anderzijds (Fountzilas, 2004; Jeremic, 1997 en Ruo Redda, 2010). Deze

studies rapporteerden resultaten van 3 verschillende trials. Er werd een klinisch relevant verschil gevonden voor totale overleving (cruciale uitkomstmaat) op 1, 2, 3 en 4 jaar, ten faveure van chemoradiotherapie, maar niet voor totale overleving op 10 jaar. De studies toonden conflicterende resultaten voor totale overleving op 5 jaar: 2 studies (n = 79 en n = 106) lieten wel een klinisch relevant verschil zien, terwijl in 1 studie (n = 164) geen klinisch relevant verschil werd gevonden. Voor ziektevrije overleving (belangrijke uitkomstmaat) werd een klinisch relevant verschil gevonden op 3 jaar, ten faveure van chemoradiotherapie, maar niet op 5 en 10 jaar. Voor geen van de acute en late bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) werd een eenduidig klinisch relevant verschil gevonden. Het percentage patiënten met een lokaal recidief (cruciale uitkomstmaat), progressievrije overleving en kwaliteit van leven werden niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege onvolledige rapportage, verschillen in patiëntkenmerken tussen de behandelarmen in een studie en het vroegtijdig stoppen van een trial), inconsistentie (vanwege conflicterende resultaten), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was) en imprecisie (vanwege het geringe aantal deelnemers per studie). Inconsistentie kon niet beoordeeld worden voor ziektevrije overleving, en publicatiebias kon in het geheel niet beoordeeld worden.

3. RT + carboplatin and 5-FU
De resterende 7 studies hadden betrekking op de vergelijking tussen radiotherapie gecombineerd met carboplatin en 5-FU enerzijds en alleen radiotherapie anderzijds (Bourhis, 2012; Calais, 1997; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001 en Semrau, 2006). Deze studies rapporteerden resultaten van 5 verschillende trials. Er werd een klinisch relevant verschil gevonden voor totale overleving (cruciale uitkomstmaat) op 1, 2, 3 en 5 jaar, ten faveure van chemoradiotherapie. Voor het percentage patiënten met een lokaal recidief (cruciale uitkomstaat) en ziektevrije overleving (belangrijke uitkomstmaat) op 2, 3 en 5 jaar werd eveneens een klinisch relevant verschil gevonden, ten faveure van chemoradiotherapie, maar niet voor progressievrije overleving (belangrijke uitkomstmaat). Voor geen van de acute bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) werd een eenduidig klinisch relevant verschil gevonden. Voor de late bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) gold dat late slikproblemen en permanente sondevoeding vaker werden gezien bij patiënten die behandeld waren met hypergefractioneerde, geaccelereerde radiotherapie in combinatie met 5-FU, vergeleken met alleen radiotherapie; dit verschil was klinisch relevant. Kwaliteit van leven werd niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was laag tot zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege onvolledige rapportage, verschillen in patiëntkenmerken tussen de behandelarmen in een studie en het vroegtijdig stoppen van 2 trials), inconsistentie (vanwege conflicterende resultaten), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was en het gebruik van verschillende radiotherapeutische regimes) en imprecisie (vanwege het geringe aantal deelnemers per studie). Inconsistentie kon niet beoordeeld worden voor het percentage patiënten met een lokaal recidief en ziekte- en progressievrije overleving, en publicatiebias kon in het geheel niet beoordeeld worden.

Op basis van de resultaten van de studie van Mehanna (2019) lijkt het toevoegen van cetuximab aan definitieve radiotherapie niet van waarde te zijn voor patiënten met een gevorderd HPV-positief orofarynxcarcinoom. De studie van Mehanna (2019) is in deze module overigens geëxcludeerd omdat er

alleen patiënten met een gevorderd HPV-positief orofarynxcarcinoom zijn geïncludeerd. Voor deze patiëntenpopulatie is een aparte module beschikbaar (RLDB: link invoegen naar module 'Behandeling HPV-positieve orofarynx tumoren'). Daarnaast wordt in de studie van Mehanna (2019) en ook de studie van Gillison (2019) geen vergelijking gemaakt tussen radiotherapie en cetuximab met alleen radiotherapie, maar wordt radiotherapie en cetuximab vergeleken met radiotherapie met cisplatin. Op basis van de huidige literatuur kan geen uitspraak gedaan worden over de rol van carboplatin met of zonder 5-FU als alternatief voor cetuximab.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Curran (2007) vonden geen statistisch significant, maar wel een beperkt klinisch relevant verschil in kwaliteit van leven tussen patiënten die behandeld werden met radiotherapie en cetuximab en patiënten die alleen radiotherapie kregen, ten nadele van de patiënten die met cetuximab werden behandeld. Er is geen onderzoek gedaan naar kwaliteit van leven bij de andere schema's. Vanwege de beperkte literatuur op dit gebied kan de werkgroep geen uitspraak doen over de waarden en voorkeuren van patiënten.

Het doel van het toevoegen van cetuximab of carboplatin met of zonder 5-FU aan definitieve radiotherapie is het verbeteren van de locoregionale controle, zonder duidelijke toename van de toxiciteit. Dit laatste is met name ook voor de patiënt van belang, omdat het hier een kwetsbare groep patiënten betreft. Uit een meta-analyse van 107 RCT's naar de effecten van chemotherapie bij hoofd-halstumoren (Lacas, 2021) bleek dat met het toenemen van de leeftijd het effect van het toevoegen van cisplatin aan radiotherapie afneemt, waarbij er in de leeftijdsgroep boven de 70 jaar geen positief effect is op overleving en dit positieve effect in de leeftijdsgroep 60-69 al weer aanzienlijk lager is dan in de groep jonger dan 50 jaar. Het is goed om te realiseren dat in de studies ook selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
Extra kosten voor de patiënt zijn het regelmatig bezoeken van het ziekenhuis voor de behandelingen. Ook de bijwerkingen kunnen leiden tot extra kosten, zoals de kosten van medicatie vanwege huiduitslag, de kosten die gepaard gaan met een eventuele infectie of bloeding en de kosten van mogelijke extra ziekenhuisopnames. De meeste van deze kosten zijn verzekerd, maar dit betekent kosten voor de samenleving en voor familie en relaties. Gezien de onzekerheid die bestaat over de gunstige effecten is het moeilijk aan te geven of dit de (extra) middelen waard is? Een kosten-batenanalyse ontbreekt in de literatuur.

Gezien de langere overleving bij HPV-positieve patiënten met een orofarynxcarcinoom zou bij deze groep adjuvante therapie meer van waarde kunnen zijn. Anderzijds zal bij oudere patiënten (> 75 jaar) met een 'WHO performance status' > 2 gezien de bijwerkingen meer terughoudendheid moeten worden betracht.

De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van de-escalatiestrategieën. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht dat de aanbeveling geen relevante impact heeft op de zorgkosten.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
In Nederland is de hoofd-halsoncologie gecentreerd in 8 werkgroepen, waardoor een hoge mate van expertise is gewaarborgd. Voor sommige patiënten betekent dit langere reistijden wat een belasting kan zijn. Er zijn geen aanwijzingen dat dit de therapietrouw ten nadele beïnvloedt. In het algemeen is in de centra sprake van voldoende capaciteit, hoewel er binnen financiële kaders er spanningen op kunnen treden. Gezien de zeer goede onderlinge samenwerking binnen een groot team, waarvan de samenstelling en benodigde expertise is vastgesteld in de SONCOS-normen, is de kwaliteit gewaarborgd. De centra worden regelmatig gevisiteerd. Alle patiënten worden besproken binnen het multidisciplinaire overleg (MDO), waarbij ook de behandelaar aanwezig is. Hierna vindt uitgebreid verleg plaats met de patiënt, waarbij op basis van de adviezen uit het MDO en de eigen voorkeur van de patiënt een beleid wordt uitgestippeld.

De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Op basis van de huidige literatuur kan geen zekere uitspraak gedaan worden over een goed alternatief voor cisplatin bij patiënten bij wie cisplatin gecontra-indiceerd is. In de voorgaande richtlijn werd cetuximab genoemd als alternatief voor patiënten bij wie cisplatin gecontra-indiceerd is. Op basis van recente studies (Gillison (2019) en Mehanna (2019)) is twijfel gerezen over de toegevoegde waarde van cetuximab aan radiotherapie in de behandeling van patiënten met een gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied, hoewel in deze studies met name patiënten met een HPV-positief orofarynxcarcinoom waren geïncludeerd. Voor patiënten met een gevorderd HPV-positief orofarynxcarcinoom lijkt het toevoegen van cetuximab aan definitieve radiotherapie niet van waarde te zijn, zie ook de module 'Behandeling HPV-positieve orofarynx tumoren').
Deze onzekerheid wat betreft het beste alternatief voor cisplatin dient besproken te worden met deze patiënten. Er kan gekozen worden voor een van de in deze richtlijnmodule besproken alternatieven, maar dan moet het risico op toegenomen toxiciteit worden afgewogen tegen de onzekere voordelen.

Onderbouwing

Achtergrond

Patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied kunnen in opzet curatief behandeld worden met radiotherapie. Het toevoegen van cisplatin aan deze behandeling leidt bij patiënten van 70 jaar of jonger en een 'WHO performance status' van 0 of 1 tot een betere lokale controle en overleving, maar gaat ook gepaard met meer toxiciteit. Met het toenemen van de leeftijd neemt het effect van het toevoegen van chemotherapie aan radiotherapie af, waarbij er bij patiënten boven de 70 jaar geen positief effect op overleving is gerapporteerd. Bij een deel van de patiënten is behandeling met cisplatin gecontra-indiceerd vanwege bijvoorbeeld cardiovasculaire problemen of nierinsufficiëntie. Mogelijke behandelalternatieven voor deze patiënten zijn cetuximab, carboplatin of carboplatin én 5-fluoro-uracil (5-FU). Het toxiciteitsprofiel van deze geneesmiddelen is weliswaar anders dan dat van cisplatin, maar het is onduidelijk hoe effectief deze middelen zijn en welk middel de voorkeur heeft.

Conclusies

1. RT + cetuximab
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bonner, 2006; Bonner, 2010)*

Local recurrence

- GRADE	No evidence was found regarding the effect of radiotherapy combined with cetuximab on local recurrence in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Disease-free survival

- GRADE	No evidence was found regarding the effect of radiotherapy combined with cetuximab on disease-free survival in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Progression-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on progression-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bonner, 2006)*

Quality of life

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on quality of life when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Curran, 2007)*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bonner, 2006)*

2. RT + carboplatin
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Fountzilas, 2004; Jeremic, 1997; Ruo Redda, 2010)*

Local recurrence

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on local recurrence in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on disease-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Ruo Redda, 2010)*

Progression-free survival

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on progression-free survival in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Quality of life

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on quality of life in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Fountzilas, 2004; Jeremic, 1997; Ruo Redda, 2010)*

3. RT + carboplatin and 5-FU
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012; Calais, 1999; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001; Semrau, 2006)*

Local recurrence

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on local recurrence when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: Calais, 1999; Denis, 2004)*

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on disease-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Calais, 1999; Denis, 2004; Olmi, 2003)*

Progression-free survival

Low GRADE	The evidence suggests that radiotherapy combined with carboplatin and 5-FU results in little to no difference in progression-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012)*

Quality of life

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin and 5-FU on quality of life in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012; Calais, 1999; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001; Semrau, 2006)*

Samenvatting literatuur

Description of studies

1. Radiotherapy + cetuximab

Bonner (2006), Curran (2007) and Bonner (2010) report on a multicenter, randomized controlled phase 3 trial that was conducted at 73 academic centers in the US and 14 other countries, including the Netherlands. Patients with previously untreated, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 60, and normal bone marrow, hepatic and renal function. Patients were randomly assigned (1:1) to receive high-dose radiotherapy and cetuximab (n = 211), or high-dose radiotherapy alone (n = 213). Investigators were required to select 1 of 3 radiotherapy-fractionation regimens (concomitant boost, once daily, or twice daily) before randomization. The final review of radiotherapy revealed that the mean and median doses for the 3 regimens did not differ between the 2 treatment groups. Administration of cetuximab was initiated 1 week before radiotherapy at a loading dose of 400 mg/m^2 over a period of 120 minutes, followed by weekly 60-minute infusions of 250 mg/m^2 for the duration of radiotherapy. The primary outcome measure was the duration of locoregional control, which was not of our interest. Secondary outcome measures of our interest included overall survival, progression-free survival, quality of life and safety. Quality of life was assessed using two validated, multidimensional instruments, namely the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC QLQ Head and Neck Cancer-Specific Module (H&N35). Acute toxic effects were assessed through the eighth week after treatment using the criteria of the Radiation Therapy Oncology Group (RTOG). Late toxic effects of radiotherapy were assessed thereafter using the criteria of the RTOG/EORTC.

2. Radiotherapy + carboplatin

Fountzilas (2004) conducted a multicenter, randomized controlled phase 3 trial at 5 hospitals in Greece, Romania and Germany. Patients aged ≥ 18 years with biopsy-proven, previously untreated, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow, hepatic and renal function, and adequate cardiovascular, pulmonary, nutritional and mental status. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy and carboplatin (n = 38), standard fractionated radiotherapy and cisplatin (n = 45) or standard fractionated radiotherapy alone (n = 41). The treatment group of patients who received standard fractionated radiotherapy and cisplatin is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 70 Gy at 1.8 Gy per fraction per day, 5 days per week. Carboplatin was administered at an AUC of 7 on days 2, 22 and 42. The primary outcome measure was the overall survival at 3 years. The authors also report the overall survival at 5 years, the median overall survival, and safety. Acute toxic effects were assessed using the criteria of the RTOG.

Jeremic (1997) conducted a single-center, randomized controlled trial in Yugoslavia. Patients aged > 18 years with histologically confirmed, previously untreated, unresectable, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the head and neck were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 50, adequate bone marrow, hepatic and renal function, and no serious concomitant disease. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy and carboplatin (n = 53), standard fractionated radiotherapy and cisplatin (n = 53) or standard fractionated

radiotherapy alone (n = 53). The treatment group of patients who received standard fractionated radiotherapy and cisplatin is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 70 Gy at 1.8 Gy per fraction per day, 5 days per week. Carboplatin was intravenously administered 45-60 minutes before the irradiation as a bolus at a daily dose of 25 mg/m^2. The primary outcome measure was the overall survival at 3 years. The authors also report the overall survival at 1 year, 2 years, 4 years and 5 years, and safety. Acute and late toxic effects of radiotherapy were assessed using the criteria of the RTOG and RTOG/EORTC, respectively. Toxic effects of chemotherapy were assessed using the criteria of the ECOG. The trial was prematurely stopped before the planned accrual of 85 patients per treatment group was reached, because the chief investigator had to leave the department.

Ruo Redda (2010) conducted a multicenter, randomized controlled phase 3 trial at 6 centers in Italy. Patients aged 18-70 with biopsy-proven, previously untreated, stage III or IV, non-metastatic, measurable, unresectable squamous cell carcinoma of the head and neck were eligible. Criteria for eligibility also included an ECOG performance status ≤ 2, adequate bone marrow, hepatic and renal function, adequate nutritional and liquid intake, and no serious concomitant disease. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy and carboplatin (n = 82), or standard fractionated radiotherapy alone (n = 82). Radiotherapy was given in a total dose of 70 Gy at 2 Gy per fraction per day, 5 days per week. Carboplatin was intravenously administered 45-60 minutes before the irradiation as a bolus at a daily dose of 45 mg/m^2 on day 1-5 of the 1st, 3rd, 5th and 7th week of the combined treatment (total dose: 900 mg/m^2). The primary outcome measure was the locoregional recurrence-free survival, which was not of our interest. Secondary outcome measures of our interest included overall survival, disease-free survival, and safety. Acute toxic effects were assessed using the criteria of the World Health Organization (WHO). Late toxic effects were assessed using the criteria of the RTOG/EORTC.

3. Radiotherapy + carboplatin and 5-FU
Bourhis (2012) conducted a multicenter, randomized controlled phase 3 trial at 22 centers in France and Belgium (GORTEC 99-02 trial). Patients with histologically confirmed, previously untreated, stage III or IV, non-metastatic, squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included an ECOG performance status ≤ 2, adequate bone marrow, hepatic and renal function, no history of other cancer in the previous 5 years, and no clinically significant cardiac disease. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 279), accelerated radiotherapy plus carboplatin and 5-FU (n = 280) or very accelerated radiotherapy alone (n = 281). Patients allocated to receive standard fractionated radiotherapy received a total dose of 70 Gy in 7 weeks: 5 fractions of 2 Gy per week, with spinal cord exclusion at 40 Gy. These patients also received 3 cycles of 4 days of carboplatin 70 mg/m² per day plus 5-FU 600 mg/m² per day on day 1 to 4, day 22-25, and day 43-46. Patients allocated to receive accelerated radiotherapy received a total dose of 70 Gy in 6 weeks: 5 fractions of 2 Gy per week until 40 Gy, with spinal cord exclusion at 40 Gy, followed by 1.5 Gy per fraction twice daily for 5 days per week for the remaining 30 Gy. These patients also received 2 cycles of 5 days of carboplatin 70 mg/m² per day and 5-FU 600 mg/m² per day on day 1 to 5 and day 29 to 33. Patients allocated to receive very accelerated radiotherapy alone received a total dose of 64.8 Gy in 3.5 weeks: 1.8 Gy per fraction twice daily for 5 days per week, with spinal cord exclusion at 34.2 Gy. The primary outcome measure was progression-free survival, defined as the time between randomisation and the first of the

following events: locoregional progression or relapse, distant relapse, or death from any cause (or the last follow-up contact for patients who did not have any of these events). Secondary outcome measures of our interest included overall survival and safety. Acute toxic effects of radiotherapy and chemotherapy occurring during treatment or within 3 months after the end of treatment were assessed using the criteria of the RTOG and WHO. Late toxic effects occurring more than 3 months after the end of treatment were assessed using the criteria of the RTOG/EORTC.

Calais (1999) and Denis (2004) report on a multicenter, randomized controlled phase 3 trial that was conducted at university hospitals, cancer centers, and private hospitals in France (GORTEC 94-01 trial). Patients aged < 75 years with previously untreated, non-metastatic, stage III or IV, squamous cell carcinoma of the oropharynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 60, and normal bone marrow and renal function. Patients were excluded if they had lost more than 20% of their body weight, if they had previously undergone treatment for this disease or any other cancer, except basal cell carcinoma of the skin, or if they had synchronous primary lesions. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 113), or standard fractionated radiotherapy alone (n = 109). Radiotherapy was given in a total dose of 70 Gy in 35 fractions at 2 Gy per fraction per day, 5 days per week. In the intervention group, patients received 3 cycles of chemotherapy during the 1st, 4th, and 7th week of radiotherapy. Chemotherapy consisted of carboplatin (i.v. bolus of 70 mg/m^2 per day for 4 days) and 5-FU (600 mg/m^2 per day infused continuously in 24 hours for 4 days). The primary outcome measure was the overall survival at 3 years. The authors also report the median overall survival, overall survival at 5 years, disease-free survival at 3 and 5 years, local recurrence rate, and safety. Acute toxic effects were assessed using the criteria of the EORTC. Late toxic effects were assessed using the criteria of the National Cancer Institute (NCI) and RTOG/EORTC.

Chitapanarux (2013) conducted a single-center, randomized controlled phase 3 trial at a university hospital in Thailand. Patients aged 18-75 years with previously untreated, stage III or IV, non-metastatic, squamous cell carcinoma of the head and neck, excluding the nasopharynx, nasal cavity, paranasal sinuses and salivary glands, were eligible. Criteria for eligibility also included an ECOG performance status ≤ 1 and adequate organ system function. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 48) or hybrid accelerated radiotherapy alone (n = 37). Patients allocated to receive standard fractionated radiotherapy received a total dose of 66 Gy in 6.5 weeks: 5 fractions of 2 Gy per week, with spinal cord exclusion at 40 Gy. These patients also received 3 cycles of 4 days of carboplatin 70 mg/m² per day plus 5-FU 600 mg/m² per day on day 1 to 4, day 22-25, and day 43-46. Patients allocated to receive hybrid accelerated radiotherapy received a total dose of 70 Gy in 6 weeks: 5 fractions of 2 Gy per week until 40 Gy, with spinal cord exclusion at 40 Gy, followed by a first daily fraction of 1.8 Gy and a second daily fraction of 1.2 Gy for 5 days per week for the remaining 30 Gy. The primary outcome measure was the locoregional control rate, which was not of our interest. Secondary end points of our interest included overall survival and safety. Acute toxic effects of radiotherapy and chemotherapy were assessed using the criteria of the NCI. Late toxic effects were assessed using the criteria of the RTOG/EORTC. Due to slow inclusion, the trial was prematurely stopped before reaching the planned accrual of 106 patients.

Olmi (2003) conducted a multicenter, randomized controlled phase 3 trial at 18 centers in Italy (ORO 93-01 trial). Patients aged < 70 years with histologically confirmed, previously untreated, stage III or IV, non-

metastatic, epidermoid tumors of the oropharynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 70 or an ECOG performance status ≤ 1, adequate bone marrow, hepatic, renal, cardiac and pulmonary function, no previous tumors, except adequately treated in situ carcinoma of the cervix and basal cell carcinoma of the skin, and no psychosis or active infectious disease. Patients were excluded if they had a T1N1 or T2N1 lesion. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 64), split-course hyperfractionated accelerated radiotherapy alone (n = 65) or standard fractionated radiotherapy alone (n = 63). The treatment group of patients who received split-course hyperfractionated accelerated radiotherapy alone is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 66-70 Gy in 33-35 fractions in 6.5-7 weeks at 2 Gy per fraction per day, 5 days per week. In the intervention group, patients received 3 cycles of chemotherapy. The first 2 cycles were given in the 1st and 5th week of radiotherapy, whereas the last cycle was given in the 9th week, therefore, after the radiotherapy was finished. Chemotherapy consisted of carboplatin (bolus of 75 mg/m^2 per day infused in 30 minutes for 4 days) and 5-FU (1000 mg/m^2 infused continuously in 96 hours for 4 days). The authors report the overall and disease-free survival at 2 year, and safety. Acute toxic effects of radiotherapy occurring within 90 days from the start of treatment were assessed using the criteria of the RTOG. Acute toxic effects of chemotherapy were assessed using the criteria of the WHO. Late toxic effects of radiotherapy occurring after 90 days from the start of treatment were assessed using the criteria of the RTOG. Due to slow inclusion, the trial was prematurely stopped before reaching the planned accrual of 260 patients.

Staar (2001) and Semrau (2006) report on a multicenter, randomized controlled phase 3 trial that was conducted at 5 centers in Germany. Patients with histologically confirmed, previously untreated, unresectable, non-metastatic, stage III or IV, squamous cell carcinoma of the oro- or hypopharynx were eligible. Criteria for eligibility also included an ECOG performance status ≥ 60, adequate bone marrow and renal function, and no history of a prior malignancy. Patients were randomly assigned (1:1) to receive hyperfractionated accelerated radiotherapy plus carboplatin and 5-FU (n = 113), or hyperfractionated accelerated radiotherapy alone (n = 127). Radiotherapy was given in a total dose of 69.9 Gy in 38 days, using a concomitant boost regimen: 5 fractions of 1.8 Gy per week in week 1-3, followed by a first daily fraction of 1.8 Gy and a second daily fraction of 1.5 Gy for 5 days per week in week 4-5.5. In the intervention group, patients received 2 cycles of chemotherapy during the 1st and 5th week of radiotherapy. Chemotherapy consisted of carboplatin (i.v. bolus of 70 mg/m^2 per day for 4 days) and 5-FU (600 mg/m^2 per day infused continuously for 4 days). The primary outcome measure was survival with local control at 1 year, which was not of our interest. The authors also report overall survival at 1, 2 and 5 years, and safety. Acute toxic effects were assessed using the criteria of the RTOG. Late toxic effects were assessed using the criteria of the RTOG/EORTC.

Results

1. Radiotherapy + cetuximab

Overall survival

Bonner (2006) found that the median duration of overall survival was 49.0 months (95%CI: 32.8-69.5) among patients treated with high-dose radiotherapy and cetuximab and 29.3 months (95%CI: 20.6-41.4) among those treated with high-dose radiotherapy alone (HR 0.74; 95%CI: 0.57 to 0.97). The overall survival rate at 3 years was 55% in the intervention group versus 45% in the control group. In the same study population, Bonner (2010) found that the overall survival rate at 5 years was 46% among patients treated with high-dose

radiotherapy and cetuximab and 36% among those treated with high-dose radiotherapy alone (HR 0.73; 95%CI: 0.56 to 0.95). Based on a subgroup analysis, cetuximab seemed to provide the most benefit for patients with an oropharyngeal tumor (n = 253). Although effect estimates and corresponding 95%-confidence intervals are not reported, the forest plot shows a statistically significant HR < 0.60, favoring the addition of cetuximab. For patients with a laryngeal or hypopharyngeal tumor, the HR did not reach the threshold for a minimal clinically important difference (i.e. HR < 0.7).

Progression-free survival
Bonner (2006) found that the median duration of progression-free survival was 17.1 months among patients treated with high-dose radiotherapy and cetuximab and 12.4 months among those treated with high-dose radiotherapy alone (HR 0.70; 95%CI: 0.54 to 0.90). The progression-free survival rates 2 and 3 years were 46% and 42%, respectively, in the intervention group versus 37% and 31%, respectively, in the control group (p-value for log-rank test = 0.04 for the comparison at 3 years, whereas no p-value is reported for the comparisor at 2 years).

Quality of life
Curran (2007) found a small, albeit statistically non-significant, absolute difference of less than 10 points in the mean global health status score (EORTC QLQ-C30) at baseline between patients treated with high-dose radiotherapy and cetuximab and patients treated with high-dose radiotherapy alone. At all visits up to and including month 12, the mean score of patients treated with high-dose radiotherapy and cetuximab was a few points higher compared with patients treated with radiotherapy alone (with higher scores representing better quality of life). The line graph shows that patients in both treatment groups had a global health score of approximately 60 at baseline. Scores decreased during treatment and had returned to baseline levels by month 12. For functional and symptom scale scores, also no statistically significant differences were found between treatment groups.

Adverse events
Bonner (2006) reported adverse events that occurred in at least 10% of patients in either treatment, regardless of the cause. The prevalence of grade $\geq$ 3 acute toxic effects did not differ significantly between patients treated with high-dose radiotherapy and cetuximab and patients treated with high-dose radiotherapy alone, except for acneiform rash (17% versus 1%; p < 0.001) and infusion reactions (3% versus 0%; p = 0.01) and anemia (1% versus 6%; p = 0.006). Severe late toxic effects related to radiotherapy were reported in about 20% of the patients in each treatment group. The sites most commonly affected were the esophagus, salivary glands, larynx, mucous membranes, subcutaneous tissues, bone, and skin. For late toxic effects, no absolute numbers or percentages per treatment group are reported.

Local recurrence and disease-free survival
No data were reported for these outcome measures.

2. RT + carboplatin
Overall survival
Fountzilas (2004) found that the median duration of overall survival was 24.5 months (range: 0.2 to 79.9) among patients treated with standard fractionated radiotherapy and carboplatin and 12.2 months (range: 1.2

to 81.7) among those treated standard fractionated radiotherapy alone (p-value for log-rank test = 0.0064). Patients treated with standard fractionated radiotherapy and carboplatin had a non-statistically significant higher overall survival than patients treated with standard fractionated radiotherapy alone (adjusted HR 0.57; 95%CI: 0.31 to 1.04). The overall survival rates at 3 and 5 years were 42% and 38%, respectively, in the intervention group versus 17.5% and 9%, respectively, in the control group.

Jeremic (1997) found that the median duration of overall survival was 30 months among patients treated with standard fractionated radiotherapy and carboplatin and 16 months (range: 1.2 to 81.7) among those treated standard fractionated radiotherapy alone (p = 0.0064). Patients in the intervention group had higher overall survival rates at 1, 2, 3, 4 and 5 years, compared with the control group: 76%, 55%, 47%, 31% and 29% versus 57%, 35%, 27%, 17% and 15%, respectively (p-value for log-rank test = 0.019).

Ruo Redda (2010) found that patients treated with standard fractionated radiotherapy and carboplatin had higher overall survival rates at 3, 5 and 10 years, compared with those treated with standard fractionated radiotherapy alone: 28.9%, 9% and 5.5% versus 11.1%, 6.9% and 6.9%, respectively (p-value for log-rank test = 0.02).

Disease-free survival
Ruo Redda (2010) found that patients treated with standard fractionated radiotherapy and carboplatin had higher disease-free survival rates at 3, 5 and 10 years, compared with those treated with standard fractionated radiotherapy alone: 28.9%, 9% and 5.5% versus 11.1%, 6.9% and 6.9%, respectively (p-value for log-rank test = 0.09).

Adverse events
Fountzilas (2004) found that the prevalence of grade ≥ 3 acute toxic effects did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone, except for thrombocytopenia (26% versus 0%; p = 0.0004), and nausea and vomiting (16% versus 0%; p = 0.0107).

Jeremic (1997) found that the prevalence of grade ≥ 3 acute non-hematological toxic effects, including mucositis, xerostomia, esophagitis, nausea and vomiting, and nephrotoxicity, did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone. Grade ≥ 3 acute hematological toxic effects, including leukopenia (11% versus 0%; p = 0.012) and thrombocytopenia (8% versus 0%; p = 0.041), occurred more frequently in patients treated with standard fractionated radiotherapy and carboplatin. The prevalence of grade ≥ 3 late toxic effects, including bone toxicity, skin toxicity and subcutaneous tissue fibrosis, was similar between treatment groups.

Ruo Redda (2010) found that the prevalence of grade ≥ 3 acute toxic effects, including mucositis, anemia, leukopenia and thrombocytopenia, did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone. The prevalence of grade ≥ 3 late toxic effects was similar between treatment groups, except for severe neck

fibrosis, which occurred more frequently in patients treated with radiotherapy and carboplatin (7 versus 3 cases). One patient treated with radiotherapy and carboplatin developed mandibular bone necrosis. No radiation myelitis or toxic-related death was observed in either treatment group.

Local recurrence, progression-free survival and quality of life
No data were reported for these outcome measures.

3. RT + carboplatin and 5-FU
Overall survival
Bourhis (2012) found that the overall survival rate at 3 years was 42.6% (95%CI: 37.0 to 48.5) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU (arm A), 39.4% (95%CI: 33.8 to 45.3) among patients treated with accelerated radiotherapy combined with carboplatin and 5-FU (arm B), and 36.5% (95%CI: 31.1 to 42.3) among patients treated with very accelerated radiotherapy alone (arm C). Resultantly, the HRs and corresponding 95%-confidence intervals are as follows: arm A versus C: HR 0.81; 95%CI: 0.67 to 0.99; arm B versus C: HR 0.87; 95%CI: 0.72 to 1.06; and arm B versus A: HR 1.05; 95%CI: 0.86 to 1.29).

Calais (1999) found that after a median follow-up of 35 months (range: 12 to 56) the median duration of overall survival was 29.2 months among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 15.4 months among those treated with standard fractionated radiotherapy alone. The overall survival rate at 3 years was 51% (95%CI: 39 to 68) in the intervention group versus 31% in the control group (p-value for log-rank test = 0.02). In the same study population, Denis (2004) found that after a median follow-up of 5.5 years (range: 4 to 7.2) the median duration of overall survival was 20 months among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 13 months among those treated with standard fractionated radiotherapy alone. The overall survival rate at 5 years was 22.4% in the intervention group versus 15.8% in the control group (p-value for log-rank test = 0.05).

Chitapanarux (2013) found that the overall survival rate at 5 years was 76.1% (95%CI: 57.8 to 7.3) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 63.5% (95%CI: 42.0 to 78.8) among patients treated with hybrid accelerated radiotherapy alone (p-value for log-rank test = 0.05).

Olmi (2003) found that the overall survival rate at 2 years was 51% among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 40% among patients treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.129).

Staar (2001) found that the overall survival rates at 1 and 2 years for all tumor types was 66% (95%CI: 57 to 75) and 48% (95%CI: 38 to 58), respectively, among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, and 60% (95%CI: 51 to 69) and 39% (95%CI: 30 to 48), respectively, among patients treated with hyperfractionated accelerated radiotherapy alone (p-value for log-rank test = 0.1139). For patients with an oropharyngeal tumor (n = 178), the overall survival rate at 1 year was 68% in the intervention group versus 57% in the control group (95%CI: ± 10; p-value for log-rank test = 0.0091). For patients with a hypopharyngeal tumor (n = 62), the overall survival curves did not differ significantly between treatment groups. In the same study population, Semrau (2006) found that the overall

survival rate at 5 years for all tumor types was 25.6% (95%CI: 15.8 to 35.4) among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, and 15.8% (95%CI: 9.1 to 22.4) among patients treated with hyperfractionated accelerated radiotherapy alone (p-value for log-rank test = 0.016). For patients with an oropharyngeal tumor (n = 178), the overall survival rate at 5 years was 26.1% (95%CI: 14.3 to 37.8) in the intervention group versus 13.0% (95%CI: 5.3 to 20.6) in the control group (p-value for log-rank test = 0.008). For patients with a hypopharyngeal tumor (n = 62), the overall survival curves did not differ significantly between treatment groups (22.2% versus 22.2%; p-value for log-rank test = 0.722).

Local recurrence
Calais (1999) found that after a median follow-up of 35 months (range: 12 to 56) the local recurrence rate was lower among patients treated with standard fractionated combined with carboplatin and 5-FU, compared with patients treated with standard fractionated radiotherapy alone (33% versus 51%; risk ratio (RR) 0.64; 95%CI: 0.47 to 0.89). In the same study population, Denis (2004) found that after a median follow-up of 5.5 years (range: 4 to 7.2) the local recurrence rate remained lower among patients treated with standard fractionated combined with carboplatin and 5-FU (41% versus 58%; RR 0.71; 95%CI: 0.54 to 0.93).

Disease-free survival
Calais (1999) found that the disease-free survival rate at 3 years was 42% (95%CI: 30 to 57) among patients treated with standard fractionated combined with carboplatin and 5-FU, and 20% among those treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.04). In the same study population, Denis (2004) found that the disease-free survival rate at 5 years was 26.6% among patients treated with standard fractionated combined with carboplatin and 5-FU, and 14.6% among those treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.01).

Olmi (2003) found that the disease-free survival rate at 2 years was 42% among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 23% among patients treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.022).

Progression-free survival
Bourhis (2012) found that the progression-free survival rate at 3 years was 37.6% (95%CI: 32.1 to 43.4) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU (arm A), 34.1% (95%CI: 28.7 to 39.8) among patients treated with accelerated radiotherapy combined with carboplatin and 5-FU (arm B), and 32.2% (95%CI: 27.0 to 37.9) among patients treated with very accelerated radiotherapy alone (arm C) (arm A versus C: HR 0.82; 95%CI: 0.67 to 0.99; arm B versus C: HR 0.83; 95%CI: 0.69 to 1.01); arm B versus A: HR 1.02; 95%CI: 0.84 to 1.23).

Adverse events
Bourhis (2012) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis was lower among patients treated with standard fractionated or accelerated radiotherapy combined with carboplatin and 5-FU (arm A and arm B, respectively), compared with patients treated with very accelerated radiotherapy alone (arm C). According to criteria of the RTOG, grade ≥ 3 mucositis occurred in 69% of patients in treatment arm A, in 76% of patients in treatment arm B, and in 84% of patients in treatment arm C (p = 0.0001). According to the criteria of the WHO, grade ≥ 3 mucositis occurred in 78% of

patients in treatment arm A, in 84% of patients in treatment arm B, and in 89% of patients in treatment arm C (p = 0.0016). The prevalence of grade ≥ 3 skin toxicity and grade ≥ 3 hematological toxic effects, including anemia, leukopenia and thrombocytopenia, did not differ significantly between treatment groups. The rate of patients in need of a feeding tube differed significantly between treatment arm A and treatment arm C, both during treatment (60% versus 70%; p = 0.013) and during 5-year follow-up (36% versus 43% at 1 year, 16% versus 23% at 2 years, 11% versus 18% at 3 years, 8% versus 14% at 4 years, and 13% versus 25% at 5 years; p = 0.027), but not between other treatment groups. The prevalence of late toxic effects, including xerostomia, neck fibrosis, mucositis, laryngeal toxicity and bone toxicity, 1 to 5 years after randomization did not differ significantly between treatment groups, but the severity (i.e. grade) of these late toxic effects is not reported.

Calais (1999) found that skin toxicity was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis (71% versus 39%; p = 0.005) and grade ≥ 3 skin toxicity (67% versus 59%; p = 0.02) was higher among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with standard fractionated radiotherapy alone. The prevalence of grade ≥ 3 hematological toxic effects, including neutropenia (4% versus 0%; p = 0.04), thrombocytopenia (6% versus 1%; p = 0.04) and anemia (3% versus 0%; p = 0.05), was also higher in the intervention group, but for anemia the result was not statistically significant. The rate of patients in need of a feeding tube during treatment differed significantly between treatment groups (36% versus 15%; p = 0.02). In the same study population, Denis (2004) found that the prevalence of late toxic effects during 5-year follow-up, including xerostomia, mucositis, skin toxicity and subcutaneous tissue fibrosis, neurological toxicity, mandibular bone necrosis, and taste-, hearing- and teeth-related toxicity, did not differ significantly between treatment groups.

Chitapanarux (2013) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis was lower among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with hybrid accelerated radiotherapy alone (42% versus 68%; p = 0.01). The prevalence of grade ≥ 3 skin toxicity, grade ≥ 3 renal toxicity and grade ≥ 3 hematological toxic effects, including anemia, leukopenia and thrombocytopenia, did not differ significantly between treatment groups. The prevalence of grade ≥ 3 late toxic effects related to radiotherapy, including xerostomia, subcutaneous tissue fibrosis, mucositis and skin toxicity, did not differ significantly between treatment groups.

Olmi (2003) found that the prevalence of grade ≥ 3 acute toxic effects related to radiotherapy did not differ significantly between patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and patients treated with standard fractionated radiotherapy alone, except for mucositis (48% versus 15%; p = 0.0003) and skin toxicity (16% versus 4%; p = 0.0461). Grade ≥ 3 acute toxic effects related to chemotherapy included leukopenia (23% of patients), thrombocytopenia (5%), anemia (2%), anorexia (2%), and 1 fatal case of renal toxicity (1%). The prevalence of grade ≥ 3 late toxic effects related to radiotherapy during 2 year follow-up, including mucositis, skin toxicity, subcutaneous tissue fibrosis, xerostomia, spinal cord toxicity and laryngeal toxicity, did not differ significantly between treatment groups.

Staar (2001) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis during treatment was higher among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with hyperfractionated

accelerated radiotherapy alone (68% versus 52%; p = 0.01). The prevalence of grade ≥ 3 skin toxicity (30% versus 28%) and grade ≥ 3 hematological toxic effects, including leukopenia (18% versus 0%) and thrombocytopenia (5% versus 0%), was also higher in the intervention group, but p-values are not reported and could not be calculated based on the data provided. Grade ≥ 3 anemia occurred less frequently in patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU (1% versus 0%), but it is unclear whether this result was statistically significant. Late toxic effects were reported for the total study population (Staar, 2001) or for all grades together (Semrau, 2006), except for swallowing problems and continuous use of a feeding tube, which occurred more frequently in patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU (51% versus 25%; p = 0.02).

Quality of life
No data were reported for this outcome measure.

Level of evidence of the literature
The evidence was derived from 13 studies reporting on 9 different randomized trials. Therefore, the level of evidence for all reported outcome measures started at 'high quality'.

1. RT + cetuximab
The level of evidence regarding the outcome measure overall survival was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT and upper boundary of confidence interval exceeding the threshold of minimal clinically important difference). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure progression-free survival was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure quality of life was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). The level of evidence was not downgraded because of study limitations (i.e., active role of sponsor in collecting and analyzing the data), because no minimal clinically important difference in quality of life was observed between treatment groups. Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure adverse events was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measures <u>local recurrence</u> and <u>disease-free survival</u> could not be assessed, because the included studies did not report these outcome measures.

2. RT + carboplatin

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by 4 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Ruo Redda (2010), and premature termination of Jeremic (1997)); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by 4 levels because of risk of bias (-2; due to incomplete reporting and imbalanced study population); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients in a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by 5 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Ruo Redda (2010), and premature termination of Jeremic (1997)); inconsistency (-1; due to conflicting results); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Publication bias could not be assessed.

The level of evidence regarding the outcome measures <u>local recurrence</u>, <u>progression-free survival</u> and <u>quality of life</u> could not be assessed, because the included studies did not report these outcome measures.

3. RT + carboplatin and 5-FU

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by 4 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Chitapanarux (2013), and premature termination of Chitapanarux (2013) and Olmi (2003)); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to low number of included patients in most studies). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>local recurrence</u> was downgraded by 3 levels because of study limitations (-1; risk of bias due to incomplete reporting); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients in a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by 3 levels because of study limitations (-1; risk of bias due to incomplete reporting); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>progression-free survival</u> was downgraded by 2 levels because of indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by 5 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Chitapanarux (2013), and premature termination of Chitapanarux (2013) and Olmi (2003)); inconsistency (-1; due to conflicting results); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to low number of included patients in most studies). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>quality of life</u> could not be assessed, because the included studies did not report this outcome measure .

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and fluorouracil (5-FU), compared with definitive radiotherapy alone, in patients with a locally advanced squamous cell carcinoma in the head and neck region who are ineligible to receive cisplatin?

P: Patients with a locally advanced squamous cell carcinoma in the head and neck region who are ineligible to receive cisplatin.
I: Definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and 5-FU.
C: Definitive radiotherapy alone.
O: Overall survival, local recurrence, disease-free survival, progression-free survival, quality of life, adverse events.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and local recurrence as critical outcome measures for decision making; and disease-free survival, progression-free survival, quality of life, and adverse events as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but, instead, used the definitions used in the studies.

The working group defined a minimal clinically important difference as follows:

- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Local recurrence: 0.8 or 1.25 as borders for risk or odds ratios.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Progression-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.

- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Adverse events: statistically significant difference in grade ≥ 3 adverse event rate.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms for systematic reviews published until November 12, 2020. The detailed search strategy is depicted under the tab Methods. Studies were selected if they fulfilled the following criteria: (a) patients with a locally advanced squamous cell carcinoma in the head and neck region; (b) comparison between definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and 5-FU, and definitive radiotherapy alone. Studies were excluded if they only included patients with HPV-positive oropharyngeal cancer, because treatment options for this group of patients are described in a separate module. This search resulted in unique 296 hits. Based on title and abstract screening, 40 studies were initially selected. After reading the full text, all 40 studies were excluded. A table with reasons for exclusion is presented under the tab Methods. One of the excluded reviews (Iocca (2018)) compared several interventions based on a network meta-analysis of 57 RCTs, of which 7 RCTs were relevant for the current clinical question. Similarly, another 5 RCTs were identified via other excluded reviews.

To update the search performed by Iocca (2018) up to 1 September 2017, we searched for relevant RCTs published from 2017 until 18 October 2021. This search resulted in 452 hits. Based on title and abstract screening, 40 studies were initially selected. After reading the full text, all 40 studies were excluded (see table with reasons for exclusion).

Results

Via an excluded systematic review and network meta-analysis (Locca, 2018), 7 relevant studies (Bourhis, 2012; Bonner, 2010; Chitapanarux, 2013; Denis, 2004; Fountzilas, 2004; Ruo Redda, 2010 and Semrau, 2006) were included in the analysis of the literature. In addition, 6 relevant studies (Bonner, 2006; Curran, 2007; Calais, 1999; Jeremic, 1997; Olmi, 2003 and Staar, 2001) were identified via other excluded systematic reviews. Together, these 13 studies report the results of 9 different randomized trials. Studies that focused on the effects of definitive radiotherapy combined with either cetuximab (Bonner, 2006; Bonner, 2010 and Curran, 2007), carboplatin (Fountzilas, 2004; Jeremic, 1997 and Ruo Redda, 2010) or carboplatin and 5-FU (Bourhis, 2012; Calais, 1999; Chitapanarux, 2013; Denis, 2004; Olmi, 2003; Semrau, 2006 and Staar, 2001), compared with definitive radiotherapy alone, are analyzed separately. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Primaire Behandeling N3 hypofarynx, orofarynx- en larynxcarcinoom

Uitgangsvraag

Welke volgorde van behandelmodaliteiten heeft de voorkeur bij patiënten met een N3 hypofarynx, orofarynx- en larynxcarcinoom: Eerst een halsklierdissectie gevolgd door (chemo)radiotherapie, of (chemo)radiotherapie gevolgd door een halsklierdissectie wanneer nodig?

Aanbeveling

Op basis van de huidige literatuur, praktijkkennis en patiëntenvoorkeuren kan geen aanbeveling gedaan worden welke volgorde van behandeling, chemoradiatie gevolgd door een halsklierdissectie dan wel een halsklierdissectie gevolgd door chemoradiatie, de voorkeur verdient.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De systematic reviews die werden gevonden bij deze uitgangsvraag (Elicin, 2016 en Gupta, 2004) vergeleken steeds een halsklierdissectie met daarna chemoradiotherapie versus chemoradiotherapie alleen. Beide studies zijn gebaseerd op de oude TNM-7 classificatie. Bij de vergelijkingen die we hebben gevonden werd er geen halsklierdissectie meer gedaan na de chemoradiotherapie. Om deze reden is het niet mogelijk om op basis van de literatuur tot een eenduidige conclusie te komen welke volgorde van interventies beter is.

Echter, wanneer na chemoradiotherapie een afwachtend beleid wordt gevoerd lijkt dit geen negatieve invloed op de overleving te hebben in vergelijking met wanneer aansluitend een halsklierdissectie wordt verricht (zie module 13.4).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Er zijn geen studies verricht die het verschil voor patiënten tussen de verschillende volgorde van behandeling vergelijken. Echter het starten met de (chemo)radiatie kan als nadeel hebben dat een salvage halsklierdissectie een hoger risico geeft op complicaties. Het starten met een halsklierdissectie heeft als nadeel dat de behandeling van de primaire tumor vertraging op kan lopen.

Kosten (middelenbeslag)
Er zijn geen studies verricht die het verschil in kosten tussen de verschillende volgorden van behandeling vergelijken.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Omdat er geen studies zijn gevonden die het verschil in volgorde van behandelingen hebben vergeleken, en er ook geen duidelijke voorkeur lijkt te zijn vanuit de praktijk of de patiënten, kan er op dit moment geen aanbeveling worden gedaan voor één van de opties.

Onderbouwing

Achtergrond

Een inventarisatie in Nederland door de Richtlijnencommissie van de NWHTT leerde dat bij het larynxcarcinoom het beleid ten aanzien van de N3 hals zeer verschillend was tussen de verschillende centra. Wanneer de N3 lymfekliermetastase op voorhand resectabel is worden óf de primaire tumor en hals behandeld met (chemo)radiatie en afhankelijk van de responsevaluatie (maar met een hoge kans hierop) een salvage halsklierdissectie verricht, óf eerst een halsklierdissectie verricht en vervolgens de primaire tumor en de hals behandeld met (chemo)radiatie. Het is aannemelijk dat dit verschil ook aanwezig is bij andere primaire tumoren die vaak primair met (chemo)radiatie behandeld worden. Het starten met de (chemo)radiatie heeft als nadeel dat het residu van de N3 lymfekliermetastase irresectabel geworden kan zijn en een salvage halsklierdissectie een hoger risico heeft op complicaties. Het starten met een halsklierdissectie heeft als nadeel dat de behandeling van de primaire tumor vertraagd wordt door de halsklierdissectie.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: Which order of interventions is preferred for N3 hypopharynx, oropharynx and larynx carcinoma patients: Up-front neck dissection followed by (chemo)-radiotherapy, or (chemo)-radiotherapy followed by neck dissection if necessary?

P: = N3 hypopharynx, oropharynx and larynx carcinoma.
I: = Up-front neck dissection followed by (chemo)-radio therapy.
C: = (Chemo)-radio therapy followed by neck dissection if necessary.
O: = Overall survival (3 to 5 year follow up), disease free survival, disease specific survival, recurrence, morbidity, surgery complications, adverse events.

Relevant outcome measures
The guideline development group considered overall survival, disease free survival and recurrence as a critical outcome measure for decision making; the group considered morbidity, surgery complications, and adverse events as an important outcome measure for decision making.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) or >3% and HR< 0.7 in overall survival.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 17th of February 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: methodology (RCT's and SR's were included), suitability with the PICO. Two studies were initially selected based on title and abstract screening. After reading the full text, both studies were excluded (see the table with reasons for exclusion under the tab Methods).

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Halsklierdissectie N3 patiënten

Uitgangsvraag

Is, voor patiënten met een stadium N2/N3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben gehad, een geplande halsklierdissectie een betere optie dan een afwachtend beleid voeren, waarbij de halsklierdissectie alleen wordt uitgevoerd indien dit na responsevaluatie nodig blijkt?

Aanbeveling

Bespreek met patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom de twee mogelijke opties na behandeling met chemoradiatie: 1) hoe dan ook een nekdissectie plannen, of 2) de respons op chemoradiatie evalueren middels PET-CT en bij onvoldoende of onduidelijke respons pas een nekdissectie verrichten.

Benoem dat:

- een afwachtend beleid niet tot een slechtere overleving lijkt te leiden;
- een afwachtend beleid niet lijkt te leiden tot meer recidief;
- een afwachtend beleid resulteert in minder chirurgische complicaties.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Om de vraag te beantwoorden of het beter is een afwachtend beleid op basis van een responsevaluatie met PET-CT te voeren of een nekdissectie te plannen na een chemoradiotherapie bij patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom, is een onderzoek uitgevoerd dat de non-inferiority toetst van een afwachtend beleid. Uit dit onderzoek blijkt dat het afwachtende beleid inderdaad niet leidt tot een slechtere overleving. Daarbij is het aantal adverse events en complicaties lager in de groep waar een afwachtend beleid wordt gevoerd (met lage bewijskracht). De meerjarenoverleving, toxiciteit, schoudermorbiditeit en de ziektevrije overleving zijn niet meegenomen. Overigens is deze studie nog gebaseerd op de oude TNM-7 classificatie, wat de geldende classificatie was ten tijde van de inclusie van de patiënten in de studie, niet op TNM 8. Het is lastig om dit goed te vertalen naar de nieuwe classificatie; de werkgroep concludeert dan ook dat dit een kennislacune is.

Tevens bleek een afwachtend beleid meer kosten-effectief (per persoon £1,492 en 0.08 QALYs per persoon). In een uitgebreidere studie naar kosten-effectiviteit (Fu, 2021) werden drie verschillende manieren van surveillance vergeleken met geplande nekdissectie, waarbij een PET-CT surveillance met herhaalde PET-scan na 6 maanden na chemoradiatie bij onduidelijke respons het meest kosten-effectief bleek. Er zijn geen studies beschikbaar die de haalbaarheid en aanvaardbaarheid van surveillance onderzochten.

Een vereiste voor het uitvoeren van een nekdissectie bij onvoldoende respons is de mogelijkheid om een PET-CT te maken. Uit de studie van Mehanna et al. blijkt dat er een hoge concordantie was tussen de beoordeling van de PET-CT door de (willekeurige) lokale specialist en de beoordeling door de ervaren

specialisten van de studie (92% voor respons van de primaire tumor en 97% voor de lymfkliermetastasen). Hieruit kan geconcludeerd worden dat het haalbaar is om de surveillance methode te implementeren in de kliniek.

Gezien beide methoden (een afwachtend beleid of een geplande nekdissectie na een chemoradiotherapie), gebaseerd op de huidige literatuur met enige onzekerheid, leiden tot een gelijke overleving, zouden de beide opties aan patiënten kunnen worden voorgelegd. Samen beslissen zal de acceptatie van patiënten maximaliseren. Daarbij is het wel goed om op te merken dat in Nederland het afwachtende beleid inmiddels vrijwel overal standaardpraktijk is. Er zijn geen duidelijke argumenten vóór een geplande nekdissectie, wat het voor de patiënt minder voor de hand liggend maakt om wel voor een geplande nekdissectie te kiezen.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er lijkt geen nadeel te zijn van het voeren van een afwachtend beleid kijkend naar de verschillende uitkomstmaten op basis van de huidige literatuur. Het aantal bijwerkingen en complicaties lijkt lager in de groep waar een afwachtend beleid wordt gevoerd.

De gradering van bewijs is laag en gebaseerd op één enkele studie, waardoor er geen sterke aanbeveling kan worden gedaan voor één van beide opties. Om deze reden is de keuze om wel of niet meteen een nekdissectie te plannen na chemotherapie een overweging die goed met de patiënt besproken kan worden. De aanbeveling is geformuleerd met de onderwerpen die in elk geval aan de patiënt voorgelegd kunnen worden.

Onderbouwing

Achtergrond

In de Nederlandse zorg bestaat er praktijkvariatie op het gebied van een halsklierdissectie bij patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben ondergaan. In sommige centra wordt als standaardprocedure een halsklierdissectie uitgevoerd, terwijl in andere centra een afwachtend beleid wordt gevoerd waarbij halsklierdissectie alleen wordt uitgevoerd indien dit uit responsevaluatie op basis van beeldvorming nodig blijkt te zijn. Er is geen consensus over wat de beste strategie is.

Conclusies

Overall survival (2 years) (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in little to no difference in overall survival compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Adverse events (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in less adverse events compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Recurrence (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in little to no difference in recurrence compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

- GRADE	No evidence was found regarding the effect of surveillance, where neck dissection is only performed based on PET-CT, on toxicity, shoulder mobility and disease-free survival, when compared with planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

Zoekvraag
Welke behandelstrategie is beter voor patiënten met een stadium N2/N3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben gehad: een geplande halsklierdissectie uitvoeren, of een afwachtend beleid voeren, waarbij de halsklierdissectie alleen wordt uitgevoerd indien dit na responsevaluatie nodig blijkt?

P: Patients who have undergone chemoradiation for a stage N2/3 hypopharynx, oropharynx or larynx carcinoma.
I: Chemoradiation + standard neck dissection.
C: Chemoradiation + neck dissection when residual is suspected after response evaluation.
O: Survival (3 to 5 years), disease free survival, recurrence, adverse events, toxicity, shoulder mobility, surgery complications.

Relevant outcome measures
The guideline development group considered survival (3 to 5 years), disease free survival, recurrence, and adverse events as critical outcome measures for decision making; and toxicity, shoulder mobility, and surgery complications as important outcome measures for decision making.

The guideline development group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as boundaries for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-free survival.
- 5% difference or more (absolute) or > 3% difference and HR< 0.7 in overall survival.

For the outcome measures adverse events, toxicity, shoulder mobility, and surgery complications no minimally clinically relevant difference was formulated.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 17th of February 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: suitability with the PICO, methodology (RCTs and SRs were included), studies in the English or Dutch language, and available full texts. Four studies were initially selected based on title and abstract screening. After reading the full text, three studies were excluded (see the table with reasons for exclusion under the tab Methods).

<u>Results</u>
One study was included in the analysis of the literature (Mehanna, 2016). Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature
<u>Description of studies</u>
Mehanna (2016) conducted a randomized controlled trial (non-inferiority study) in the UK assessing the non-inferiority of PET-CT guided surveillance that could lead to neck dissection, with planned neck dissection, in patients who received chemoradiotherapy as a primary treatment. In total, 564 patients participated in the trial, of which the randomization was 1:1. All patients were evaluated 12 weeks after chemoradiotherapy, either by CT or MRI (in the planned surgery group) or PET-CT (in the surveillance group). Incomplete or equivocal response in the lymph nodes led to a neck dissection within 4 weeks in the surveillance group. There were less neck dissections in the PET-CT–guided surveillance group compared to the planned surgery group (54 versus 221). The follow-up lasted for at least 24 months after randomization, and the outcomes that were measured were survival rate (primary endpoint), disease-specific mortality, mortality from other causes, adverse events, locoregional control, surgery complications, quality of life and cost-effectiveness.

<u>Results</u>
Survival (2 years)
3-to-5 year survival was not measured in the included study. However, the guideline development group decided to use the 2-year survival that was reported in the study. The 2-year overall survival rate was 84.9% (95% CI, 80.7 to 89.1) in the surveillance group and 81.5% (95% CI, 76.9 to 86.3) in the planned surgery group. The hazard ratio for death with surveillance as compared with planned surgery was 0.92 (95% CI, 0.65 to 1.32); this outcome slightly favored the surveillance group and met the prespecified definition of noninferiority (an overall survival rate that was no more than 10 percentage points below the estimated 75% 2-year overall

survival rate in patients in the planned surgery group).

Recurrence
Recurrence was measured as rate of locoregional control. The 2-year rate of locoregional control was 91.9% (95% CI, 88.5 to 95.3%) in the surveillance group and 91.4% (95% CI, 87.8 to 95.0%) in the planned-surgery group, with a RR of 1.00 (95% CI, 0.95 to 1.05).

Adverse events
A total of 282 serious adverse events occurred: 169 in the planned surgery group and 113 in the surveillance group (59.9% versus 40.1%, with a RR of 1.50 (95% CI, 1.26 to 1.78)).

Disease-free survival
This outcome was not measured in the included trial.

Toxicity
This outcome was not measured in the included trial.

Shoulder mobility
This outcome was not measured in the included trial.

Complications
A total of 22 surgical complications after neck dissection were noted in the surveillance group, as compared with 83 in the planned-surgery group, with a RR of 3.77 (95% CI, 2.43 to 5.86).

Level of evidence of the literature
Survival (2 years)
The level of evidence regarding the outcome survival started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies (1) and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Adverse events
The level of evidence regarding the outcome adverse events started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Recurrence
The level of evidence regarding the outcome adverse events started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Toxicity, shoulder mobility, disease-free survival
The study did not report on the outcome measures toxicity, shoulder mobility and disease-free survival and therefore GRADE could not be applied, and no conclusions could be drawn.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Recidief T2-T4

Uitgangsvraag

Wanneer en hoe is re-irradiatie in een curatieve setting mogelijk in een recidief hoofd-halscarcinoom na chemo-radiotherapie, wanneer salvage chirurgie niet meer mogelijk is?

Aanbeveling

Bespreek met de patiënt de nadelen van re-irradiatie van een hoofd-halsplaveiselcelcarcinoom wat betreft toxiciteit. Voorspellende factoren voor toxiciteit die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: dosis eerdere radiotherapie, eerdere chirurgie, tumorlokalisatie, leeftijd, en orgaan(dys)functie.

Bespreek bij patiënten met een nasofarynxcarcinoom de kans op overleving na re-irradiatie. Factoren die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: leeftijd, tumorstadium en EBV-concentratie in het bloed.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De werkgroep heeft een literatuuronderzoek verricht naar de prestatie van (multivariabele) modellen welke (de kans op) toxiciteit en overleving tijdens of na re-irradiatie voorspellen. Er werden twee gevalideerde modellen gevonden die overleving en toxiciteit voorspellen. Vanwege een zeer lage bewijskracht kan geen uitspraak worden gedaan over de prestatie van deze modellen. De zeer lage bewijskracht wordt voornamelijk veroorzaakt door beperkingen in de studieopzet ten aanzien van de ontwikkeling van de modellen en het ontbreken van externe validatie van de modellen. De werkgroep concludeert dan ook dat er een kennislacune bestaat omtrent het bestaan van beslissingsmodellen welke op basis van risicofactoren overleving en toxiciteit tijdens of na re-irradiatie bij patiënten, bij wie opereren geen mogelijkheid meer is, kunnen voorspellen.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Toxiciteit is een belangrijke uitkomst voor patiënten, waarbij de balans tussen toxiciteit en overleving een belangrijke afweging is. Toxiciteit geeft veel bijwerkingen, zoals necrose, mucositis, zwelling, slikproblemen, en pijn. Daarom moet met de patiënt worden besproken wat de nadelen kunnen zijn van re-irradiatie, en wat de eventuele voordelen zijn wat betreft overleving.

Kosten (middelenbeslag)
Re-irradiatie heeft geen grote impact op de kosten. Alternatieven van re-irradiatie zijn palliatieve opties, wanneer resectie niet meer mogelijk is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Vanwege de zeer lage bewijskracht van de gevalideerde modellen, kan er geen sterke aanbeveling worden gedaan welke factoren van belang zijn bij de keuze voor re-irradiatie. Het is belangrijk de voor- en nadelen met de patiënt te bespreken.

Onderbouwing

Achtergrond

Het doel van deze module is om de beste behandeling van een recidief hoofd-halscarcinoom na (chemo)radiotherapie als primaire behandeling dan wel adjuvant na resectie in beeld te brengen. Daarbij is het vooral van belang uit te zoeken wanneer re-irradiatie mogelijk is, als chirurgie niet meer mogelijk is, bij een recidief hoofd-halscarcinoom of tweede primaire tumor in een gebied dat eerder (chemo)radiotherapie gehad heeft. Daarbij zouden schade aan normale weefsels, overleving, toxiciteit, complicaties en kwaliteit van leven mogelijke uitkomsten kunnen zijn, en de factoren die bepalen of re-irradiatie nog mogelijk is, zouden type tumor, locatie tumor, reeds aanwezige postradiatie-effecten, tijdsinterval tot eerdere radiotherapie en patiëntgeschiedenis.

Conclusies

Toxicity: The level of evidence regarding the outcome measure toxicity started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (one level, no external validation) and imprecision (only one study with relatively low numbers of patients and events).

Overall survival: The level of evidence regarding the outcome measure started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (two levels, no external validation and different population).

<u>Toxicity</u>

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Ward, 2019, where dose of radiotherapy during first course, tumor site, organ dysfunction, any surgery, age and recurrent or second primary are selected as factors that predict toxicity after re-irradiation for head and neck squamous cell carcinoma. *Sources: (Ward, 2019)*

Overall survival

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Sun, 2022, where patient age, rT stage, and EBV DNA level are selected as factors that predict overall survival after re-irradiation for nasopharyngeal carcinoma. *Sources: (Sun, 2022)*

Samenvatting literatuur

<u>Description of studies</u>
Ward, 2019: From 9 institutions, 505 patients were included with recurrent or second primary (RSP) squamous carcinoma originating in a field previously irradiated to ≥ 40 Gy and treated with IMRT-based re irradiation to ≥ 40 Gy. A multivariable competing-risk model was fit to the actuarial risk of late toxicity with progression or death as the competing risk, using a backwards stepdown procedure. The final bootstrap optimized model was converted into a nomogram.

Sun, 2022: A prognostic model was established and validated for locally recurrent nasopharyngeal carcinoma (lrNPC) patients. In total, 531 patients from one center with lrNPC were retrospectively reviewed, including 271 patients from 2006 to 2012 as the training cohort and 260 patients from 2013 to 2016 as the validation cohort. Overall survival (OS) was the primary endpoint. Multivariate analysis was performed to select the significant prognostic factors (P < 0.05). A prognostic model for OS was derived by recursive partitioning analysis (RPA) combining independent predictors using the algorithm of optimized binary partition.

Results

Toxicity:
Ward, 2019: The final model included six clinical factors:

- Dose of radiotherapy during first course (continuous, per Gy) (HR 1.075 (95%CI 1.031 to 1.122)).
- Tumor site (oropharynx, larynx or lypopharynx versus other) (HR 1.575 (95%CI 0.984 to 2.519)).
- Organ dysfunction (yes versus no) (HR 3.029 (95%CI 1.919 to 4.783)).
- Any surgery (yes versus no) (HR 1.232 (95%CI 0.781 to 1.943)).
- Age (continuous, per year) (HR 0.977 (95%CI 0.955 to 0.998)).
- RSP (second primary versus recurrence) (HR 1.061 {95% CI 0.656 to 1.713)).

The final model demonstrated an average bootstrapped C-index of 0.698.

Overall survival:
Sun, 2022: The final model included 3 factors:

- Patient age (> 60 versus 60: hazard ratio (HR): 1.757, 95% confidence interval (CI): 1.181 to 2.615, P = 0.005).
- rT stage (rT2 versus rT1: HR: 1.725, 95% CI: 0.919 to 3.241, P = 0.090; rT3 versus rT1: HR: 2.439, 95% CI: 1.453 to 4.096, P = 0.001; rT4 versus rT1: HR: 5.007, 95% CI: 2.989 to 8.388, P < 0.001).
- EBV DNA level (detectable versus undetectable: HR: 1.825, 95% CI: 1.355 to 2.459, P < 0.001).

The study reported that re-irradiation could benefit patients in the low (P < 0.001) and intermediate-risk subgroups (P = 0.017), while no association between re-RT and survival benefit was found in the high-risk subgroup (P = 0.328).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the prognostic factors of successful re-irradiation in patients in a curative setting with a locoregional recurrent head and neck carcinoma after primary or adjuvant (chemo)radiotherapy, where salvage surgery is no longer possible?

P: (Patients) = Patients with a head and neck carcinoma that is recurring after primary or adjuvant (chemo)-radiotherapy, where salvage surgery is no longer possible.
I: (Intervention)= A model that predicts for which patients re-irradiation is successful, defined by intervention success, tissue damage, overall survival, toxicity, complications and quality of life.

C: (Comparison)= A different model/care as usual.
O: (Outcomes)= Predictive value of the model.
T:(Timing)= When in recurring head/neck carcinoma a treatment plan is determined.
S: (Setting)= Specialized care.

Relevant outcome measures
The guideline development group considered overall survival and toxicity as critical outcomes.

The working group defined the performance of the included models in Area Under the ROC Curve (AUC) as follows:

- 0.7 ≤AUC< 0.8: acceptable.
- 0.8 ≤AUC< 0.9: excellent.
- AUC≥ 0.9: outstanding.

Prognostic research: Study design and hierarchy
When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, the effectiveness of a clinical decision model is evaluated in a randomized clinical trial. Unfortunately, these studies are very rare. If not available, studies in which prediction models are developed and validated in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to studies that are not externally validated. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prediction models internally (e.g. bootstrapping or cross validation) can be used to answer the research question, but downgrading the level of evidence is necessary due to risk of bias and/or indirectness as it is not clear whether models perform sufficiently in target populations. The confidence in the results of unvalidated prediction models is very low. Therefore, such models will not be graded. This is also applicable for association models.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 14th of February 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 133 hits. Studies were selected based on the following criteria:

- Being a systematic review, randomized controlled trial (RCT) or observational study (cohort study).
- Reporting multivariable longitudinal association model or prediction model with outcome (mortality or complications periprocedural or within 30 days) as dependent variable and independent variables (patient characteristics) determined before the treatment plan was made.
- Models do not take independent variables into account that were determined after the treatment plan was made.

Four studies were initially selected based on title and abstract screening. After reading the full text, two studies were excluded (see the table with reasons for exclusion under the tab Methods) and two studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Hypofarynxcarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Behandeling T1-T2N0 hypofarynxcarcinoom

Uitgangsvraag

Wat is de optimale behandeling van de primaire tumor van T1-T2N0 hypofarynxcarcinomen?

Aanbeveling

Gebruik radiotherapie als standaardbehandeling.

TLM en TORS kunnen met de patiënt besproken worden indien:

- TLM en/of TORS technisch mogelijk zijn;
- er geen contra-indicaties zijn voor chirurgie;
- radiotherapie als gevolg van eerdere radiotherapie niet meer mogelijk is.

Ondersteun de patiënt bij het maken van een behandelkeuze waarbij de individuele patiëntkarakteristieken dienen te worden afgewogen.

En bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- Behandelduur:
  De duur van de behandelingen zonder complicaties bij TLM or TORS is één ingreep met een opnameduur van enkele dagen. Voor radiotherapie is de behandelduur zes tot zeven weken en behandeling omvat meerdere bezoeken. Voor beide behandelingen is een korte poliklinische voorbereiding nodig.
- Procedures:
  TLM en TORS worden onder narcose op een operatiekamer verricht. Radiotherapie wordt poliklinisch in 30 tot 35 korte sessies verricht. Radiotherapie zal volgens een behandelschema verlopen en vraagt om tandheelkundig focusvrij maken voorafgaand aan de radiotherapie.
- Korte en lange termijn complicaties en toxiciteit:
  Bij TLM en TORS kunnen bloedingen, pijnklachten en ontstekingen optreden. Bij radiotherapie kan smaakverlies, een droge mond en slikklachten optreden. Ook kunnen hypothyroïdie, versnelling van artherosclerose en, met een zeer gering risico, secundaire tumoren ontstaan ten gevolge van radiotherapie.
- Kans op adjuvante behandeling:
  Er bestaat afhankelijk van de patiëntselectie een kans van 48 tot 83% voor TLM en 84% voor TORS op een adjuvante behandeling met (chemo)radiatie. In een beperkt aantal patiënten zal na radiotherapie bij residu of recidief tumor salvage chirurgie nodig zijn.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden naar het effect van radiotherapie in vergelijking met chirurgie bij patiënten met een primaire tumor van kleine hypofarynxcarcinomen. Er kunnen daarom geen aanbevelingen worden gedaan op basis van de wetenschappelijke literatuur.

De chirurgische behandeling voor T1- of T2-hypofarynxcarcinomen kan bestaan uit Transoral Laser Microsurgery (TLM) of Transoral Robotic Laser Surgery (TORS). Het doel is om lokale controle te bereiken en tegelijkertijd orgaansparend te werk te gaan.

In een case series uit 2008 werd bij 172 patiënten met een T1-T4 hypofarynxcarcinoom de tumor gereseceerd met een CO_2 laser (Martin, 2008). Slechts 15% van de patiëntenpopulatie had een T1- of T2 tumor. De onderzoekers rapporteerden een 5-jaars lokale controle van 84% voor de T1-tumoren en 70% voor de T2-tumoren. Recidief-vrije overleving was 73% voor stadium I en II. De algehele 5-jaarsoverleving van patiënten met een T1- of T2-tumor was 68%. De onderzoekers concludeerden dat het mogelijk is om een oncologische resectie te verrichten met goede functionele uitkomsten. De functionele uitkomsten werden echter niet gerapporteerd per tumorstadium. De onderzoekers benadrukten dat er maximaal één arytenoïd mag worden gereseceerd om de larynxfunctie te behouden.

Een prospectieve studie uit 2002 met 29 patiënten met hypofarynxtumoren die allen behandeld werden met TLM, toonde in 24% van deze patiënten een complicatie (Vilaseca-González, 2003). Het artikel bestudeert zowel patiënten met hypofarynx- als laryxntumoren in meerdere stadia (275 patiënten totaal, waarvan 94,7% man en gemiddelde leeftijd van 62.6 ± 10.4), en noemt voor alle soorten tumoren de volgende postoperatieve complicaties: lokale infectie, emfyseem en cervicale fistel, kortademigheid, postoperatieve bloeding en longontsteking. Als intra-operatieve complicatie wordt bij één patiënt ontbranding van de plakstrips voor de katheter gerapporteerd. Er wordt niet vermeld welke complicaties bij welk stadium of welke tumorsoort voorkomen. Er werd voor geen van de patiënten met een T1 tumor complicaties gerapporteerd, terwijl voor 17,6% van de patiënten met een T2 tumor een complicatie werd gerapporteerd.

Een recentere chirurgische benadering is de TransOrale Robot Chirurgie (TORS), uitgevoerd met de Da Vinci robot. TORS wordt al vaker gebruikt bij patiënten met orofarynxcarcinomen, maar wordt de laatste tijd ook ingezet bij patiënten met hypofarynx- en larynxtumoren. TORS lijkt een haalbare en veilige behandelmodaliteit te zijn, maar data met betrekking tot overleving en functionele uitkomsten ontbreken (Durmus, 2015).

Een groot voordeel van TLM en TORS is dat radiotherapie achter de hand gehouden kan worden indien er een recidief of een tweede primaire tumor optreedt, mits er sprake is van adequate oncologische controle van de primaire tumor. Een goede patiëntselectie is hierbij van groot belang en de chirurg moet uitgebreide ervaring hebben met deze modaliteiten.

Met de juiste patiëntenselectie, informatie over eventuele uitbreiding van de tumor en een ervaren chirurg kunnen TLM of TORS goede behandelopties zijn voor patiënten met een T1- of T2-hypofarynxcarcinoom.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Naast lokale controle en ziektevrije overleving is het aannemelijk dat kwaliteit van leven en functie van de larynx van belang is voor patiënten. Het doel van de behandeling van T1-T2 hypofarynxtumoren is naast oncologische controle dan ook om orgaansparend te werk te gaan. Er zijn geen studies gevonden waarin (chemo-)radiotherapie versus chirurgie (TLM of TORS) wordt onderzocht met betrekking tot de kwaliteit van leven en larynxfunctie. Bij gelijke resultaten zou een voordeel van chirurgie kunnen zijn dat patiënten slechts eenmalig worden behandeld en opgenomen, versus meerdere ziekenhuisbezoeken voor radiotherapie. Dit is met name het geval voor patiënten die slecht ter been zijn en veel steun van mantelzorgers behoeven. Het is echter onduidelijk welke waarde patiënten hechten aan deze voor- en nadelen omdat dit nooit is onderzocht.

Het streven is om een patiënt met zo min mogelijk verschillende modaliteiten te hoeven behandelen. Op basis van het resultaat van het histopathologisch onderzoek van het resectiepreparaat kan er een indicatie ontstaan voor adjuvante radiotherapie met of zonder chemotherapie. De noodzaak hiertoe is afhankelijk van een goede patiëntselectie voor TLM en TORS. De frequentie van het gebruik van twee of drie in plaats van één behandelingsmodaliteit kan afhankelijk van de patiëntselectie aanzienlijk zijn. Mogelijk dat de radiotherapie dosis bij adjuvante radiotherapie wel lager kan zijn dan bij primaire radiotherapie.

Kosten (middelenbeslag)
Een case series met 10 patiënten toonde aan dat de gemiddelde operatietijd met TORS 62,4 minuten was en er 17,4 minuten nodig waren om het systeem in te stellen (Park, 2010). Een andere case series met 5 patiënten vond een gemiddelde opnameduur van 4 tot 6 dagen (uitersten 4 tot 5 dagen) (Durmus, 2015). Verwacht mag worden dat de operatietijd met TLM vergelijkbaar is. Patiënten zullen doorgaans 6 weken lang 5 keer per week poliklinisch bestraald worden.

Aanvaardbaarheid, haalbaarheid en implementatie
Radiotherapie is een behandeling die routinematig in alle hoofd-halscentra wordt toegepast. TLM wordt in alle hoofd-halscentra routinematig toegepast bij de behandeling van (kleine) larynxcarcinomen. In sommige centra worden ook andere tumoren met TLM behandeld. TORS wordt nog niet in alle centra toegepast. De ervaring met TORS voor de behandeling van hypofarynxcarcinomen is nog beperkt.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De werkgroep is van mening dat radiotherapie de standaardbehandeling van patiënten met T1-2N0-1 hypopharynxcarcinoom blijft. Het gebrek aan studies waarin radiotherapie direct met TORS en/of TLM wordt vergeleken geeft vooralsnog geen richting om TORS of TLM als standaardbehandeling boven radiotherapie te verkiezen. De resultaten van de lopende gerandomiseerde studies dienen afgewacht te worden. Een goede patiëntselectie lijkt cruciaal te zijn.

De werkgroep is van mening dat patiënten door de verschillende complicatie- en toxiciteitspatronen die ontstaan wegens de aard van beide interventies een voorkeur voor één van beide interventies kunnen hebben. De werkgroep acht het daarom belangrijk dat de voor- en nadelen van beide interventies besproken moeten worden, maar ook dat aangegeven wordt dat radiotherapie vooralsnog de huidige standaardzorg is.

Vanwege het ontbreken van vergelijkende studies én het feit dat radiotherapie op dit moment al reguliere zorg is, dient een behandeling middels TLM of TORS alléén te geschieden bij een patiëntvoorkeur voor een chirurgische behandeling, in centra én wanneer TLM of TORS als adequaat alternatief kan worden gezien voor de patiënt.

Onderbouwing

Achtergrond

Hypofarynxcarcinomen komen relatief weinig voor: ze vormen 7% van alle hoofd-halstumoren. Elk jaar worden ongeveer 190 nieuwe patiënten gediagnosticeerd (Parkin, 2002). Vanwege verborgen tekenen van ziekte en symptomen had meer dan 80% van de patiënten een vergevorderd tumorstadium op het moment van diagnose (Kuo, 2014). Sinds de jaren '90 worden T1-T2N0 kleine hypofarynxcarcinomen behandeld met radiotherapie van de primaire tumor en electieve radiotherapie van de ipsi- en contralaterale nek. Recent worden echter ook Transoral Micro Surgery (TLM) en minimaal invasieve Transoral Robotic Surgery (TORS) gebruikt voor de behandeling van farynx- en larynxtumoren (Meulemans, 2019). Een primaire behandeling met TORS zou kunnen zorgen dat (chemo)radiotherapie bewaard kan blijven als behandeloptie bij een mogelijke secundaire primaire tumor of een recidief. Het is niet duidelijk welke behandeling de beste resultaten oplevert in termen van overleving, morbiditeit en functionele uitkomsten. Behandelopties voor een primaire tumor van een klein hypofarynxcarcinoom (T1-T2, N0) zijn radiotherapie of chirurgie. Het is onduidelijk wat de beste keuze is.

Conclusies

No studies reported on the crucial and important outcome measures. Therefore, GRADE assessment could not be applied. As a result, no literature conclusions can be drawn about the effect of radiotherapy compared to surgery, on the pre-specified outcome measures.

Samenvatting literatuur

No studies reported on the crucial and important outcome measures.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of radiation versus surgery for patients with a primary tumor of small hypopharyngeal carcinomas (T1-T2, N0) on predefined outcomes?

P: (Patients) patients with a primary T1-T2N0 hypopharyngeal carcinoma;
I: (Intervention) radiation;
C: (Comparison) surgery (TLM or TORS);
O: (Outcomes) overall survival (3 to 5 years), disease-free survival, morbidity, functional outcomes, quality of life, head-neck specific quality of life, EORTC QLQ-C30, EORTC QLQ-H&N35, H&N43.

Relevant outcome measures

The working group considered survival (3 to 5 years), disease free survival, morbidity and functional outcomes as critical outcome measures for decision making; and quality of life, head-neck specific quality of life, EORTC QLQ-C30, EORTC QLQ-H&N35, H&N43 as important outcome measures for decision making.

Clinically relevant difference
The working group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free *survival:*

- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases MEDLINE (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 15th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 64 hits.

Studies were selected based on the following criteria: included patients with a primary tumor of small hypopharyngeal carcinomas (T1-T2, N0), compared radiation with surgery, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and were written in English.

Eleven studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
None of the studies retrieved from the search compared the two interventions of interest in a randomized or observational design, therefore no studies were included.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Behandeling T3-T4aN0 hypofarynxcarcinoom

Uitgangsvraag

Wat is de beste behandeling van T3-T4aN0 hypofarynxcarcinomen?

Aanbeveling

De behandeling van T3-T4N0 hypofarynxcarcinoom kan plaatsvinden met primaire chemoradiatie en met primaire chirurgie, afhankelijk van de pathologie uitslag gevolgd door radiotherapie dan wel chemoradiatie. De werkgroep kan op basis van de literatuur geen aanbevelingen geven over een voorkeur voor primaire chemoradiatie of primaire chirurgie met postoperatieve (chemo-)radiatie omdat geen verschil is gevonden in oncologische en functionele uitkomsten.

Bespreek de behandelopties en ondersteun de patiënt bij het maken van een behandelkeuze waarbij de individuele patiëntkarakteristieken afgewogen dienen te worden.

Bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- **Behandelduur:**

  ○ De duur van de behandelingen zonder complicaties is bij chirurgie gemiddeld twee tot drie weken gevolgd door gemiddeld vijf tot zeven weken (chemo-)radiatie.
  ○ Voor radiotherapie is de behandeling poliklinisch en de behandelduur vijf tot zeven weken.

- **Overblijvende behandelopties:**

  ○ Na radiotherapie is doorgaans geen radiotherapie meer mogelijk voor een recidief of tweede primaire tumor in het bestraalde gebied.
  ○ Na chirurgie is hernieuwde chirurgie zelden nog mogelijk.

- **Procedures:**

  ○ Een dergelijke operatie wordt onder narcose verricht.

- **Korte en lange termijn complicaties en toxiciteit:**

  ○ Bij chirurgie kunnen bloedingen, pijn en ontstekingen optreden. Als langetermijneffect kunnen slikklachten als gevolg van stenosering optreden. Door het verrichten van een laryngopharyngectomie wordt de larynxfunctie geheel opgeheven.
  ○ Bij radiotherapie kunnen heesheid en slikklachten optreden. Zes weken na afronding van radiotherapie verbeteren deze klachten in het algemeen. Voor deze klachten kan logopedische sliktraining of een blijvende gastrostomie nodig zijn.
  ○ De kans op een disfunctionele larynx met slikklachten, passageklachten en slechte stem is reëel, wat een indicatie kan zijn voor een permanente tracheotomie of zelfs een laryngopharyngectomie. De kans op radionecrose is reëel, de kans op een secundaire tumor door de radiotherapie is zeer klein.

- **Kans op adjuvante behandeling:**

  ○ Er zal na een resectie vrijwel altijd reden zijn (chemo-)radiatie te adviseren, na een chemoradiatietraject kan er ook resectie aan de orde zijn indien er residu ziekte is, of een recidief optreedt.

- **Kans op genezing:**

  ○ Er is geen verschil gevonden tussen beide behandelopties met betrekking tot genezing.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Om de vergelijking van chemoradiatie met chirurgie voor patiënten met T3-T4N0 hypofarynxcarcinomen te kunnen beantwoorden, werden 2 RCT's en 7 observationele studies geïncludeerd. De bewijskracht van deze studies is zeer laag, door een inadequate blindering in de RCT's, de observationele aard van de geïncludeerde studies, de variatie in gebruikte behandelingen tussen sommige studies, en wegens het lage aantal geïncludeerde patiënten.

De cruciale uitkomstmaten *overall survival* en *disease free survival* werden gerapporteerd. Door de zeer lage bewijskracht, zijn we onzeker of overall survival en disease free survival beter zijn na behandeling met chemoradiatie, of na behandeling met chirurgie. Daarnaast werd informatie gerapporteerd voor de belangrijke uitkomstmaat morbiditeit (met name larynxpreservatie). De bewijskracht is echter zeer laag waardoor geen uitspraak kan worden gedaan over het verschil tussen de groepen wat betreft de kans op behoud van een functionele larynx. Logischerwijs mag verwacht mag worden dat chemoradiotherapie in vergelijking met chirurgie resulteert in een hoger percentage larynxpreservatie, mogelijk bij T4a tumoren met een mindere locoregionale tumor controle. Larynxpreservatie betekent echter niet altijd dat ook de functies van de larynx behouden blijven.

Conform expert opinion is er een indicatie voor primaire TLE als er sprake is van een disfunctionele larynx, voorafgaande aan de therapie. Hierbij moet gedacht worden aan slikklachten waarbij logopedische behandeling onvoldoende resultaat heeft opgeleverd en ernstige dyspnoe. De reden hiervoor is dat de larynx na (chemo-)radiatie dysfunctioneel blijft bestaan en deze waarschijnlijk toeneemt. Ondanks een mogelijke locoregionale controle blijven patiënten dan afhankelijk van een tracheostoma en/of sondevoeding.

Op basis van een uitgebreide observationele analyse van de algehele overleving voor het hypofarynxcarcinoom in Nederland (n=2999 waarvan n=1881 voor T3-T4), lijkt er voor het T4 hypofarynxcarcinoom voorkeur uit te gaan voor een primaire TLE. Voor het T3 hypofarynxcarcinoom was de algehele overleving gelijk voor TLE en chemoradiatie, maar lager voor radiotherapie alleen. Met radiotherapie alleen voor een T3 tumor was er wel een duidelijk verbetering in de jaren 2001 tot 2010 ten opzichte van 1991 tot 2000. Er zijn echter wel duidelijke methodologische beperkingen gezien de observationele aard van de studie. Daarnaast werd er bij de specifieke analyse voor T4 carcinomen geen correctie voor confounding toegepast. In deze studie ontbraken details aangaande radiotherapie data en sommige tumor- en patiëntgerelateerde karakteristieken. De studie bericht niet over ziektevrije overleving, toxiciteit of kwaliteit van leven, terwijl die ook een rol spelen bij de therapiekeuze.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
Naast lokale controle en ziektevrije overleving is het aannemelijk dat kwaliteit van leven, behoud van zelfstandigheid (Festen, 2021) en functie van de larynx van belang zijn voor patiënten. Het doel van de behandeling van T3-T4 hypofarynxtumoren is naast oncologische controle dan ook om orgaansparend te werk te gaan. Er zijn geen studies gevonden waarin (chemo-)radiotherapie versus chirurgie met postoperatieve (chemo)radiatie wordt onderzocht met betrekking tot de kwaliteit van leven en larynxfunctie. Bij gelijke oncologische resultaten zou een voordeel van primaire (chemo-)radiotherapie kunnen zijn dat patiënten hun normale spreekfunctie behouden, wat de kwaliteit van leven voor patiënten vergroot. Echter in een onbekend percentage van deze patiënten zal de in opzet larynxsparende behandeling resulteren in een disfunctionele larynx. Wat uiteindelijk als gevolg heeft dat patiënt dan wel tracheotomie afhankelijk wordt, dan wel alsnog een laryngopharyngectomie moet ondergaan. In de studie van Petersen (2018) wordt een salvage surgery of functionele totale laryngectomie binnen 5 jaar verricht voor 7% van de patiënten behandeld met radiotherapie, en voor 4% van de patiënten behandeld met chemoradiatie.

Het is echter onduidelijk welke waarde patiënten hechten aan deze voor- en nadelen omdat dit nooit is onderzocht. Het is dus belangrijk alle risico's en mogelijke complicaties mee te nemen, en alle voor- en nadelen met een patiënt te bespreken.

Het streven is om een patiënt met zo min mogelijk verschillende modaliteiten te hoeven behandelen, maar in een aanzienlijk deel van de patiënten zal salvage chirurgie nodig zijn. Bij primaire chirurgie zal in het geval van een T3-4 tumor er altijd een indicatie zijn voor adjuvante radiotherapie met of zonder chemotherapie. Bij primair (chemo-)radiatie zal dat beperkt kunnen worden tot één of twee modaliteiten.

<u>Kosten (middelenbeslag)</u>
De voorkeur voor primaire chirurgie met postoperatieve (chemo-)radiatie versus primaire (chemo-)radiatie met eventuele salvage chirurgie laten een kostenanalyse nauwelijks toe.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
Er wordt geen effect verwacht van de aanbeveling op de gezondheidsgelijkheid. Ook worden er geen belemmerende factoren verwacht op het gebied van implementatie van de interventies.

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
De werkgroep is van mening dat er geen voorkeur is voor chemoradiatie of chirurgie als primaire behandeling van patiënten met T3-4N0 hypofarynxcarcinoom. Het gebrek aan studies waarin chemoradiotherapie direct met chirurgie wordt vergeleken geeft vooralsnog geen richting om chirurgie als standaardbehandeling boven chemoradiatie te verkiezen of vice versa. Primaire radiotherapie lijkt niet de behandeling van voorkeur te zijn, maar kan bij contra-indicatie voor chemotherapie, met name voor het T3N0 hypofarynxcarcinoom een optie zijn als larynxsparende therapie.

Op basis van beperkte data uit de momenteel beschikbare literatuur lijkt er een voorkeur te zijn voor primaire TLE bij het T4 hypofarynxcarcinoom. Bij een functionele larynx en wanneer een patiënt de voorkeur heeft voor larynxsparing, kan primaire chemoradiatie worden overwogen, waarbij een mogelijk lagere algehele overleving wordt geaccepteerd.

TLE heeft als voordeel een mogelijk betere overleving, alhoewel het verschil in overleg mogelijk te verklaren is door andere selectiecriteria. Nadelen van TLE zijn verlies van de normale spreekfunctie en het feit dat nagenoeg alle patiënten alsnog (chemo-)radiatie krijgen.

De werkgroep is van mening dat patiënten door de verschillende complicatie- en toxiciteitspatronen die ontstaan wegens de aard van beide interventies een voorkeur voor één van beide interventies kunnen hebben. De werkgroep acht het daarom belangrijk dat de voor- en nadelen van beide interventies besproken worden.

Onderbouwing

Achtergrond

Het hypofarynxcarcinoom is vaak bij initiële diagnose al vergevorderd wat betreft T-stadiëring. Op dit moment is niet duidelijk wat de beste behandeling voor operabele T3-T4a hypofarynxcarcinomen is. Zowel primaire chirurgie, afhankelijk van de pathologie uitslag gevolgd door radiotherapie dan wel chemoradiatie, als primaire chemoradiotherapie, eventueel gevolgd door salvage surgery, worden beschouwd al behandelopties. In de literatuur ligt de frequentie van salvage chirurgie tussen de 6 en 15%. De frequentie hiervan zal echter afhankelijk van het behandelcentrum waarschijnlijk zeer variëren naar gelang de culturele achtergrond, chirurgische ervaring en patiëntkenmerken. Voor de behandeling heeft de keuze tussen chirurgie, met eventuele postoperatieve (chemo-)radiatie en primaire radiotherapie (met eventuele chemotherapie) naast curatieve uitkomsten ook belangrijke consequenties voor de kwaliteit van leven.

Conclusies

Overall survival (3 to 5 years)

Very low GRADE	The evidence is very uncertain about the effect of treatment with chemoradiation compared to surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy) on overall survival in patients with a T3-T4, N0 hypopharyngeal carcinoma. *Sources: (Beauvillain, 1997; Lefebvre, 1996; Chung, 2019; Harris, 2015; Hung, 2006; Jang, 2016; Kim, 2016; Kim, 2018; Petersen, 2018)*

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of treatment with chemoradiation compared to surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy) on disease-free survival in patients with a T3-T4, N0 hypopharyngeal carcinoma. *Sources: (Lefebvre, 1996; Chung, 2019; Harris, 2015; Hung, 2006; Kim, 2016)*

Morbidity

Very low GRADE	The evidence is very uncertain about the effect of treatment with chemoradiation compared to surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy) on morbidity in patients with a T3-T4, N0 hypopharyngeal carcinoma. *Sources:* (*Chung, 2019; Jang, 2016; Kim, 2016; Lefebvre, 1996*)

Quality of life

- GRADE	No conclusion can be drawn about the effect of treatment with chemoradiation versus surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy) on quality of life.

Dry mouth

- GRADE	No conclusion can be drawn about the effect of treatment with chemoradiation versus surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy) on dry mouth.

Head-neck specific quality of life

- GRADE	No conclusion can be drawn about the effect of treatment with chemoradiation versus surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy) on head-neck specific quality of life.

Samenvatting literatuur

Description of studies
The systematic review of **Cui (2020**) included 17 studies in their analysis. The table AMSTAR (see risk of bias tables) contains a quality assessment for the systematic review. The AMSTAR tool shows that the systematic review does not meet the following criteria: description of all included and excluded studies, description of all relevant characteristics of included studies, appropriate adjustment for potential confounders in observational studies, enough similarity between studies to make combining reasonable, and reporting of potential conflicts of interest.

The 17 included studies in Cui (2020) contained 2 RCT's, these will be described here. Next to that 15 retrospective cohort studies were included. Of these 15 observational studies, 6 fulfilled all selection criteria and were included in the analysis. Due to the study design of these six studies pooling was not possible. Table 13.1 (see Appendix) contains an overview per observational study on why the studies were either excluded, or not suitable for pooling. Study characteristics of the two RCTs and six eligible observational studies included in the review and the observational study by Petersen (2018) are described here.

Randomised controlled trials
The RCT performed by **Beauvillain (1997**) included patients with a locally advanced resectable hypopharyngeal carcinoma (T3-T4, N0-N3 resectable squamous cell hypopharyngeal carcinoma) and was performed in France. They compared neoadjuvant chemotherapy, followed by laryngopharyngectomy, plus postoperative radiotherapy, with neoadjuvant chemotherapy followed by radiotherapy, with or without salvage surgery. The outcome Overall survival (OS) was studied. They included 90 patients, with 45 patients in

the chemoradiation group and 47 patients in the surgery group. In the chemoradiation group the mean age was 54.5 years and 100% was male, in the surgery group the mean age of the patients was 56 years and 100% was male. The mean follow up was not mentioned, but follow-up took place with 3 months intervals during the first and second year, thereafter 6-month intervals for 3 to 5th year, thereafter 12 months intervals.

The RCT performed by **Lefebvre (1996)** included patients with squamous cell carcinoma of the hypopharynx, T2-T4, N0-N2b, defined as: "histologically proven squamous cell carcinoma of the pyriform sinus or of the hypopharyngeal aspect of the aryepiglottic fold (which are hardly distinguishable from true pyriform sinus tumors when they are advanced)." Data was collected in multiple European countries. They compared larynx-preserving treatment (induction chemotherapy plus definitive, radiation therapy in patients who showed a complete response or surgery in those who did not respond) with conventional treatment (total laryngectomy with partial pharyngectomy, radical neck dissection, and postoperative irradiation). The outcomes disease-free survival (DFS) and OS were studied. A total of 194 patients was included, 100 received chemoradiation and 94 received surgery. Originally a total number of patients of 99 in the surgery arm and 103 in the chemotherapy arm was enrolled. However six patients were found to be ineligible, and for two other patients no information was received after randomization, which lead to the total number of 194 included patients. All 94 eligible patients in the surgery arm were included in the analysis, however 89 (95%) of patients received the planned treatment, due to inoperability or not receiving postoperative radiotherapy. For the chemotherapy arm, all 100 eligible patients were included in analysis, but 93 (93%) of patients underwent the planned treatment. Three patients did not start chemotherapy, of the patients treated with chemotherapy three had no subsequent treatment, and one patient treated with surgery died after the procedure. The mean age for the total sample was 55 years, and 96% of all patients were male. The mean follow-up was 51 months for all patients. Different numbers are reported in Cui (2020) and the original study Lefebvre (1996), here we report the numbers originating from Lefebvre (1996).

Observational studies

The retrospective cohort study performed by **Chung (2019)** included patients with locally advanced stage III/IV hypopharyngeal carcinomas and was performed in Korea. They compared different forms of chemoradiation: induction chemotherapy followed by (chemo)radiotherapy (ICT) and definitive chemoradiotherapy (CRT) as intervention, with surgery-based therapy (SRT) as a control. The outcomes DFS and OS were studied. A total of 266 patients was included, of which 127 were treated with a form of chemoradiation, and 139 were treated with SRT. The mean age of the patients was 63.7 years, and 93.6% of all patients was male. The mean follow-up of the study was 32.9 months of all patients, age, gender, and follow-up were not described per specific treatment.

The retrospective cohort study performed by **Harris (2015)** included patients with advanced stage hypopharyngeal squamous cell carcinoma and was performed in the USA. They compare definitive chemoradiotherapy with or without salvage surgery as intervention, with primary surgery, with either adjuvant radiotherapy (RT) or chemoradiotherapy (CRT) as control. The outcomes DFS and OS were studied. A total of 76 patients was included, where 48 received definitive chemoradiotherapy and 28 received primary surgery. Patients receiving chemoradiotherapy had a mean age of 62.9 and 78% was male, patients receiving primary surgery had a mean age of 65.3 and 76% was male. The mean follow-up of the study was 30 months.

The retrospective cohort study performed by **Hung (2006)** included patients with advanced hypopharyngeal cancer and was performed in Taiwan. They compared definitive concurrent chemoradiation (CCRT) followed by adjuvant systemic chemotherapy as intervention, with surgery plus postoperative CCRT followed by adjuvant systemic chemotherapy (SCCRT) as control. The outcomes DFS and OS were studied. A total of 60 patients was included, where 38 were treated with definitive CCRT followed by adjuvant systemic chemotherapy and 22 were treated with surgery plus postoperative CCRT followed by adjuvant SCCRT. Patients receiving the intervention had a mean age of 61 years and 100% was male, patients receiving the control had a mean age of 55 years and 100% was male. The mean follow-up of the study was 20 months.

The retrospective cohort study performed by **Jang (2016**) included patients with hypopharyngeal cancer. The study includes both T1-T2 and T3-T4 patients together and individually, numbers described here are specifically for T3-T4 patients. The study was performed in Korea. They compared initial concurrent chemoradiation treatment (iCRT) as treatment with surgery (OP) ± adjuvant concurrent chemoradiation treatment (aCRT) as control. The outcome OS was studied. A total of 177 T3-T4 patients was included, 107 were treated with iCRT and 70 were treated with OP ± aCRT. Patients receiving iCRT had a mean age of 63.7 years and 95.3% was male. Patients receiving OP ± aCRT had a mean age of 66.7 years and 95.7% was male. The mean follow-up was 19 months.

The retrospective cohort study performed by **Kim (2016)** included patients with resectable stage III/IV hypopharyngeal cancer and was performed in Korea. They compared organ preserving chemoradiotherapy (CRT) as intervention, with surgery followed by radiotherapy (SRT) as control. The outcomes DFS and OS were studied. A total of 91 patients was included, 34 were treated with CRT and 57 were treated with SRT. Patients receiving CRT had a mean age of 65.5 years and 88.2% was male, patients receiving SRT had a mean age of 64 years and 98.2% was male. The mean follow-up was 50 months.

The retrospective cohort study performed by **Kim (2018**) included patients with locally advanced hypopharyngeal cancer and was performed in Korea. They compared chemoradiotherapy as intervention, with surgery as control. The outcome OS was studied. In the article OS is described for both T2-T4a together as for T4a individually. Only for T4a individually correction for confounding was performed, as to match the PICO only T4a is described here. For T4a carcinomas, 126 patients received chemoradiotherapy and 111 patients received surgery. Age and gender were only described for all T2-T4a patients together. For patients receiving chemoradiotherapy 55.2% of patients was < 65 years and 44.8% of patients > 65 years, and 82.6% was male. For patients receiving surgery 47.8% was < 65 years and 52.2% was >65 years, and 81.8% was male. The mean follow up was not described.

The retrospective population-based cohort study **Petersen (2018)** included patients with T1-T4N0-N3M0 squamous cell carcinoma of the hypopharynx and was performed in the Netherlands. All available data from all patients diagnosed in the Netherlands between 1991 and 2010 was retrieved and the treatments total laryngectomy (with/without (partial) pharyngectomy) and chemoradiotherapy were studied. The outcome OS was studied, and separately described for T1-T2, T3 and T4 hypopharynx cancer. We specifically retrieved data for patients with T3 and T4 hypopharynx cancer treated with the interventions total laryngectomy and chemoradiotherapy. For T3 carcinomas, 222 patients were included that received chemoradiotherapy, and 155 patients that received total laryngectomy. For T4 carcinomas, 316 patients received chemoradiotherapy

and 294 patients received total laryngectomy. Age and gender were described for all T1-T4 stage carcinoma patients together. Of patients receiving chemoradiotherapy 82% was male, and they had the following age: < 50 years: 119/752 (15.8%) patients, 50-59 years: 309/752 (41%) patients, 60 to 69 years: 245/752 (32.6%) patients, > 70 years: 79/752 (10.5%) patients. Of patients receiving total laryngectomy 82% was male, and they had the following age: < 50 years: 83/567 (14.6%) patients, 50 to -59 years: 175/567 (30.9%) patients, 60 to 69 years: 191/567 (33.7%) patients, > 70 years: 118/567 (20.8%) patients. The mean follow up was not described.

Results

Overall survival (3 to 5 years)

Overall survival was reported by two RCT's, Beauvillain (1997) and Lefebvre (1996), and by seven observational studies: Chung (2019), Harris (2015), Hung (2006), Jang (2016), Kim (2016), Kim (2018) and Petersen (2018).

The studies Chung (2019), Harris (2015), Hung (2006), Jang (2016) and Kim (2016) reported risk ratios (RR) for overall survival. As these are observational studies, odds ratios (OR) were calculated and are reported here, as risk ratios do not take residual confounding into account for observational studies. The calculated odds ratios are:

- Chung (2019): OR = 1.12 (95%CI = 0.69 to 1.82), in favour of surgery.
- Harris (2015): OR = 2.52 (95%CI = 0.96 to 6.60), in favour of surgery.
- Hung (2006): OR = 1.19 (95%CI = 0.40 to 3.48), in favour of surgery.
- Jang (2016): OR = 0.90 (95%CI = 0.38 to 2.12), in favour of surgery.
- Kim (2016): OR = 0.98 (95%CI = 0.68 to 1.43), in favour of chemoradiation.

The studies Beauvillain (1997), Lefebvre (1996) and Kim (2018) reported the overall survival rate (%). In addition to the original data, for the RCTs Lefebvre (1996) and Beauvillain (1997) the RR is calculated. The reported and calculated overall survival rates are:

- Beauvillain (1997): the overall survival rate was 19% in the chemoradiation group with a median survival of 20 months, and 37% in the surgery group with a median survival of 40 months, p=0.04. The calculated RR is 1.25 (95%CI = 0.97 to 1.63), in favour of surgery.
- Lefebvre (1996): the overall survival rate at 3 years was 57% in the chemoradiation group and 43% in the surgery group, the overall survival rate at 5 years was 30% in the chemoradiation group and 35% in the surgery group. The calculated RR at 5 years is 2.06 (95%CI = 1.51 to 2.80), in favour of surgery.
- Kim (2018): only for the overall survival rate for T4a stage carcinomas correction for confounders was performed, these data will be reported here. No significant difference in OR was found between surgery and chemoradiotherapy groups, the reported HR of the chemoradiotherapy group = 0.880 (95%CI = 0.617 to 1.256, p = 0.481).

The study Petersen (2018) reported the hazard ratio (HR) for T3-T4 stage carcinomas, after multivariable analysis using Cox regression analysis. They report a HR of 1.10 (95%CI = 0.94 to 1.28), p = 0.22 in favour of chemoradiation. Petersen (2018) also describes 5 year OS separately for T3 and T4 carcinomas. When

described separately, a significant better OS is found for T4 stage carcinomas when treated with surgery, however, it should be noted that no correction for confounding was performed for these separated data.

Disease-free survival
Disease-free survival was reported by one RCT, Lefebvre (1996), and 4 observational studies, Chung (2019), Harris (2015), Hung (2006) and Kim (2016).

The studies Chung (2019), Harris (2015), Hung (200 6) and Kim (2016) reported risk ratios for disease-free survival. As these are observational studies, odds ratios (OR) were calculated and are reported here, as risk ratios do not take residual confounding into account for observational studies. The calculated odds ratios are:

- Chung (2019): OR = 1.70 (95%CI = 1.04 to 2.78), in favour of surgery.
- Harris (2015): OR = 2.31 (95%CI = 0.89 to 6.00), in favour of surgery.
- Hung (2006): OR = 1.19 (95%CI = 0.40 to 3.48), in favour of surgery.
- Kim (2016): OR = 1.11 (95%CI = 0.47 to 2.60), in favour of surgery.

The study of Lefebvre (1996) reported the 3- and 5-years disease free survival rate (%). In addition to the original data, the RR is calculated for the 5-year DFS. The reported overall survival rates are:

- The disease-free survival rate at 3 years was 43% in the chemoradiation group and 32% in the surgery group. The disease-free survival rate at 5 years was 25% in the chemoradiation group and 27% in the surgery group. The calculated RR at 5 years is 2.71 (95%CI = 1.92 to 3.83) in favour of surgery.

Morbidity

Larynx preservation was reported by one RCT (Lefebvre, 1996) and three observational studies (Chung, 2019; Jang, 2016 and Kim, 2016). The studies by Chung (2019), Jang (2016) and Kim (2016) reported risk ratios for larynx preservation. As these are observational studies, odds ratios (OR) were calculated and are reported here, as risk ratios do not take residual confounding into account for observational studies. The calculated odds ratios are:

- Chung (2019): OR = 0.32 (95%CI 0.19 to 0.53), in favour of chemoradiation
- Jang (2016): OR = 0.10 (95%CI 0.05 to 0.23), in favour of initial concurrent chemoradiation treatment
- Kim (2016): OR = 0.06 (95%CI 0.02 to 0.19), in favour of chemoradiation

The study by Lefebvre (1996) reported that 43 out of 100 patients (43%) in the chemotherapy group underwent radical surgery.

(Head-neck specific) Quality of Life, dry mouth
None of the studies reported on these outcomes.

<u>Level of evidence of the literature</u>
Overall survival (3 to 5 years)

The level of evidence regarding the outcome measure **overall survival** started low, as the evidence originated from both observational studies and RCTs, and was downgraded by three levels because of study limitations: one level because of serious risk of bias (risk of bias in the observational studies due to inadequate adjustment for all important prognostic factors), one level because of indirectness (both the two RCTs and the observational study Harris (2015) deviate a bit from the PICO), one level because of imprecision (small number of patients in the studies), Publication bias could not be assessed. The certainty of the evidence was graded as very low.

Disease-free survival
The level of evidence regarding the outcome measure **disease-free survival** started low as the evidence originated from both observational studies and an RCT, and was downgraded by four levels because of study limitations: two levels because of serious risk of bias (risk of bias in the RCTs due to inadequate blinding of participants, care providers and outcome assessors, and risk of bias in the observational studies due to inadequate adjustment for all important prognostic factors), one level because of indirectness (both RCTs and the observational study Harris (2015) deviate a bit from the PICO), one level because of imprecision (small number of patients in the studies), Publication bias could not be assessed. The certainty of the evidence was graded as very low.

Morbidity
The level of evidence regarding the outcome measure **morbidity (larynx preservation)** started low as the evidence originated from both observational studies and an RCT, and was downgraded by three levels because of study limitations: one level because of risk of bias (risk of bias in the observational studies due to inadequate adjustment for all important prognostic factors), one level because of indirectness (the RCT deviates a bit from the PICO), one level because of imprecision (small number of patients in the studies), Publication bias could not be assessed. The certainty of the evidence was graded as very low.

(head-neck specific) Quality of life, Dry mouth
None of the studies reported on the outcome measures **(head-neck specific) quality of life, or dry mouth** and therefore GRADE could not be applied, and no conclusions could be drawn.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What is the best treatment of T3-T4a hypopharynx carcinomas? The focus is on the surgical versus nonsurgical approach.

P: (Patients)= Patients with a primary hypopharyngeal carcinoma (T3-T4a, N0).
I: (Intervention)= Chemoradiation.
C: (Comparison)= Surgery (optionally with postoperative radiotherapy or with postoperative chemoradiotherapy).
O: (Outcomes)= Overall survival (3 to 5 years), disease-free survival, morbidity, quality of life, dry mouth, head-neck specific quality of life.

Relevant outcome measures

The guideline development group considered overall survival and disease-free survival as critical outcome measures for decision making; and morbidity, dry mouth, head-neck specific quality of life and quality of life as measured with EORTC QLQ-C30, EORTC QLQ-H&N35, H&N43 as an important outcome measure for decision making.

The working group defined the outcome measures as follows:
Head-neck specific quality of life: measured using EORTC QLQ-C30, EORTC QLQ-H&N35, H&N43

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR <0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important difference of 10 points on the quality-of-life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until August 11, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 745 hits.

Studies were selected based on the following criteria: included patients with a primary hypopharyngeal carcinoma (T3-T4, N0), compared chemoradiation with either surgery, surgery with postoperative radiotherapy, or surgery with postoperative chemoradiotherapy, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and were written in English language.

After the systematic search was performed, the working group brought forward the retrospective population-based cohort study Petersen (2018). This study was judged to be relevant to include as the study specifically contains data from Dutch clinical settings, and includes a large number of patients. Although the study did not meet the criteria for study design due to its observational character, it was decided to include the study of Petersen (2018) after the systematic search was performed, because of the importance of the study.

All in all, 5 studies were initially selected based on title and abstract screening from the systematic search. After reading the full text, 4 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 1 systematic review was included. Next to that, 1 retrospective cohort study was included.

Data-synthesis

The systematic review of Cui (2020) included 17 studies in their analysis, including two RCTs and 15 retrospective cohort studies. Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis) separately. For all included observational studies, the following criteria were used: a priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:

- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results
One systematic review and one retrospective cohort study were included in the analysis of the literature. From the systematic review, for 2 RCTs and 6 observational studies the important study characteristics and results are summarized in the evidence tables, as not all included observational studies corrected for confounding. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Dosering cisplatin lokaal gevorderde tumoren

Uitgangsvraag

Welke dosering van cisplatin heeft de voorkeur in combinatie met radiotherapie bij de definitieve behandeling van lokaal gevorderde hoofd-halstumoren?

Aanbeveling

Geef patiënten tot en met 70 jaar met een locoregionaal vergevorderd plaveiselcelcarcinoom van het hoofdhalsgebied (Stadium III-IV) die een indicatie hebben voor chemoradiatie bij voorkeur concomitante chemotherapie met cisplatin (100 mg/m2 op dag 1, 22 en 43) in combinatie met conventioneel gefractioneerde radiotherapie (voorbeeld 70 Gy in zeven weken).

Op basis van bijvoorbeeld ingeschat toxiciteitsrisico kan een wekelijks (40 mg/m^2) schema een te verdedigen alternatieve optie zijn.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Onze systematische zoekactie in Medline en Embase resulteerde in acht RCT's (Mashhour, 2020; Sahoo, 2017; Noronha, 2018; Rawat, 2016; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012). In vier van deze RCT's werden (ook) patiënten geïncludeerd die adjuvant behandeld werden (Mashhour, 2020; Noronha, 2018; Kiyota, 2022; Tsan, 2012).

Voor beide cruciale uitkomsten (overleving en terugkeer van de kanker) werden resultaten gerapporteerd. Overleving werd gerapporteerd in vijf studies, één studie rapporteerde een slechtere overleving in de groep die wekelijks 40 mg/m^2 cisplatin kreeg, vergeleken met driewekelijks cisplatin. Het ging hierbij echter om zeer kleine aantallen patiënten die waren overleden en een ongelijke grootte van de studiearmen (10/25 versus 9/31). Eén studie rapporteerde een betere overleving in de groep die wekelijks 40 mg/m2 cisplatin kreeg in de adjuvante setting, vergeleken met driewekelijks cisplatin.

Terugkeer van de kanker werd op twee verschillende manieren gerapporteerd: het wel of niet bereiken van een complete respons op de behandeling of locoregionale controle. Informatie over het bereiken van een complete respons was beschikbaar in vijf studies. Eén studie liet zien dat de frequentie van complete respons hoger was in de groep die wekelijks cisplatin kreeg (Nanda, 2020, 81% versus 75%; 40 mg/m^2, 100% definitieve behandeling).
Twee studies lieten geen verschil zien (Mashhour, 2020, 30 mg/m^2, 50% adjuvant behandeld en 50% definitief; Rawat, 2016, 35 mg/m2, 100% definitieve behandeling). Twee studies lieten zien dat de frequentie van complete respons lager was in de groep die wekelijks cisplatin kreeg (Sahoo, 2017, 72% versus 86%; 30 mg/m^2, 100% definitieve behandeling; Nair, 2017, 75% versus 90%, 40 mg/m2, 100% definitieve behandeling). Locoregionale controle werd gerapporteerd in zes studies. In drie studies was de frequentie van locoregionale controle lager in de groep die wekelijks cisplatin kreeg, waarbij het in twee studies ging om een zeer klein aantal patiënten waarbij de kanker terugkeerde (4/29 versus 2/31 en 13/30 versus 8/30). In één van deze studies werd een dosering van 40 mg/m^2 gebruikt in de definitieve setting en in de overige twee

studies werd in de definitieve of adjuvante setting een dosering van 30 mg/m^2 gebruikt. In één studie was de frequentie van locoregionale controle hoger in de groep die wekelijks 40 mg/m^2 cisplatin kreeg in de adjuvante setting, vergeleken met driewekelijks cisplatin.

Ook voor alle belangrijke uitkomsten (ziektevrije overleving, kwaliteit van leven en bijwerkingen) werden resultaten gerapporteerd. Ziektevrije overleving werd in vier studies gerapporteerd. Eén studie (40 mg/m^2) liet een slechtere 2-jaars overleving zien in de wekelijkse behandelgroep (53% versus 65%), twee studies (30 mg/m^2 en 40 mg/m^2) lieten geen verschil zien en in één studie (40 mg/m^2) was het niet mogelijk om te bepalen of het verschil klinisch relevant was, de mediane ziektevrije overleving was echter vrijwel gelijk tussen de groepen (26,4 maanden versus 27,4 maanden).

Bijwerkingen werden in alle studies gerapporteerd. De frequentie acute bijwerkingen van graad 3 of hoger lag in één studie (30 mg/m^2) lager in de wekelijkse behandelgroep (72% versus 85%; p=0.006), terwijl in een andere studie (40 mg/m2) geen verschil werd gevonden in de frequentie van bijwerkingen van graad 3 of hoger (81% versus 80%; p=0.87), maar wel in de frequentie van graad 4 bijwerkingen (8% versus 19%; p=0.017). Een andere studie analyseerde de frequentie van niet-hematologische bijwerkingen van graad 3 of hoger,
waarbij een lagere frequentie werd gerapporteerd in de wekelijkse behandelgroep (57% versus 77%). In sommige studies werd voor afzonderlijke niet-hematologische bijwerkingen van graad 3 of hoger een lagere frequentie in de wekelijkse groep gerapporteerd, bijvoorbeeld een verschil in de frequentie van dysfagie (63% versus 26%), maar dit werd niet consistent in alle studies teruggezien. Voor hematologische bijwerkingen werd in de meerderheid van de studies geen verschil in bijwerkingen van graad 3 of hoger tussen de groepen gerapporteerd.

Kwaliteit van leven werd in één studie gerapporteerd, waarbij zowel de scores voor de Trial Outcome Index (een combinatie van drie subschalen) als de scores voor vijf subschalen werden gerapporteerd. Scores op de Trial Outcome Index lagen op alle vier de meetmomenten wat lager (wat een lagere kwaliteit van leven inhoudt) in de wekelijkse behandelgroep. Alleen op het laatste meetmoment, drie maanden na het afronden van de behandeling, ging het om een klinisch relevant verschil tussen de groepen (9.7 punten verschil op een schaal van 0 tot 96). Voor de subschalen werd een wisselend beeld gezien.

De bewijskracht voor alle uitkomstmaten was zeer laag. Er werd afgewaardeerd wegens een risico op bias omdat de randomisatie en allocatie niet beschreven waren, omdat er niet geblindeerd was (voor de uitkomst kwaliteit van leven) en omdat één van de studies voortijdig stopgezet was wegens tegenvallende inclusie. Daarnaast werd in twee gevallen afgewaardeerd voor inconsistentie wegens verschillen in gerapporteerde effecten tussen de studies. Voor alle uitkomsten werd afgewaardeerd wegens indirectheid, omdat vier studies (ook) patiënten includeerden die in de adjuvante setting behandeling werden met chemoradiatie en omdat zeven van de acht studies waren uitgevoerd in Azië. Daarnaast ging het in zes van de acht studies om kleine patiëntaantallen (range 30 tot 71) wat leidde tot brede betrouwbaarheidsintervallen waardoor afgewaardeerd werd wegens imprecisie.

Uit de geïncludeerde studies bleek dat patiënten die wekelijks cisplatin kregen over het algemeen een lagere cumulatieve dosis ontvingen vergeleken met patiënten die driewekelijks cisplatin kregen. In twee

Nederlandse retrospectieve studies werd voor patiënten waarbij dosisbeperkende toxiciteit optrad een minder goede overleving gerapporteerd (Bril, 2022; Wendrich, 2017).

In de literatuursamenvatting zijn alleen RCT's geïncludeerd. De RCT's zijn over het algemeen relatief klein en hebben hun beperkingen. Er zijn diverse niet-gerandomiseerde studies verschenen die zich met name op een vergelijking van toxiciteit hebben gericht. Hieruit komen aanwijzingen naar voren dat het wekelijks toedienen van cisplatin (40 mg/m^2) tot minder (renale) toxiciteit zou kunnen leiden (Bauml, 2019; Driessen, 2016; Espeli, 2012; Ho, 2008). Daarnaast werd er één RCT geëxcludeerd omdat deze was uitgevoerd onder patiënten met een nasofarynxcarcinoom (Lee, 2016). Deze kleine RCT uit Korea suggereerde dat een wekelijkse dosis van 40 mg/m^2 niet inferieur zou zijn aan driewekelijkse toediening van cisplatin.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Het doel van het toedienen van cisplatin in een wekelijks schema in plaats van een driewekelijks schema is het verminderen van toxiciteit, zonder duidelijke afname van de effectiviteit. Er is geen onderzoek gedaan naar de waarden en voorkeuren van patiënten wat betreft deze twee doseringsschema's. Uit een meta-analyse van 107 RCT's naar de effecten van chemotherapie bij hoofd-halstumoren (Lacas, 2021) bleek dat met het toenemen van de leeftijd het effect van het toevoegen van cisplatin aan radiotherapie afneemt, waarbij er in de leeftijdsgroep boven de 70 jaar geen positief effect is op overleving en dit positieve effect in de leeftijdsgroep 60-69 ook aanzienlijk lager is dan in de groep jonger dan 50 jaar. Het is goed om te realiseren dat in de studies ook selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van het wekelijkse doseringsschema ten opzichte van het driewekelijkse schema. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht dat de aanbeveling geen relevante impact heeft op de zorgkosten.

Aanvaardbaarheid, haalbaarheid en implementatie
Patiënten bezoeken het ziekenhuis dagelijks voor de radiotherapie, daarom is de belasting van wekelijkse ten opzichte van driewekelijkse toediening wat minder groot. .

In Nederland is de hoofd-halsoncologie gecentreerd in 8 werkgroepen, waardoor een hoge mate van expertise is gewaarborgd. Voor sommige patiënten betekent dit langere reistijden wat een belasting kan zijn. Er zijn geen aanwijzingen dat dit de therapie trouw ten nadele beïnvloedt. In het algemeen is in de centra sprake van voldoende capaciteit, hoewel er binnen financiële kaders spanningen op kunnen treden. Gezien de zeer goede onderlinge samenwerking binnen een groot team, waarvan de samenstelling en benodigde expertise is vastgesteld in de SONCOS-normen, is de kwaliteit gewaarborgd. De centra worden regelmatig gevisiteerd. Alle patiënten worden besproken binnen het multidisciplinaire overleg (MDO), waarbij ook de behandelaar aanwezig is. Hierna vindt overleg plaats met de patiënt, waarbij op basis van de adviezen uit het MDO met aandacht voor de eigen voorkeur van de patiënt een beleid wordt vastgesteld.

De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Concomitante chemotherapie met cisplatin (100 mg/m^2 dag 1,22 en 43) in combinatie met conventioneel gefractioneerde radiotherapie (voorbeeld 70 Gy in zeven weken) wordt beschouwd als de standaard in de definitieve behandeling van het plaveiselcelcarcinoom van het hoofd-halsgebied. Op basis van de beschikbare literatuur is het onzeker of het wekelijkse schema tenminste net zo effectief is als het driewekelijkse schema met minder bijwerkingen.

Retrospectieve studies geven aanwijzingen dat de wekelijkse toediening gepaard zou kunnen gaan met minder (met name nefro-)toxiciteit. Een studie met dezelfde behandeling, maar voor een andere indicatie (nasofarynxcarcinoom) suggereerde dat wekelijkse toediening in een dosis van 40 mg/m^2 niet inferieur is aan driewekelijkse toediening. De weging van argumenten voor en tegen de ene dan wel de andere behandeling dient besproken te worden met patiënten.

Onderbouwing

Achtergrond

Bij de definitieve behandeling van lokaal gevorderde hoofdhals-tumoren leidt chemoradiatie met cisplatin tot betere uitkomsten dan radiotherapie alleen. Van oudsher wordt een driewekelijks schema gebruikt met een dosering van 100 mg/m^2 cisplatin op dag 1, 22 en 43 van de radiotherapie. Echter, dit gaat gepaard met aanzienlijke toxiciteit (in het bijzonder renale toxiciteit). In Nederland krijgt tegenwoordig ongeveer de helft van de patiënten cisplatin toegediend in een wekelijks schema, waarbij vaak een dosis van 40 mg/m^2 wordt gegeven. Er zijn ook studies gedaan met een lagere wekelijkse dosis van bijvoorbeeld 30 of 35 mg/m^2. De vraag is echter of een wekelijks doseringsschema even effectief is als het driewekelijkse schema en minder toxiciteit geeft.

Conclusies

Overall survival (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on overall survival when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Noronha, 2018; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Recurrence (complete tumour response) (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on recurrence (complete tumour response) when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Sources: (Mashhour, 2020; Sahoo, 2017; Rawat, 2016; Nanda, 2019; Nair, 2017; Tsan, 2012)

Recurrence (locoregional control) (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on recurrence (locoregional control) when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Sources: (Mashhour, 2020; Kiyota, 2022; Noronha, 2018; Nanda, 2019; Nair, 2017; Tsan, 2012)

Disease-free survival (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on disease-free survival when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Sources: (Noronha, 2018; Kiyota, 2022; Nanda, 2019; Nair, 2017)

Adverse events (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on adverse events when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Sources: (Mashhour, 2020; Sahoo, 2017; Noronha, 2018; Rawat, 2016; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012)

Quality of life (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on quality of life when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Sources: (Tsan, 2012)

Samenvatting literatuur

Samenvatting literatuur

Description of studies

Eight randomized controlled trials were included. Different doses of cisplatin (30, 35, or 40 mg/m^2) were used in the weekly treatment arms. Studies are grouped according to the dose provided. This clinical question is focused on patients treated with definitive chemoradiation. Four studies (also) included patients who received cisplatin in adjuvant setting (Mashhour, 2020; Noronha, 2018; Kiyota, 2022; Tsan, 2012). Most studies included patients with a carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, however the study of Nanda (2019) only included patients with an oropharyngeal carcinoma and Tsan (2012) only included patients with an oral cavity carcinoma. One study was performed in Egypt, the other seven studies were conducted in Asia.

30 mg/m^2

Mashhour (2020) conducted a randomized controlled trial in Egypt. Patients with a locally advanced head and neck squamous cell carcinoma, aged between 18 to 70 years, with an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2 were eligible. Patients were treated with adjuvant (52%) or definitive (48%) intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=30) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=30). Both groups received cisplatin concurrently with intensity modulated radiation therapy. Radiotherapy was given in a total dose of 70Gy in 33 fractions, delivered five days a week. Treatment compliance in terms of completing all planned cycles was higher in the weekly treatment group, where 70% of patients received at least six cycles of weekly chemotherapy with minor dose reductions because of toxicity. In the group receiving cisplatin every three weeks, 60% of patients completed three cycles of treatment and 40% received only two cycles. However, the median cumulative cisplatin dose was lower in the weekly treatment group (170 mg/m^2 versus 200 mg/m^2). In the weekly treatment group, 46% of patients received at least 200 mg/m^2, while in the three-weekly treatment group 75% received at least 200 mg/^{2}. Outcome measures included tumour response, locoregional control, and treatment toxicities. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

Sahoo (2017) conducted a randomized controlled trial at a regional cancer centre in India. Patients with advanced stage squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx, aged between 18 and 70 years, with an ECOG performance status $\leq$ 2 were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=15) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=15). External beam radiotherapy was delivered to a dose of 66 Gy in a conventional fractionation schedule. Treatment compliance in terms of completing all planned cycles was 67% in the weekly treatment arm (six cycles) and 47% in the three-weekly treatment arm (three cycles). Completion of 66 Gy radiotherapy was 87% in the weekly treatment group and 80% in the three-weekly treatment group. Outcome measures included tumour response, locoregional control, and acute and late toxicity. Toxicities were assessed using the Radiation Therapy Oncology Group Acute Radiation Morbidity Criteria.

Noronha (2018) conducted a randomized controlled trial at an academic oncology hospital in India. Patients with locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx or metastatic cervical lymphadenopathy of unknown primary, aged between 18 and 70 years, with an ECOG

performance status ≤ 2 were eligible. Patients were treated with adjuvant (93%) or definitive (7%) intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=150) or at a planned dose of 100 mg/m2 every three weeks (on days 1, 22, and 43) (n=150). External beam radiotherapy in a conventional fractionation schedule was delivered to a dose of 70 Gy in 35 fractions for patients receiving definitive treatment, and a dose of 60 Gy for patients receiving adjuvant treatment. Treatment compliance in terms of completing the planned chemoradiation was 89% in the weekly treatment arm and 94% in the three-weekly treatment arm. The chemotherapy dose was reduced in 9% of patients in the weekly treatment arm and 8% of patients in the three-weekly treatment arm, while dosing was delayed for 25% in the weekly arm and 28% in the three-weekly arm. The median cumulative cisplatin dose was 210 mg/m^2 in the weekly arm and 300 mg/m^2 in the three-weekly arm. Outcome measures included overall survival, tumour response, locoregional control, progression-free survival and acute and chronic toxicity. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (version 4.03).

35 mg/m^2
Rawat (2016) conducted a randomized controlled trial at a single centre in India. Patients with locally advanced (stage III – IV B) squamous cell carcinoma of the head and neck, aged between 18 and 65 years were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 35 mg/m2 weekly (n=30) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=30). Radiotherapy was given in a total dose of 70 Gy in 35 fractions. Treatment compliance in terms of completing all planned chemotherapy cycles was 90% in the weekly arm and 79% in the three-weekly arm. Mean cisplatin dose received was lower in the weekly arm as compared with the three-weekly arm (292 mg/m^2 versus 438 mg/m^2).
The mean dose of radiotherapy received was comparable between the arms (69.86 Gy versus 69.22 Gy). Radiotherapy had to be interrupted for 17% of patients in the weekly arm and 34% of patients in the three-weekly arm. Outcome measures included tumour response and toxicity. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Toxicity was assessed using the CTCAE version 4.03.
40 mg/m^2

Kiyota (2022) conducted a randomized controlled non-inferiority trial in 28 centres in Japan. Patients with postoperative high-risk locally advanced squamous cell carcinoma of the head and neck, aged between 20 and 75 years, with an ECOG performance score of 0 or 1 were eligible. All patients received treatment with adjuvant intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=129) or at a planned dose of 100 mg/m^2 every three weeks (n=132). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. The median number of chemotherapy cycles received was 6 (IQR 5 to 7) in the weekly arm and 3 (IQR 3 to 3) in the three-weekly arm. The median cumulative cisplatin dose was lower in the weekly treatment group (239 mg/m^2 [IQR 199 to 277] versus 280 mg/m^2 [IQR 250 to 299]). The median total radiotherapy dose was 66 Gy in both groups (IQR 66 to 66). Outcome measures included overall survival, relapse-free survival, local relapse-free survival, and adverse events. Toxicity was assessed using the CTACE version 4.0.

Nanda (2019) conducted a randomized controlled trial at a single centre in India. Patients with locally advanced oropharyngeal carcinoma, aged between 20 and 70 years, with a Karnofsky performance score > 70

were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=39) or at a planned dose of 100 mg/m^2 every three weeks (n=31). Radiotherapy was given in a total dose of 70 Gy in 35 fractions. The median number of chemotherapy cycles received was five in the weekly arm and two in the three-weekly arm. The median cumulative cisplatin dose was lower in the weekly treatment group (272 mg/m^2 versus 303 mg/m^2). Fewer patients in the weekly treatment group as compared with the three-weekly group received at least 200 mg/m^2 cisplatin (89% versus 97%). In the weekly arm, 54% of patients discontinued chemotherapy beyond four cycles, mostly because of toxicity. All patients received the planned radiation dose of 70 Gy. Outcome measures included overall survival, tumour response, locoregional control, disease-free survival, and toxicities. Tumour response was evaluated according to the WHO criteria. Toxicity was assessed using the Radiation Therapy Oncology Group criteria for radiotherapy-induced acute toxicities, and Common Toxicity Criteria for chemotherapy-induced toxicity.

Nair (2017) conducted a randomized controlled trial at a regional cancer centre in India. Patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx or larynx, aged between 18 and 70 years, with an ECOG performance status 0 or 1 were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=25) or at a planned dose of 100 mg/m^2 every three weeks (n=31). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. Treatment compliance in terms of completing all planned chemotherapy cycles was 63% in the weekly treatment group (six cycles) and 35% in the three-weekly treatment group (three cycles). The mean cumulative cisplatin dose was slightly lower in the weekly treatment group (339 mg/m^2 versus 357 mg/m^2). All patients completed radiation apart from one patient who died during treatment. Outcome measures included overall survival, locoregional control, tumour response, disease-free survival, and toxicities. Tumour response was evaluated using RECIST criteria. Toxicity was assessed using the Radiation Therapy Oncology Group criteria for radiotherapy-induced toxicities, and Common Terminology Criteria version 4 for chemotherapy-induced toxicity.

Tsan (2012) conducted a randomized controlled trial at a single centre in Taiwan. Patients with high-risk oral cavity squamous cell carcinoma, aged between 18-70 years, with an ECOG performance status 0 to 2 were eligible. All patients received treatment with adjuvant intent. The trial aimed to recruit 371 patients but the trial was stopped after recruiting only 55 patients (of which 50 were randomized) over 30 months. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=24) or at a planned dose of 100 mg/m^2 every three weeks (n=26). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. The mean cumulative doses of cisplatin and radiotherapy were comparable between the groups. However, fewer patients in the weekly treatment group received at least 200 mg/m^2 cisplatin (63% versus 89%). Outcome measures included (preliminary) overall survival, (preliminary) locoregional recurrence-free survival, quality of life (Chinese version of the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) questionnaire) and adverse events. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results

No meta-analysis was performed because of clinical and methodological heterogeneity, but the results for overall survival and locoregional recurrence are shown in Figures 13.9.1 and 13.9.2 to provide more insight in the effects found.

30 mg/m²
Overall survival
Noronha (2018) observed 60 deaths in the weekly treatment arm (40%) and 53 deaths in the three-weekly treatment arm (35%). Median overall survival was 39.5 months in the weekly treatment arm, while median overall survival was not reached in the three-weekly treatment arm (HR 1.14 (95%CI 0.79 to 1.65; p=0.48).

Recurrence (tumour response)
Mashhour reported tumour response, a complete response was seen in 77% of patients receiving weekly cisplatin and 76% of patients receiving three-weekly cisplatin. A partial response was seen in 13.2% of patients receiving weekly cisplatin and 12.6% of patients receiving three-weekly cisplatin. Two months after treatment, stable disease was observed in 4.6% of patients in the weekly treatment group and 4.1% of patients in the three-weekly treatment group.

Sahoo (2017) reported that after a median follow-up of seven months, complete response was achieved by 73% of patients in the weekly arm and 86% of patients in the three-weekly arm (not statistically significant).

Recurrence (locoregional control)
Mashhour (2020) reported that after a median follow-up of 24 months, locoregional control rates were 57.6% in the weekly treatment group and 72.8% in the three-weekly treatment group (HR 1.78; p=0.015).

Noronha (2018) reported that the 2-year locoregional control rate was 58.5% in the study arm receiving weekly cisplatin and 73.1% in the group receiving three-weekly cisplatin (HR 1.76 (95%CI 1.11 to 2.79; p=0.014).

Disease-free survival
In the trial by Noronha (2018), the estimated median progression-free survival was 17.7 months (95%CI 0.42 to 35.05) in the weekly treatment arm and 28.6 months (95%CI 15.9 to 41.3) in the three-weekly treatment arm (HR 1.24 (95%CI 0.89 to 1.73); p=0.21).

Quality of life
Quality of life was not reported in any of the RCTs using a dose of 30 mg/m².

Adverse events
Mashhour (2020) reported non-haematological and haematological adverse events. For non-haematological adverse events, acute toxicities grade ≥ 3 were observed less frequently in the weekly treatment group (56.6%) compared with the three-weekly treatment group (76.6%) (p=0.007). No statistically significant differences were found for individual grade ≥ 3 toxicities, including mucositis (53% in the weekly cisplatin

group versus 47% in the three-weekly cisplatin group), dysphagia (47% versus 67%) , nausea/vomiting (13% versus 20%), xerostomia (17% versus 20%), dermatitis (13% versus 10%), and laryngeal oedema (17% versus 17%).

For haematological adverse events, grade $\geq$ 3 leukopenia (20% versus 37%; p<0.05) and neutropenia (10% versus 20%; p<0.05) occurred less frequently in the weekly cisplatin group compared with the three-weekly cisplatin group. No differences were found between the frequency of grade $\geq$ 3 anemia (17% versus 30%) and thrombocytopenia (3% versus 10%) in the weekly and three-weekly treatment groups.

Sahoo (2017) reported that grade 3 mucositis and vomiting were less frequent in the weekly cisplatin arm compared with the three-weekly cisplatin arm (53% versus 40%; p=0.729) and (20% versus 7%; p=0.360). In contrast, grade 3 dermatitis was more frequent in the weekly arm compared with the three-weekly arm (27% versus 7%; p=0.360). The frequencies of grade 3 dysphagia, anemia, and leukopenia were (almost) similar between the arms (0% versus 7%, 7% versus 7%, 13% versus 7%). The frequency of late toxicities (xerostomia and skin fibrosis) was comparable between the study arms.

Noronha (2018) reported acute (within 90 days from the start of treatment) and chronic (more than 90 days from the start of treatment) toxicities. For acute toxicities, any acute toxicity grade $\geq$ 3 was observed in 72% of patients receiving weekly cisplatin and 85% of patients receiving three-weekly cisplatin (p=0.006). Toxicities that occurred less frequently in the weekly treatment group included vomiting (1% versus 7%; p=0.019), infection (21% versus 34%; p=0.015), deafness (5% versus 13%; p=0.013), hyponatremia (23% versus 52%; p<0.001), leukopenia (3% versus16%; p<0.001), neutropenia (1% versus 13%; p<0.001), febrile neutropenia (1% versus 6%; p=0.019), and lymphocytopenia (72% versus 89%; p=0.001). No differences between the weekly and three-weekly treatment group were observed in the frequency of mucositis, dysphagia, odynophagia, xerostomia, dysgeusia, dermatitis, diarrhoea, fatigue, weight loss, hoarseness, hypertension, hypokalemia, transaminase elevation, anemia and thrombocytopenia. There were no patients experiencing $\geq$ 3 neuropathy or renal dysfunction.

For chronic toxicities, any chronic toxicity grade $\geq$ 3 was observed in 10% of patients receiving weekly cisplatin and 14% of patients receiving three-weekly cisplatin (p=0.55). The only toxicity that occurred less frequency in the weekly treatment group was deafness (4% versus 16%; p=0.004). No differences between the weekly and three-weekly treatment group were observed in the frequency of mucositis, dysphagia, odynophagia, infection, xerostomia, subcutaneous, trismus, and hypertriglyceridemia. There were no patients experiencing $\geq$ 3 dysgeusia, skin toxicity, hypothyroidism, or thromboembolic events.

_35 mg/m^2_
Overall survival
Rawat (2016) did not report on overall survival.

Recurrence (tumour response)
Rawat (2016) reported that three months after treatment completion, complete response was 67% in the group receiving weekly cisplatin and 62% in the group receiving three-weekly cisplatin. Partial responses were received in 33% of patients receiving weekly treatment and 38% of patients receiving three-weekly treatment. No statistically significant differences were found between the arms (p=0.20).

Recurrence (locoregional control)
Rawat (2016) did not report on locoregional control.

Disease-free survival
Rawat (2016) did not report on disease-free survival.

Quality of life
Rawat (2016) did not report on quality of life.

Adverse events
For non-haematological toxicities, Rawat (2016) reported that the frequency of grade 3 mucositis (70% versus 76%; p=0.20) was similar between the groups, while the frequency of grade 3 vomiting was lower in the group receiving weekly treatment (20% versus 35%; p=0.03). For haematological toxicities, no differences were found for grade 3 anemia (33% versus 31%; p=0.22) and thrombocytopenia (7% versus 10%; p=0.32), while grade 3 neutropenia was less frequent in the group receiving weekly treatment (27% versus 55%; p=0.02). Rawat (2016) also reported on a number of other toxicities. For acute renal toxicity, only mild toxicity was observed, while for significant weight loss, hyponatremia and hypomagnesemia it was not clear whether the frequencies involved grade 3 toxicity.

40 mg/m^2
Overall survival

Kiyota (2022) reported estimated 2-year and 3-year survival rates of 77.7% and 71.6% in the weekly treatment arm and 74.5% and 59.1% in the three-weekly treatment arm. The hazard ratio was 0.69 (99.1%CI 0.37 to 1.27; one-sided p-value for non-inferiority=0.0027). Since the upper limit of the confidence interval was below the prespecified threshold of 1.32, the authors concluded that weekly treatment is non-inferior with regard to survival.

Nanda (2020) reported that median overall survival was 35.4 months in the weekly treatment group and 32.9 months in the three-weekly treatment group (p=0.303). The two-year and five-year survival rates were 55% and 42% in the weekly treatment group and 58% and 32% in the three-weekly treatment group (not statistically significant, no p-value provided).

Nair (2017) reported two-year survival rates of 61% in the weekly treatment arm and 71% in the three-weekly treatment arm (p=0.610).

Tsan (2012) reported preliminary overall survival after a median follow-up of 12 months. In each group, six patients had died. One-year overall survival rates were 72% in the weekly treatment group and 79% in the three-weekly treatment group (p=0.978).

Recurrence (tumour response)
Nanda (2020) reported that complete response was seen in 81% of patients receiving weekly treatment and

75% of patients receiving three-weekly treatment. Partial responses were seen in 14% of patients receiving weekly treatment and 13% of patients receiving three-weekly treatment. Eight weeks after completion of treatment, stable disease was 5% in the weekly treatment group and 4% in the three-weekly treatment group.

Nair (2017) reported that complete responses were observed in 75% of patients in the weekly treatment arm and 90% of patients in the three-weekly arm. Partial response rates were 12% and 6%. Twelve weeks after completion of treatment, two patients in each arm (8% versus 6%) had residual disease.

Recurrence (locoregional control)
Kiyota (2022) reported recurrences in 29% of patients receiving weekly treatment and 39% of patients received three-weekly treatment.

Nanda (2020) observed locoregional relapses in 14% of patients receiving weekly treatment and 6% of patients receiving three-weekly treatment. Three months after completion of treatment, stable or progressive disease was observed in 29% of patients in the weekly treatment group and 42% of patients in the three-weekly treatment group.

Nair (2017) reported that two patients in the weekly treatment group developed local recurrence and one patient developed lung metastasis (13%), while four patients in the three-weekly treatment group developed local recurrence (13%). In the weekly treatment group, three patients developed a second primary tumour (in the esophagus or tongue) (13%), while in the three-weekly group two patients developed a second primary tumour in the esophagus (6%). Two-year locoregional control rates were 63% in the weekly cisplatin arm and 61% in the three-weekly cisplatin arm.

Tsan (2012) reported preliminary locoregional recurrence-free survival after a median follow-up of 12 months. In the weekly arm, 9 patients had experienced a recurrence while in the three-weekly arm, 8 patients had experienced a recurrence. One-year locoregional recurrence-free survival rates were 60% in the weekly treatment group and 71% in the three-weekly treatment group (p=0.806).

Disease-free survival
Kiyota (2022) reported hazard ratios of 0.71 (95%CI 0.48 to 1.06) for relapse-free survival and 0.73 (95%CI 0.47 to 1.13) for local relapse-free survival.

Nanda (2020) reported that median progression-free survival was 26.4 months in the weekly treatment group and 27.4 months in the three-weekly treatment group (p=0.953).

Nair (2017) reported that two-year disease-free survival rates were 53% in the weekly arm and 65% in the three-weekly arm (p=0.674).

Adverse events

Kiyota (2022) reported no difference in the proportion of patients experiencing at least one grade $\geq$ 3 event (81.1% versus 79.8%; p=0.87), while fewer patients in the weekly group experienced a grade 4 event (8.2%

versus 18.6%; p=0.017). For haematological adverse events, there were no differences in the frequency of grade ≥ 3 events (64.8% versus 61.2%; p=0.06) and grade 4 events (7.4% versus 14.7%; p=0.07). Specific grade ≥ 3 adverse events that were reported to be lower in the weekly treatment group included neutropenia (35% versus 49%) and infection (7% versus 12%).

Nanda (2020) observed no statistically significant differences in the frequency of grade ≥ 3 radiation toxicities and haematological toxicities between the two groups. Radiation toxicities included mucositis (32% versus 29%; p=1.00), dysphagia (46% versus 32%; p=0.27), dermatitis (14% versus 19%; p=0.73), larynx (11% versus 10%; p=1.00), and nausea/vomiting (7% versus 0%; p=0.22). Haematological toxicities included anemia (0% versus 3%; p=1.00), leukopenia (25% versus 13%; p=0.32), neutropenia (18% versus 7%; p=0.24), and thrombocytopenia (0% versus 3%; p=1.00).

Nair (2017) reported a lower frequency of grade ≥ 3 dysphagia (63% versus 26%; p<0.05) in the weekly cisplatin group. No other statistically significant differences were reported in the frequency of grade ≥ 3 non-haematological and haematological toxicities between the two groups. Non-haematological toxicities included mucositis (54% versus 52%; p>0.05), and dermatitis (13% versus3%; p>0.05). Haematological toxicities included anemia (4% versus 0%; p>0.05), neutropenia (8% versus 3%; p>0.05), and thrombocytopenia (no grade 3 adverse events observed). No grade ≥ 3 renal toxicity was observed.

Tsan (2012) reported that overall, more grade ≥ 3 toxicities were observed in the weekly group (92%) compared with the three-weekly group (81%) (p=0.02). For non-haematological toxicities, mucositis was reported more frequency in the weekly treatment group (75%) compared with the three-weekly group (39%) (p=0.012). The frequencies of the following toxicities were comparable between the groups: pharyngitis (54% versus 54%; p=1.0), stomatitis (54% versus 54%; p=1.0), laryngeal edema (4% versus 12%; p=0.611), dermatitis (8% versus 8%; p=1.0), and nausea/vomiting (21% versus 12%; p=0.456).

For haematological toxicities, no differences were observed between the groups for anemia (4% versus 4%; p=1.0), leukopenia (13% versus 0%; p=0.103), neutropenia (4% versus 0%; p=0.480), and thrombocytopenia (0% versus 0%).

Quality of life
Tsan (2012) reported results for five subscales of the FACT H&N questionnaire and the Trial Outcome Index (TOI) which is a combined scale for the subscales physical well-being, functional well-being and the head and neck subscale. Higher scores represent better QoL. It was not reported how many patients completed the questionnaires at each time point.

For the physical well-being scale (range 0 to 28), lower scores were seen in the weekly treatment group at week 2 (difference of 4.5 points between the groups), week 4 (5.7 points), at the end of radiotherapy (7.8 points) and follow-up after three months (4.3 points). For the social well-being scale (range 0 to 28), higher scores were seen in the weekly treatment group at week 4 (difference of 2.9 points between the groups), at the end of radiotherapy (5.7 points), and follow-up after three months (5 points). Emotional well-being scores were comparable between the groups at all time points. Functional well-being scores (range 0 to 28) were only different between the groups at three months follow-up, with lower scores seen in the weekly treatment

group (3.3 points difference between the groups). Scores on the head and neck subscale were comparable between the groups at all time points. TOI scores (range 0 to 96) were only different between the groups at three months follow-up, with lower scores seen in the weekly treatment group (difference 9.7 points).

Level of evidence of the literature
All studies were RCTs, therefore the level of evidence started at 'high' for all outcome measures.

The level of evidence was downgraded for all outcomes because most (7/8) studies were conducted in Asia (India, Taiwan, and Japan), while it has been described that head and neck cancers in Asian countries have a different etiology and molecular biology. Publication bias was not assessed because of the low number of studies found.

The level of evidence regarding the outcome measure overall survival was downgraded by four levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one trial was stopped prematurely); applicability (-1; bias due to indirectness because three studies were conducted among patients who were treated (mainly) with adjuvant intent and all studies were conducted in Asia); and number of included patients (-2; imprecision because of wide confidence intervals including the possibility of a negative effect, no effect, and a positive effect). Publication bias was not assessed.

The level of evidence regarding the outcome measure recurrence (tumour response) was downgraded by five levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); conflicting results (-1; inconsistency because two studies showed worse tumour response rates, two studies showed no effect and one study showed better tumour response rates); applicability (-1; bias due to indirectness because in one study 52% of patients were treated with adjuvant intent and most studies were conducted in Asia); and number of included patients (-2; imprecision because of the low sample sizes). Publication bias was not assessed.

The level of evidence regarding the outcome measure recurrence (locoregional control) was downgraded by five levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one trial was stopped prematurely); conflicting results (-1; inconsistency because three studies showed worse locoregional control, two studies showed no effect, and one study showed better locoregional control); applicability (-1; bias due to indirectness because four studies were conducted among patients who were treated (mainly) with adjuvant intent and most studies were conducted in Asia); and number of included patients (-2; imprecision because of wide confidence intervals including the possibility of a negative effect, no effect, and a positive effect). Publication bias was not assessed.

The level of evidence regarding the outcome measure disease-free survival was downgraded by three levels because of conflicting results (-1; inconsistency because one study showed worse DFS and two showed no difference); applicability (-1; bias due to indirectness because two studies were conducted among patients who were treated (mainly) with adjuvant intent and all studies were conducted in Asia); and number of included patients (-1; imprecision because of confidence intervals including the possibility of a negative effect and no effect (and a positive effect)). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one study was stopped prematurely); applicability (-1; bias due to indirectness because four studies were conducted among patients who were treated (mainly) with adjuvant intent and most studies were conducted in Asia); and number of included patients (-1; imprecision because of the low number of patients included in individual studies). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>quality of life</u> was downgraded by five levels because of study limitations (-2 risk of bias because of incomplete reporting of study methodology, lack of blinding, and study stopped prematurely); applicability (-1; bias due to indirectness because the study was conducted among patients who were treated with adjuvant intent and was conducted in Asia); number of included patients (-2; imprecision because of the low sample size in a single study). Publication bias was not assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the benefits and risks of weekly versus three-weekly cisplatin concurrent with definitive radiotherapy for patients with locally advanced head and neck squamous cell carcinoma?

P: Patients with locally advanced head and neck squamous cell carcinoma.
I: Weekly cisplatin concurrent with definitive radiotherapy.
C: Three-weekly cisplatin concurrent with definitive radiotherapy.
O: Overall survival, recurrence (tumour response and locoregional control), disease-free survival, quality of life, adverse events.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and recurrence as critical outcome measures for decision making; and disease-free survival, adverse events, and quality of life as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically important difference as follows:

- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Tumour response: absolute difference > 5% in complete response rates
- Local recurrence: 0.8 or 1.25 as borders for risk or odds ratios.
- Locoregional control: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Progression-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Adverse events: statistically significant difference in grade ≥ 3 adverse event rate.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 12 November 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 534 hits (60 SRs and 474 RCTs). Studies were selected based on the following criteria: (1) patients with a locally advanced squamous cell carcinoma in the head and neck region; (2) comparison between radiotherapy combined with weekly or three-weekly cisplatin; (3) systematic review or randomized controlled trial; (4) full-text English language publication. Studies including only patients with nasopharyngeal cancer were excluded.

24 studies were initially selected based on title and abstract screening. After reading the full text, 17 studies were excluded (see the table with reasons for exclusion under the tab Methods) and seven studies were included. The working group identified an additional RCT that was published after the search date. This RCT was also included in the summary of literature. We cannot exclude the possibility that other relevant reviews or RCTs were published after the search date.

Results

Eight original studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Alternatief voor cisplatin bij chemoradiatie

Uitgangsvraag

Wat is de rol van systemische therapie in aanvulling op definitieve radiotherapie bij patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied bij wie cisplatin is gecontra-indiceerd?

Aanbeveling

Bespreek met patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied bij wie cisplatin gecontra-indiceerd is de alternatieven voor cisplatin in aanvulling op definitieve radiotherapie, te weten cetuximab, carboplatin of carboplatin in combinatie met 5-FU, en wijs daarbij op de voor- en nadelen van deze alternatieven.

Op basis van prospectief onderzoek kan geen aanbeveling worden gedaan voor patiënten boven de 70 jaar.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Onze systematische zoekactie in diverse databases resulteerde in 13 relevante studies die resultaten rapporteren van 9 verschillende RCT's.

1. RT + cetuximab
In totaal hadden 3 van de 13 studies betrekking op de vergelijking tussen radiotherapie en cetuximab enerzijds en alleen radiotherapie anderzijds (Bonner, 2006; Curran, 2007 en Bonner, 2010). Deze studies rapporteerden resultaten van een en dezelfde trial. Er werden klinisch relevante verschillen gevonden voor totale overleving (cruciale uitkomstmaat) op 3 en 5 jaar en progressievrije overleving (belangrijke uitkomstmaat) op 2 en 3 jaar, ten faveure van bioradiotherapie. Er werd geen klinisch relevant verschil gevonden voor kwaliteit van leven (belangrijke uitkomstmaat). Van de acute bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) traden een acné-achtige huiduitslag, infusiereacties en anemie statistisch significant vaker op bij patiënten die behandeld werden met radiotherapie en cetuximab, vergeleken met patiënten die alleen radiotherapie kregen. Het percentage patiënten met een late bijwerking van graad 3 of hoger verschilde niet tussen de behandelgroepen. Een subgroepanalyse liet zien dat voor totale overleving patiënten met een orofarynxtumor mogelijk het meeste baat hebben bij de toevoeging van cetuximab aan radiotherapie. Het percentage patiënten met een lokaal recidief (cruciale uitkomstmaat) werd niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege de actieve rol van de studiesponsor bij het verzamelen en analyseren van de data), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was) en imprecisie (vanwege het geringe aantal deelnemers en het feit dat de 3 studies betrekking hadden op slechts 1 RCT). Inconsistentie en publicatiebias konden niet beoordeeld worden.

2. RT + carboplatin
Eveneens 3 van de 13 studies hadden betrekking op de vergelijking tussen radiotherapie en carboplatin enerzijds en alleen radiotherapie anderzijds (Fountzilas, 2004; Jeremic, 1997 en Ruo Redda, 2010). Deze

studies rapporteerden resultaten van 3 verschillende trials. Er werd een klinisch relevant verschil gevonden voor totale overleving (cruciale uitkomstmaat) op 1, 2, 3 en 4 jaar, ten faveure van chemoradiotherapie, maar niet voor totale overleving op 10 jaar. De studies toonden conflicterende resultaten voor totale overleving op 5 jaar: 2 studies (n = 79 en n = 106) lieten wel een klinisch relevant verschil zien, terwijl in 1 studie (n = 164) geen klinisch relevant verschil werd gevonden. Voor ziektevrije overleving (belangrijke uitkomstmaat) werd een klinisch relevant verschil gevonden op 3 jaar, ten faveure van chemoradiotherapie, maar niet op 5 en 10 jaar. Voor geen van de acute en late bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) werd een eenduidig klinisch relevant verschil gevonden. Het percentage patiënten met een lokaal recidief (cruciale uitkomstmaat), progressievrije overleving en kwaliteit van leven werden niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege onvolledige rapportage, verschillen in patiëntkenmerken tussen de behandelarmen in een studie en het vroegtijdig stoppen van een trial), inconsistentie (vanwege conflicterende resultaten), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was) en imprecisie (vanwege het geringe aantal deelnemers per studie). Inconsistentie kon niet beoordeeld worden voor ziektevrije overleving, en publicatiebias kon in het geheel niet beoordeeld worden.

3. RT + carboplatin and 5-FU
De resterende 7 studies hadden betrekking op de vergelijking tussen radiotherapie gecombineerd met carboplatin en 5-FU enerzijds en alleen radiotherapie anderzijds (Bourhis, 2012; Calais, 1997; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001 en Semrau, 2006). Deze studies rapporteerden resultaten van 5 verschillende trials. Er werd een klinisch relevant verschil gevonden voor totale overleving (cruciale uitkomstmaat) op 1, 2, 3 en 5 jaar, ten faveure van chemoradiotherapie. Voor het percentage patiënten met een lokaal recidief (cruciale uitkomstaat) en ziektevrije overleving (belangrijke uitkomstmaat) op 2, 3 en 5 jaar werd eveneens een klinisch relevant verschil gevonden, ten faveure van chemoradiotherapie, maar niet voor progressievrije overleving (belangrijke uitkomstmaat). Voor geen van de acute bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) werd een eenduidig klinisch relevant verschil gevonden. Voor de late bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) gold dat late slikproblemen en permanente sondevoeding vaker werden gezien bij patiënten die behandeld waren met hypergefractioneerde, geaccelereerde radiotherapie in combinatie met 5-FU, vergeleken met alleen radiotherapie; dit verschil was klinisch relevant. Kwaliteit van leven werd niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was laag tot zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege onvolledige rapportage, verschillen in patiëntkenmerken tussen de behandelarmen in een studie en het vroegtijdig stoppen van 2 trials), inconsistentie (vanwege conflicterende resultaten), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was en het gebruik van verschillende radiotherapeutische regimes) en imprecisie (vanwege het geringe aantal deelnemers per studie). Inconsistentie kon niet beoordeeld worden voor het percentage patiënten met een lokaal recidief en ziekte- en progressievrije overleving, en publicatiebias kon in het geheel niet beoordeeld worden.

Op basis van de resultaten van de studie van Mehanna (2019) lijkt het toevoegen van cetuximab aan definitieve radiotherapie niet van waarde te zijn voor patiënten met een gevorderd HPV-positief orofarynxcarcinoom. De studie van Mehanna (2019) is in deze module overigens geëxcludeerd omdat er

alleen patiënten met een gevorderd HPV-positief orofarynxcarcinoom zijn geïncludeerd. Voor deze patiëntenpopulatie is een aparte module beschikbaar (RLDB: link invoegen naar module 'Behandeling HPV-positieve orofarynx tumoren'). Daarnaast wordt in de studie van Mehanna (2019) en ook de studie van Gillison (2019) geen vergelijking gemaakt tussen radiotherapie en cetuximab met alleen radiotherapie, maar wordt radiotherapie en cetuximab vergeleken met radiotherapie met cisplatin. Op basis van de huidige literatuur kan geen uitspraak gedaan worden over de rol van carboplatin met of zonder 5-FU als alternatief voor cetuximab.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Curran (2007) vonden geen statistisch significant, maar wel een beperkt klinisch relevant verschil in kwaliteit van leven tussen patiënten die behandeld werden met radiotherapie en cetuximab en patiënten die alleen radiotherapie kregen, ten nadele van de patiënten die met cetuximab werden behandeld. Er is geen onderzoek gedaan naar kwaliteit van leven bij de andere schema's. Vanwege de beperkte literatuur op dit gebied kan de werkgroep geen uitspraak doen over de waarden en voorkeuren van patiënten.

Het doel van het toevoegen van cetuximab of carboplatin met of zonder 5-FU aan definitieve radiotherapie is het verbeteren van de locoregionale controle, zonder duidelijke toename van de toxiciteit. Dit laatste is met name ook voor de patiënt van belang, omdat het hier een kwetsbare groep patiënten betreft. Uit een meta-analyse van 107 RCT's naar de effecten van chemotherapie bij hoofd-halstumoren (Lacas, 2021) bleek dat met het toenemen van de leeftijd het effect van het toevoegen van cisplatin aan radiotherapie afneemt, waarbij er in de leeftijdsgroep boven de 70 jaar geen positief effect is op overleving en dit positieve effect in de leeftijdsgroep 60-69 al weer aanzienlijk lager is dan in de groep jonger dan 50 jaar. Het is goed om te realiseren dat in de studies ook selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
Extra kosten voor de patiënt zijn het regelmatig bezoeken van het ziekenhuis voor de behandelingen. Ook de bijwerkingen kunnen leiden tot extra kosten, zoals de kosten van medicatie vanwege huiduitslag, de kosten die gepaard gaan met een eventuele infectie of bloeding en de kosten van mogelijke extra ziekenhuisopnames. De meeste van deze kosten zijn verzekerd, maar dit betekent kosten voor de samenleving en voor familie en relaties. Gezien de onzekerheid die bestaat over de gunstige effecten is het moeilijk aan te geven of dit de (extra) middelen waard is? Een kosten-batenanalyse ontbreekt in de literatuur.

Gezien de langere overleving bij HPV-positieve patiënten met een orofarynxcarcinoom zou bij deze groep adjuvante therapie meer van waarde kunnen zijn. Anderzijds zal bij oudere patiënten (> 75 jaar) met een 'WHO performance status' > 2 gezien de bijwerkingen meer terughoudendheid moeten worden betracht.

De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van de-escalatiestrategieën. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht dat de aanbeveling geen relevante impact heeft op de zorgkosten.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
In Nederland is de hoofd-halsoncologie gecentreerd in 8 werkgroepen, waardoor een hoge mate van expertise is gewaarborgd. Voor sommige patiënten betekent dit langere reistijden wat een belasting kan zijn. Er zijn geen aanwijzingen dat dit de therapietrouw ten nadele beïnvloedt. In het algemeen is in de centra sprake van voldoende capaciteit, hoewel er binnen financiële kaders er spanningen op kunnen treden. Gezien de zeer goede onderlinge samenwerking binnen een groot team, waarvan de samenstelling en benodigde expertise is vastgesteld in de SONCOS-normen, is de kwaliteit gewaarborgd. De centra worden regelmatig gevisiteerd. Alle patiënten worden besproken binnen het multidisciplinaire overleg (MDO), waarbij ook de behandelaar aanwezig is. Hierna vindt uitgebreid verleg plaats met de patiënt, waarbij op basis van de adviezen uit het MDO en de eigen voorkeur van de patiënt een beleid wordt uitgestippeld.

De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Op basis van de huidige literatuur kan geen zekere uitspraak gedaan worden over een goed alternatief voor cisplatin bij patiënten bij wie cisplatin gecontra-indiceerd is. In de voorgaande richtlijn werd cetuximab genoemd als alternatief voor patiënten bij wie cisplatin gecontra-indiceerd is. Op basis van recente studies (Gillison (2019) en Mehanna (2019)) is twijfel gerezen over de toegevoegde waarde van cetuximab aan radiotherapie in de behandeling van patiënten met een gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied, hoewel in deze studies met name patiënten met een HPV-positief orofarynxcarcinoom waren geïncludeerd. Voor patiënten met een gevorderd HPV-positief orofarynxcarcinoom lijkt het toevoegen van cetuximab aan definitieve radiotherapie niet van waarde te zijn, zie ook de module 'Behandeling HPV-positieve orofarynx tumoren').
Deze onzekerheid wat betreft het beste alternatief voor cisplatin dient besproken te worden met deze patiënten. Er kan gekozen worden voor een van de in deze richtlijnmodule besproken alternatieven, maar dan moet het risico op toegenomen toxiciteit worden afgewogen tegen de onzekere voordelen.

Onderbouwing

Achtergrond

Patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied kunnen in opzet curatief behandeld worden met radiotherapie. Het toevoegen van cisplatin aan deze behandeling leidt bij patiënten van 70 jaar of jonger en een 'WHO performance status' van 0 of 1 tot een betere lokale controle en overleving, maar gaat ook gepaard met meer toxiciteit. Met het toenemen van de leeftijd neemt het effect van het toevoegen van chemotherapie aan radiotherapie af, waarbij er bij patiënten boven de 70 jaar geen positief effect op overleving is gerapporteerd. Bij een deel van de patiënten is behandeling met cisplatin gecontra-indiceerd vanwege bijvoorbeeld cardiovasculaire problemen of nierinsufficiëntie. Mogelijke behandelalternatieven voor deze patiënten zijn cetuximab, carboplatin of carboplatin én 5-fluoro-uracil (5-FU). Het toxiciteitsprofiel van deze geneesmiddelen is weliswaar anders dan dat van cisplatin, maar het is onduidelijk hoe effectief deze middelen zijn en welk middel de voorkeur heeft.

Conclusies

1. RT + cetuximab
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bonner, 2006; Bonner, 2010)*

Local recurrence

- GRADE	No evidence was found regarding the effect of radiotherapy combined with cetuximab on local recurrence in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Disease-free survival

- GRADE	No evidence was found regarding the effect of radiotherapy combined with cetuximab on disease-free survival in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Progression-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on progression-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bonner, 2006)*

Quality of life

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on quality of life when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Curran, 2007)*

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bonner, 2006)*

2. RT + carboplatin
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Fountzilas, 2004; Jeremic, 1997; Ruo Redda, 2010)*

Local recurrence

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on local recurrence in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on disease-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Ruo Redda, 2010)*

Progression-free survival

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on progression-free survival in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Quality of life

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on quality of life in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Fountzilas, 2004; Jeremic, 1997; Ruo Redda, 2010)*

3. RT + carboplatin and 5-FU
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012; Calais, 1999; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001; Semrau, 2006)*

Local recurrence

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on local recurrence when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: Calais, 1999; Denis, 2004)*

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on disease-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Calais, 1999; Denis, 2004; Olmi, 2003)*

Progression-free survival

Low GRADE	The evidence suggests that radiotherapy combined with carboplatin and 5-FU results in little to no difference in progression-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012)*

Quality of life

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin and 5-FU on quality of life in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012; Calais, 1999; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001; Semrau, 2006)*

Samenvatting literatuur

Description of studies

1. Radiotherapy + cetuximab

Bonner (2006), Curran (2007) and Bonner (2010) report on a multicenter, randomized controlled phase 3 trial that was conducted at 73 academic centers in the US and 14 other countries, including the Netherlands. Patients with previously untreated, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 60, and normal bone marrow, hepatic and renal function. Patients were randomly assigned (1:1) to receive high-dose radiotherapy and cetuximab (n = 211), or high-dose radiotherapy alone (n = 213). Investigators were required to select 1 of 3 radiotherapy-fractionation regimens (concomitant boost, once daily, or twice daily) before randomization. The final review of radiotherapy revealed that the mean and median doses for the 3 regimens did not differ between the 2 treatment groups. Administration of cetuximab was initiated 1 week before radiotherapy at a loading dose of 400 mg/m^2 over a period of 120 minutes, followed by weekly 60-minute infusions of 250 mg/m^2 for the duration of radiotherapy. The primary outcome measure was the duration of locoregional control, which was not of our interest. Secondary outcome measures of our interest included overall survival, progression-free survival, quality of life and safety. Quality of life was assessed using two validated, multidimensional instruments, namely the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC QLQ Head and Neck Cancer-Specific Module (H&N35). Acute toxic effects were assessed through the eighth week after treatment using the criteria of the Radiation Therapy Oncology Group (RTOG). Late toxic effects of radiotherapy were assessed thereafter using the criteria of the RTOG/EORTC.

2. Radiotherapy + carboplatin

Fountzilas (2004) conducted a multicenter, randomized controlled phase 3 trial at 5 hospitals in Greece, Romania and Germany. Patients aged ≥ 18 years with biopsy-proven, previously untreated, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow, hepatic and renal function, and adequate cardiovascular, pulmonary, nutritional and mental status. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy and carboplatin (n = 38), standard fractionated radiotherapy and cisplatin (n = 45) or standard fractionated radiotherapy alone (n = 41). The treatment group of patients who received standard fractionated radiotherapy and cisplatin is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 70 Gy at 1.8 Gy per fraction per day, 5 days per week. Carboplatin was administered at an AUC of 7 on days 2, 22 and 42. The primary outcome measure was the overall survival at 3 years. The authors also report the overall survival at 5 years, the median overall survival, and safety. Acute toxic effects were assessed using the criteria of the RTOG.

Jeremic (1997) conducted a single-center, randomized controlled trial in Yugoslavia. Patients aged > 18 years with histologically confirmed, previously untreated, unresectable, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the head and neck were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 50, adequate bone marrow, hepatic and renal function, and no serious concomitant disease. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy and carboplatin (n = 53), standard fractionated radiotherapy and cisplatin (n = 53) or standard fractionated

radiotherapy alone (n = 53). The treatment group of patients who received standard fractionated radiotherapy and cisplatin is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 70 Gy at 1.8 Gy per fraction per day, 5 days per week. Carboplatin was intravenously administered 45-60 minutes before the irradiation as a bolus at a daily dose of 25 mg/m^2. The primary outcome measure was the overall survival at 3 years. The authors also report the overall survival at 1 year, 2 years, 4 years and 5 years, and safety. Acute and late toxic effects of radiotherapy were assessed using the criteria of the RTOG and RTOG/EORTC, respectively. Toxic effects of chemotherapy were assessed using the criteria of the ECOG. The trial was prematurely stopped before the planned accrual of 85 patients per treatment group was reached, because the chief investigator had to leave the department.

Ruo Redda (2010) conducted a multicenter, randomized controlled phase 3 trial at 6 centers in Italy. Patients aged 18-70 with biopsy-proven, previously untreated, stage III or IV, non-metastatic, measurable, unresectable squamous cell carcinoma of the head and neck were eligible. Criteria for eligibility also included an ECOG performance status ≤ 2, adequate bone marrow, hepatic and renal function, adequate nutritional and liquid intake, and no serious concomitant disease. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy and carboplatin (n = 82), or standard fractionated radiotherapy alone (n = 82). Radiotherapy was given in a total dose of 70 Gy at 2 Gy per fraction per day, 5 days per week. Carboplatin was intravenously administered 45-60 minutes before the irradiation as a bolus at a daily dose of 45 mg/m^2 on day 1-5 of the 1st, 3rd, 5th and 7th week of the combined treatment (total dose: 900 mg/m^2). The primary outcome measure was the locoregional recurrence-free survival, which was not of our interest. Secondary outcome measures of our interest included overall survival, disease-free survival, and safety. Acute toxic effects were assessed using the criteria of the World Health Organization (WHO). Late toxic effects were assessed using the criteria of the RTOG/EORTC.

3. Radiotherapy + carboplatin and 5-FU
Bourhis (2012) conducted a multicenter, randomized controlled phase 3 trial at 22 centers in France and Belgium (GORTEC 99-02 trial). Patients with histologically confirmed, previously untreated, stage III or IV, non-metastatic, squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included an ECOG performance status ≤ 2, adequate bone marrow, hepatic and renal function, no history of other cancer in the previous 5 years, and no clinically significant cardiac disease. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 279), accelerated radiotherapy plus carboplatin and 5-FU (n = 280) or very accelerated radiotherapy alone (n = 281). Patients allocated to receive standard fractionated radiotherapy received a total dose of 70 Gy in 7 weeks: 5 fractions of 2 Gy per week, with spinal cord exclusion at 40 Gy. These patients also received 3 cycles of 4 days of carboplatin 70 mg/m² per day plus 5-FU 600 mg/m² per day on day 1 to 4, day 22-25, and day 43-46. Patients allocated to receive accelerated radiotherapy received a total dose of 70 Gy in 6 weeks: 5 fractions of 2 Gy per week until 40 Gy, with spinal cord exclusion at 40 Gy, followed by 1.5 Gy per fraction twice daily for 5 days per week for the remaining 30 Gy. These patients also received 2 cycles of 5 days of carboplatin 70 mg/m² per day and 5-FU 600 mg/m² per day on day 1 to 5 and day 29 to 33. Patients allocated to receive very accelerated radiotherapy alone received a total dose of 64.8 Gy in 3.5 weeks: 1.8 Gy per fraction twice daily for 5 days per week, with spinal cord exclusion at 34.2 Gy. The primary outcome measure was progression-free survival, defined as the time between randomisation and the first of the

following events: locoregional progression or relapse, distant relapse, or death from any cause (or the last follow-up contact for patients who did not have any of these events). Secondary outcome measures of our interest included overall survival and safety. Acute toxic effects of radiotherapy and chemotherapy occurring during treatment or within 3 months after the end of treatment were assessed using the criteria of the RTOG and WHO. Late toxic effects occurring more than 3 months after the end of treatment were assessed using the criteria of the RTOG/EORTC.

Calais (1999) and Denis (2004) report on a multicenter, randomized controlled phase 3 trial that was conducted at university hospitals, cancer centers, and private hospitals in France (GORTEC 94-01 trial). Patients aged < 75 years with previously untreated, non-metastatic, stage III or IV, squamous cell carcinoma of the oropharynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 60, and normal bone marrow and renal function. Patients were excluded if they had lost more than 20% of their body weight, if they had previously undergone treatment for this disease or any other cancer, except basal cell carcinoma of the skin, or if they had synchronous primary lesions. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 113), or standard fractionated radiotherapy alone (n = 109). Radiotherapy was given in a total dose of 70 Gy in 35 fractions at 2 Gy per fraction per day, 5 days per week. In the intervention group, patients received 3 cycles of chemotherapy during the 1st, 4th, and 7th week of radiotherapy. Chemotherapy consisted of carboplatin (i.v. bolus of 70 mg/m^2 per day for 4 days) and 5-FU (600 mg/m^2 per day infused continuously in 24 hours for 4 days). The primary outcome measure was the overall survival at 3 years. The authors also report the median overall survival, overall survival at 5 years, disease-free survival at 3 and 5 years, local recurrence rate, and safety. Acute toxic effects were assessed using the criteria of the EORTC. Late toxic effects were assessed using the criteria of the National Cancer Institute (NCI) and RTOG/EORTC.

Chitapanarux (2013) conducted a single-center, randomized controlled phase 3 trial at a university hospital in Thailand. Patients aged 18-75 years with previously untreated, stage III or IV, non-metastatic, squamous cell carcinoma of the head and neck, excluding the nasopharynx, nasal cavity, paranasal sinuses and salivary glands, were eligible. Criteria for eligibility also included an ECOG performance status ≤ 1 and adequate organ system function. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 48) or hybrid accelerated radiotherapy alone (n = 37). Patients allocated to receive standard fractionated radiotherapy received a total dose of 66 Gy in 6.5 weeks: 5 fractions of 2 Gy per week, with spinal cord exclusion at 40 Gy. These patients also received 3 cycles of 4 days of carboplatin 70 mg/m² per day plus 5-FU 600 mg/m² per day on day 1 to 4, day 22-25, and day 43-46. Patients allocated to receive hybrid accelerated radiotherapy received a total dose of 70 Gy in 6 weeks: 5 fractions of 2 Gy per week until 40 Gy, with spinal cord exclusion at 40 Gy, followed by a first daily fraction of 1.8 Gy and a second daily fraction of 1.2 Gy for 5 days per week for the remaining 30 Gy. The primary outcome measure was the locoregional control rate, which was not of our interest. Secondary end points of our interest included overall survival and safety. Acute toxic effects of radiotherapy and chemotherapy were assessed using the criteria of the NCI. Late toxic effects were assessed using the criteria of the RTOG/EORTC. Due to slow inclusion, the trial was prematurely stopped before reaching the planned accrual of 106 patients.

Olmi (2003) conducted a multicenter, randomized controlled phase 3 trial at 18 centers in Italy (ORO 93-01 trial). Patients aged < 70 years with histologically confirmed, previously untreated, stage III or IV, non-

metastatic, epidermoid tumors of the oropharynx were eligible. Criteria for eligibility also included a Karnofsky performance score $\geq$ 70 or an ECOG performance status $\leq$ 1, adequate bone marrow, hepatic, renal, cardiac and pulmonary function, no previous tumors, except adequately treated in situ carcinoma of the cervix and basal cell carcinoma of the skin, and no psychosis or active infectious disease. Patients were excluded if they had a T1N1 or T2N1 lesion. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 64), split-course hyperfractionated accelerated radiotherapy alone (n = 65) or standard fractionated radiotherapy alone (n = 63). The treatment group of patients who received split-course hyperfractionated accelerated radiotherapy alone is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 66-70 Gy in 33-35 fractions in 6.5-7 weeks at 2 Gy per fraction per day, 5 days per week. In the intervention group, patients received 3 cycles of chemotherapy. The first 2 cycles were given in the 1st and 5th week of radiotherapy, whereas the last cycle was given in the 9th week, therefore, after the radiotherapy was finished. Chemotherapy consisted of carboplatin (bolus of 75 mg/m^2 per day infused in 30 minutes for 4 days) and 5-FU (1000 mg/m^2 infused continuously in 96 hours for 4 days). The authors report the overall and disease-free survival at 2 year, and safety. Acute toxic effects of radiotherapy occurring within 90 days from the start of treatment were assessed using the criteria of the RTOG. Acute toxic effects of chemotherapy were assessed using the criteria of the WHO. Late toxic effects of radiotherapy occurring after 90 days from the start of treatment were assessed using the criteria of the RTOG. Due to slow inclusion, the trial was prematurely stopped before reaching the planned accrual of 260 patients.

Staar (2001) and Semrau (2006) report on a multicenter, randomized controlled phase 3 trial that was conducted at 5 centers in Germany. Patients with histologically confirmed, previously untreated, unresectable, non-metastatic, stage III or IV, squamous cell carcinoma of the oro- or hypopharynx were eligible. Criteria for eligibility also included an ECOG performance status $\geq$ 60, adequate bone marrow and renal function, and no history of a prior malignancy. Patients were randomly assigned (1:1) to receive hyperfractionated accelerated radiotherapy plus carboplatin and 5-FU (n = 113), or hyperfractionated accelerated radiotherapy alone (n = 127). Radiotherapy was given in a total dose of 69.9 Gy in 38 days, using a concomitant boost regimen: 5 fractions of 1.8 Gy per week in week 1-3, followed by a first daily fraction of 1.8 Gy and a second daily fraction of 1.5 Gy for 5 days per week in week 4-5.5. In the intervention group, patients received 2 cycles of chemotherapy during the 1st and 5th week of radiotherapy. Chemotherapy consisted of carboplatin (i.v. bolus of 70 mg/m^2 per day for 4 days) and 5-FU (600 mg/m^2 per day infused continuously for 4 days). The primary outcome measure was survival with local control at 1 year, which was not of our interest. The authors also report overall survival at 1, 2 and 5 years, and safety. Acute toxic effects were assessed using the criteria of the RTOG. Late toxic effects were assessed using the criteria of the RTOG/EORTC.

Results
1. Radiotherapy + cetuximab
Overall survival
Bonner (2006) found that the median duration of overall survival was 49.0 months (95%CI: 32.8-69.5) among patients treated with high-dose radiotherapy and cetuximab and 29.3 months (95%CI: 20.6-41.4) among those treated with high-dose radiotherapy alone (HR 0.74; 95%CI: 0.57 to 0.97). The overall survival rate at 3 years was 55% in the intervention group versus 45% in the control group. In the same study population, Bonner (2010) found that the overall survival rate at 5 years was 46% among patients treated with high-dose

radiotherapy and cetuximab and 36% among those treated with high-dose radiotherapy alone (HR 0.73; 95%CI: 0.56 to 0.95). Based on a subgroup analysis, cetuximab seemed to provide the most benefit for patients with an oropharyngeal tumor (n = 253). Although effect estimates and corresponding 95%-confidence intervals are not reported, the forest plot shows a statistically significant HR < 0.60, favoring the addition of cetuximab. For patients with a laryngeal or hypopharyngeal tumor, the HR did not reach the threshold for a minimal clinically important difference (i.e. HR < 0.7).

Progression-free survival
Bonner (2006) found that the median duration of progression-free survival was 17.1 months among patients treated with high-dose radiotherapy and cetuximab and 12.4 months among those treated with high-dose radiotherapy alone (HR 0.70; 95%CI: 0.54 to 0.90). The progression-free survival rates 2 and 3 years were 46% and 42%, respectively, in the intervention group versus 37% and 31%, respectively, in the control group (p-value for log-rank test = 0.04 for the comparison at 3 years, whereas no p-value is reported for the comparisor at 2 years).

Quality of life
Curran (2007) found a small, albeit statistically non-significant, absolute difference of less than 10 points in the mean global health status score (EORTC QLQ-C30) at baseline between patients treated with high-dose radiotherapy and cetuximab and patients treated with high-dose radiotherapy alone. At all visits up to and including month 12, the mean score of patients treated with high-dose radiotherapy and cetuximab was a few points higher compared with patients treated with radiotherapy alone (with higher scores representing better quality of life). The line graph shows that patients in both treatment groups had a global health score of approximately 60 at baseline. Scores decreased during treatment and had returned to baseline levels by month 12. For functional and symptom scale scores, also no statistically significant differences were found between treatment groups.

Adverse events
Bonner (2006) reported adverse events that occurred in at least 10% of patients in either treatment, regardless of the cause. The prevalence of grade ≥ 3 acute toxic effects did not differ significantly between patients treated with high-dose radiotherapy and cetuximab and patients treated with high-dose radiotherapy alone, except for acneiform rash (17% versus 1%; p < 0.001) and infusion reactions (3% versus 0%; p = 0.01) and anemia (1% versus 6%; p = 0.006). Severe late toxic effects related to radiotherapy were reported in about 20% of the patients in each treatment group. The sites most commonly affected were the esophagus, salivary glands, larynx, mucous membranes, subcutaneous tissues, bone, and skin. For late toxic effects, no absolute numbers or percentages per treatment group are reported.

Local recurrence and disease-free survival
No data were reported for these outcome measures.

2. RT + carboplatin
Overall survival
Fountzilas (2004) found that the median duration of overall survival was 24.5 months (range: 0.2 to 79.9) among patients treated with standard fractionated radiotherapy and carboplatin and 12.2 months (range: 1.2

to 81.7) among those treated standard fractionated radiotherapy alone (p-value for log-rank test = 0.0064). Patients treated with standard fractionated radiotherapy and carboplatin had a non-statistically significant higher overall survival than patients treated with standard fractionated radiotherapy alone (adjusted HR 0.57; 95%CI: 0.31 to 1.04). The overall survival rates at 3 and 5 years were 42% and 38%, respectively, in the intervention group versus 17.5% and 9%, respectively, in the control group.

Jeremic (1997) found that the median duration of overall survival was 30 months among patients treated with standard fractionated radiotherapy and carboplatin and 16 months (range: 1.2 to 81.7) among those treated standard fractionated radiotherapy alone (p = 0.0064). Patients in the intervention group had higher overall survival rates at 1, 2, 3, 4 and 5 years, compared with the control group: 76%, 55%, 47%, 31% and 29% versus 57%, 35%, 27%, 17% and 15%, respectively (p-value for log-rank test = 0.019).

Ruo Redda (2010) found that patients treated with standard fractionated radiotherapy and carboplatin had higher overall survival rates at 3, 5 and 10 years, compared with those treated with standard fractionated radiotherapy alone: 28.9%, 9% and 5.5% versus 11.1%, 6.9% and 6.9%, respectively (p-value for log-rank test = 0.02).

Disease-free survival
Ruo Redda (2010) found that patients treated with standard fractionated radiotherapy and carboplatin had higher disease-free survival rates at 3, 5 and 10 years, compared with those treated with standard fractionated radiotherapy alone: 28.9%, 9% and 5.5% versus 11.1%, 6.9% and 6.9%, respectively (p-value for log-rank test = 0.09).

Adverse events
Fountzilas (2004) found that the prevalence of grade ≥ 3 acute toxic effects did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone, except for thrombocytopenia (26% versus 0%; p = 0.0004), and nausea and vomiting (16% versus 0%; p = 0.0107).

Jeremic (1997) found that the prevalence of grade ≥ 3 acute non-hematological toxic effects, including mucositis, xerostomia, esophagitis, nausea and vomiting, and nephrotoxicity, did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone. Grade ≥ 3 acute hematological toxic effects, including leukopenia (11% versus 0%; p = 0.012) and thrombocytopenia (8% versus 0%; p = 0.041), occurred more frequently in patients treated with standard fractionated radiotherapy and carboplatin. The prevalence of grade ≥ 3 late toxic effects, including bone toxicity, skin toxicity and subcutaneous tissue fibrosis, was similar between treatment groups.

Ruo Redda (2010) found that the prevalence of grade ≥ 3 acute toxic effects, including mucositis, anemia, leukopenia and thrombocytopenia, did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone. The prevalence of grade ≥ 3 late toxic effects was similar between treatment groups, except for severe neck

fibrosis, which occurred more frequently in patients treated with radiotherapy and carboplatin (7 versus 3 cases). One patient treated with radiotherapy and carboplatin developed mandibular bone necrosis. No radiation myelitis or toxic-related death was observed in either treatment group.

Local recurrence, progression-free survival and quality of life
No data were reported for these outcome measures.

3. RT + carboplatin and 5-FU
Overall survival
Bourhis (2012) found that the overall survival rate at 3 years was 42.6% (95%CI: 37.0 to 48.5) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU (arm A), 39.4% (95%CI: 33.8 to 45.3) among patients treated with accelerated radiotherapy combined with carboplatin and 5-FU (arm B), and 36.5% (95%CI: 31.1 to 42.3) among patients treated with very accelerated radiotherapy alone (arm C). Resultantly, the HRs and corresponding 95%-confidence intervals are as follows: arm A versus C: HR 0.81; 95%CI: 0.67 to 0.99; arm B versus C: HR 0.87; 95%CI: 0.72 to 1.06; and arm B versus A: HR 1.05; 95%CI: 0.86 to 1.29).

Calais (1999) found that after a median follow-up of 35 months (range: 12 to 56) the median duration of overall survival was 29.2 months among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 15.4 months among those treated with standard fractionated radiotherapy alone. The overall survival rate at 3 years was 51% (95%CI: 39 to 68) in the intervention group versus 31% in the control group (p-value for log-rank test = 0.02). In the same study population, Denis (2004) found that after a median follow-up of 5.5 years (range: 4 to 7.2) the median duration of overall survival was 20 months among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 13 months among those treated with standard fractionated radiotherapy alone. The overall survival rate at 5 years was 22.4% in the intervention group versus 15.8% in the control group (p-value for log-rank test = 0.05).

Chitapanarux (2013) found that the overall survival rate at 5 years was 76.1% (95%CI: 57.8 to 7.3) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 63.5% (95%CI: 42.0 to 78.8) among patients treated with hybrid accelerated radiotherapy alone (p-value for log-rank test = 0.05).

Olmi (2003) found that the overall survival rate at 2 years was 51% among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 40% among patients treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.129).

Staar (2001) found that the overall survival rates at 1 and 2 years for all tumor types was 66% (95%CI: 57 to 75) and 48% (95%CI: 38 to 58), respectively, among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, and 60% (95%CI: 51 to 69) and 39% (95%CI: 30 to 48), respectively, among patients treated with hyperfractionated accelerated radiotherapy alone (p-value for log-rank test = 0.1139). For patients with an oropharyngeal tumor (n = 178), the overall survival rate at 1 year was 68% in the intervention group versus 57% in the control group (95%CI: ± 10; p-value for log-rank test = 0.0091). For patients with a hypopharyngeal tumor (n = 62), the overall survival curves did not differ significantly between treatment groups. In the same study population, Semrau (2006) found that the overall

survival rate at 5 years for all tumor types was 25.6% (95%CI: 15.8 to 35.4) among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, and 15.8% (95%CI: 9.1 to 22.4) among patients treated with hyperfractionated accelerated radiotherapy alone (p-value for log-rank test = 0.016). For patients with an oropharyngeal tumor (n = 178), the overall survival rate at 5 years was 26.1% (95%CI: 14.3 to 37.8) in the intervention group versus 13.0% (95%CI: 5.3 to 20.6) in the control group (p-value for log-rank test = 0.008). For patients with a hypopharyngeal tumor (n = 62), the overall survival curves did not differ significantly between treatment groups (22.2% versus 22.2%; p-value for log-rank test = 0.722).

Local recurrence
Calais (1999) found that after a median follow-up of 35 months (range: 12 to 56) the local recurrence rate was lower among patients treated with standard fractionated combined with carboplatin and 5-FU, compared with patients treated with standard fractionated radiotherapy alone (33% versus 51%; risk ratio (RR) 0.64; 95%CI: 0.47 to 0.89). In the same study population, Denis (2004) found that after a median follow-up of 5.5 years (range: 4 to 7.2) the local recurrence rate remained lower among patients treated with standard fractionated combined with carboplatin and 5-FU (41% versus 58%; RR 0.71; 95%CI: 0.54 to 0.93).

Disease-free survival
Calais (1999) found that the disease-free survival rate at 3 years was 42% (95%CI: 30 to 57) among patients treated with standard fractionated combined with carboplatin and 5-FU, and 20% among those treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.04). In the same study population, Denis (2004) found that the disease-free survival rate at 5 years was 26.6% among patients treated with standard fractionated combined with carboplatin and 5-FU, and 14.6% among those treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.01).

Olmi (2003) found that the disease-free survival rate at 2 years was 42% among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 23% among patients treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.022).

Progression-free survival
Bourhis (2012) found that the progression-free survival rate at 3 years was 37.6% (95%CI: 32.1 to 43.4) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU (arm A), 34.1% (95%CI: 28.7 to 39.8) among patients treated with accelerated radiotherapy combined with carboplatin and 5-FU (arm B), and 32.2% (95%CI: 27.0 to 37.9) among patients treated with very accelerated radiotherapy alone (arm C) (arm A versus C: HR 0.82; 95%CI: 0.67 to 0.99; arm B versus C: HR 0.83; 95%CI: 0.69 to 1.01); arm B versus A: HR 1.02; 95%CI: 0.84 to 1.23).

Adverse events
Bourhis (2012) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis was lower among patients treated with standard fractionated or accelerated radiotherapy combined with carboplatin and 5-FU (arm A and arm B, respectively), compared with patients treated with very accelerated radiotherapy alone (arm C). According to criteria of the RTOG, grade ≥ 3 mucositis occurred in 69% of patients in treatment arm A, in 76% of patients in treatment arm B, and in 84% of patients in treatment arm C (p = 0.0001). According to the criteria of the WHO, grade ≥ 3 mucositis occurred in 78% of

patients in treatment arm A, in 84% of patients in treatment arm B, and in 89% of patients in treatment arm C (p = 0.0016). The prevalence of grade ≥ 3 skin toxicity and grade ≥ 3 hematological toxic effects, including anemia, leukopenia and thrombocytopenia, did not differ significantly between treatment groups. The rate of patients in need of a feeding tube differed significantly between treatment arm A and treatment arm C, both during treatment (60% versus 70%; p = 0.013) and during 5-year follow-up (36% versus 43% at 1 year, 16% versus 23% at 2 years, 11% versus 18% at 3 years, 8% versus 14% at 4 years, and 13% versus 25% at 5 years; p = 0.027), but not between other treatment groups. The prevalence of late toxic effects, including xerostomia, neck fibrosis, mucositis, laryngeal toxicity and bone toxicity, 1 to 5 years after randomization did not differ significantly between treatment groups, but the severity (i.e. grade) of these late toxic effects is not reported.

Calais (1999) found that skin toxicity was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis (71% versus 39%; p = 0.005) and grade ≥ 3 skin toxicity (67% versus 59%; p = 0.02) was higher among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with standard fractionated radiotherapy alone. The prevalence of grade ≥ 3 hematological toxic effects, including neutropenia (4% versus 0%; p = 0.04), thrombocytopenia (6% versus 1%; p = 0.04) and anemia (3% versus 0%; p = 0.05), was also higher in the intervention group, but for anemia the result was not statistically significant. The rate of patients in need of a feeding tube during treatment differed significantly between treatment groups (36% versus 15%; p = 0.02). In the same study population, Denis (2004) found that the prevalence of late toxic effects during 5-year follow-up, including xerostomia, mucositis, skin toxicity and subcutaneous tissue fibrosis, neurological toxicity, mandibular bone necrosis, and taste-, hearing- and teeth-related toxicity, did not differ significantly between treatment groups.

Chitapanarux (2013) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis was lower among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with hybrid accelerated radiotherapy alone (42% versus 68%; p = 0.01). The prevalence of grade ≥ 3 skin toxicity, grade ≥ 3 renal toxicity and grade ≥ 3 hematological toxic effects, including anemia, leukopenia and thrombocytopenia, did not differ significantly between treatment groups. The prevalence of grade ≥ 3 late toxic effects related to radiotherapy, including xerostomia, subcutaneous tissue fibrosis, mucositis and skin toxicity, did not differ significantly between treatment groups.

Olmi (2003) found that the prevalence of grade ≥ 3 acute toxic effects related to radiotherapy did not differ significantly between patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and patients treated with standard fractionated radiotherapy alone, except for mucositis (48% versus 15%; p = 0.0003) and skin toxicity (16% versus 4%; p = 0.0461). Grade ≥ 3 acute toxic effects related to chemotherapy included leukopenia (23% of patients), thrombocytopenia (5%), anemia (2%), anorexia (2%), and 1 fatal case of renal toxicity (1%). The prevalence of grade ≥ 3 late toxic effects related to radiotherapy during 2 year follow-up, including mucositis, skin toxicity, subcutaneous tissue fibrosis, xerostomia, spinal cord toxicity and laryngeal toxicity, did not differ significantly between treatment groups.

Staar (2001) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis during treatment was higher among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with hyperfractionated

accelerated radiotherapy alone (68% versus 52%; p = 0.01). The prevalence of grade ≥ 3 skin toxicity (30% versus 28%) and grade ≥ 3 hematological toxic effects, including leukopenia (18% versus 0%) and thrombocytopenia (5% versus 0%), was also higher in the intervention group, but p-values are not reported and could not be calculated based on the data provided. Grade ≥ 3 anemia occurred less frequently in patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU (1% versus 0%), but it is unclear whether this result was statistically significant. Late toxic effects were reported for the total study population (Staar, 2001) or for all grades together (Semrau, 2006), except for swallowing problems and continuous use of a feeding tube, which occurred more frequently in patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU (51% versus 25%; p = 0.02).

Quality of life
No data were reported for this outcome measure.

Level of evidence of the literature
The evidence was derived from 13 studies reporting on 9 different randomized trials. Therefore, the level of evidence for all reported outcome measures started at 'high quality'.

1. RT + cetuximab
The level of evidence regarding the outcome measure overall survival was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT and upper boundary of confidence interval exceeding the threshold of minimal clinically important difference). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure progression-free survival was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure quality of life was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). The level of evidence was not downgraded because of study limitations (i.e., active role of sponsor in collecting and analyzing the data), because no minimal clinically important difference in quality of life was observed between treatment groups. Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure adverse events was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measures <u>local recurrence</u> and <u>disease-free survival</u> could not be assessed, because the included studies did not report these outcome measures.

2. RT + carboplatin

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by 4 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Ruo Redda (2010), and premature termination of Jeremic (1997)); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by 4 levels because of risk of bias (-2; due to incomplete reporting and imbalanced study population); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients in a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by 5 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Ruo Redda (2010), and premature termination of Jeremic (1997)); inconsistency (-1; due to conflicting results); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Publication bias could not be assessed.

The level of evidence regarding the outcome measures <u>local recurrence</u>, <u>progression-free survival</u> and <u>quality of life</u> could not be assessed, because the included studies did not report these outcome measures.

3. RT + carboplatin and 5-FU

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by 4 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Chitapanarux (2013), and premature termination of Chitapanarux (2013) and Olmi (2003)); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to low number of included patients in most studies). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>local recurrence</u> was downgraded by 3 levels because of study limitations (-1; risk of bias due to incomplete reporting); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients in a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by 3 levels because of study limitations (-1; risk of bias due to incomplete reporting); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>progression-free survival</u> was downgraded by 2 levels because of indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by 5 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Chitapanarux (2013), and premature termination of Chitapanarux (2013) and Olmi (2003)); inconsistency (-1; due to conflicting results); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to low number of included patients in most studies). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>quality of life</u> could not be assessed, because the included studies did not report this outcome measure .

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and fluorouracil (5-FU), compared with definitive radiotherapy alone, in patients with a locally advanced squamous cell carcinoma in the head and neck region who are ineligible to receive cisplatin?

P: Patients with a locally advanced squamous cell carcinoma in the head and neck region who are ineligible to receive cisplatin.
I: Definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and 5-FU.
C: Definitive radiotherapy alone.
O: Overall survival, local recurrence, disease-free survival, progression-free survival, quality of life, adverse events.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and local recurrence as critical outcome measures for decision making; and disease-free survival, progression-free survival, quality of life, and adverse events as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but, instead, used the definitions used in the studies.

The working group defined a minimal clinically important difference as follows:

- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Local recurrence: 0.8 or 1.25 as borders for risk or odds ratios.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Progression-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.

- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Adverse events: statistically significant difference in grade ≥ 3 adverse event rate.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms for systematic reviews published until November 12, 2020. The detailed search strategy is depicted under the tab Methods. Studies were selected if they fulfilled the following criteria: (a) patients with a locally advanced squamous cell carcinoma in the head and neck region; (b) comparison between definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and 5-FU, and definitive radiotherapy alone. Studies were excluded if they only included patients with HPV-positive oropharyngeal cancer, because treatment options for this group of patients are described in a separate module. This search resulted in unique 296 hits. Based on title and abstract screening, 40 studies were initially selected. After reading the full text, all 40 studies were excluded. A table with reasons for exclusion is presented under the tab Methods. One of the excluded reviews (Iocca (2018)) compared several interventions based on a network meta-analysis of 57 RCTs, of which 7 RCTs were relevant for the current clinical question. Similarly, another 5 RCTs were identified via other excluded reviews.

To update the search performed by Iocca (2018) up to 1 September 2017, we searched for relevant RCTs published from 2017 until 18 October 2021. This search resulted in 452 hits. Based on title and abstract screening, 40 studies were initially selected. After reading the full text, all 40 studies were excluded (see table with reasons for exclusion).

Results

Via an excluded systematic review and network meta-analysis (Locca, 2018), 7 relevant studies (Bourhis, 2012; Bonner, 2010; Chitapanarux, 2013; Denis, 2004; Fountzilas, 2004; Ruo Redda, 2010 and Semrau, 2006) were included in the analysis of the literature. In addition, 6 relevant studies (Bonner, 2006; Curran, 2007; Calais, 1999; Jeremic, 1997; Olmi, 2003 and Staar, 2001) were identified via other excluded systematic reviews. Together, these 13 studies report the results of 9 different randomized trials. Studies that focused on the effects of definitive radiotherapy combined with either cetuximab (Bonner, 2006; Bonner, 2010 and Curran, 2007), carboplatin (Fountzilas, 2004; Jeremic, 1997 and Ruo Redda, 2010) or carboplatin and 5-FU (Bourhis, 2012; Calais, 1999; Chitapanarux, 2013; Denis, 2004; Olmi, 2003; Semrau, 2006 and Staar, 2001), compared with definitive radiotherapy alone, are analyzed separately. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Primaire Behandeling N3 hypofarynx, orofarynx- en larynxcarcinoom

Uitgangsvraag

Welke volgorde van behandelmodaliteiten heeft de voorkeur bij patiënten met een N3 hypofarynx, orofarynx- en larynxcarcinoom: Eerst een halsklierdissectie gevolgd door (chemo)radiotherapie, of (chemo)radiotherapie gevolgd door een halsklierdissectie wanneer nodig?

Aanbeveling

Op basis van de huidige literatuur, praktijkkennis en patiëntenvoorkeuren kan geen aanbeveling gedaan worden welke volgorde van behandeling, chemoradiatie gevolgd door een halsklierdissectie dan wel een halsklierdissectie gevolgd door chemoradiatie, de voorkeur verdient.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De systematic reviews die werden gevonden bij deze uitgangsvraag (Elicin, 2016 en Gupta, 2004) vergeleken steeds een halsklierdissectie met daarna chemoradiotherapie versus chemoradiotherapie alleen. Beide studies zijn gebaseerd op de oude TNM-7 classificatie. Bij de vergelijkingen die we hebben gevonden werd er geen halsklierdissectie meer gedaan na de chemoradiotherapie. Om deze reden is het niet mogelijk om op basis van de literatuur tot een eenduidige conclusie te komen welke volgorde van interventies beter is.

Echter, wanneer na chemoradiotherapie een afwachtend beleid wordt gevoerd lijkt dit geen negatieve invloed op de overleving te hebben in vergelijking met wanneer aansluitend een halsklierdissectie wordt verricht (zie module 13.4).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Er zijn geen studies verricht die het verschil voor patiënten tussen de verschillende volgorde van behandeling vergelijken. Echter het starten met de (chemo)radiatie kan als nadeel hebben dat een salvage halsklierdissectie een hoger risico geeft op complicaties. Het starten met een halsklierdissectie heeft als nadeel dat de behandeling van de primaire tumor vertraging op kan lopen.

Kosten (middelenbeslag)
Er zijn geen studies verricht die het verschil in kosten tussen de verschillende volgorden van behandeling vergelijken.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Omdat er geen studies zijn gevonden die het verschil in volgorde van behandelingen hebben vergeleken, en er ook geen duidelijke voorkeur lijkt te zijn vanuit de praktijk of de patiënten, kan er op dit moment geen aanbeveling worden gedaan voor één van de opties.

Onderbouwing

Achtergrond

Een inventarisatie in Nederland door de Richtlijnencommissie van de NWHTT leerde dat bij het larynxcarcinoom het beleid ten aanzien van de N3 hals zeer verschillend was tussen de verschillende centra. Wanneer de N3 lymfekliermetastase op voorhand resectabel is worden óf de primaire tumor en hals behandeld met (chemo)radiatie en afhankelijk van de responsevaluatie (maar met een hoge kans hierop) een salvage halsklierdissectie verricht, óf eerst een halsklierdissectie verricht en vervolgens de primaire tumor en de hals behandeld met (chemo)radiatie. Het is aannemelijk dat dit verschil ook aanwezig is bij andere primaire tumoren die vaak primair met (chemo)radiatie behandeld worden. Het starten met de (chemo)radiatie heeft als nadeel dat het residu van de N3 lymfekliermetastase irresectabel geworden kan zijn en een salvage halsklierdissectie een hoger risico heeft op complicaties. Het starten met een halsklierdissectie heeft als nadeel dat de behandeling van de primaire tumor vertraagd wordt door de halsklierdissectie.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: Which order of interventions is preferred for N3 hypopharynx, oropharynx and larynx carcinoma patients: Up-front neck dissection followed by (chemo)-radiotherapy, or (chemo)-radiotherapy followed by neck dissection if necessary?

P: = N3 hypopharynx, oropharynx and larynx carcinoma.
I: = Up-front neck dissection followed by (chemo)-radio therapy.
C: = (Chemo)-radio therapy followed by neck dissection if necessary.
O: = Overall survival (3 to 5 year follow up), disease free survival, disease specific survival, recurrence, morbidity, surgery complications, adverse events.

Relevant outcome measures
The guideline development group considered overall survival, disease free survival and recurrence as a critical outcome measure for decision making; the group considered morbidity, surgery complications, and adverse events as an important outcome measure for decision making.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) or >3% and HR< 0.7 in overall survival.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 17th of February 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: methodology (RCT's and SR's were included), suitability with the PICO. Two studies were initially selected based on title and abstract screening. After reading the full text, both studies were excluded (see the table with reasons for exclusion under the tab Methods).

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Halsklierdissectie N3 patiënten

Uitgangsvraag

Is, voor patiënten met een stadium N2/N3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben gehad, een geplande halsklierdissectie een betere optie dan een afwachtend beleid voeren, waarbij de halsklierdissectie alleen wordt uitgevoerd indien dit na responsevaluatie nodig blijkt?

Aanbeveling

Bespreek met patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom de twee mogelijke opties na behandeling met chemoradiatie: 1) hoe dan ook een nekdissectie plannen, of 2) de respons op chemoradiatie evalueren middels PET-CT en bij onvoldoende of onduidelijke respons pas een nekdissectie verrichten.

Benoem dat:

- een afwachtend beleid niet tot een slechtere overleving lijkt te leiden;
- een afwachtend beleid niet lijkt te leiden tot meer recidief;
- een afwachtend beleid resulteert in minder chirurgische complicaties.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Om de vraag te beantwoorden of het beter is een afwachtend beleid op basis van een responsevaluatie met PET-CT te voeren of een nekdissectie te plannen na een chemoradiotherapie bij patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom, is een onderzoek uitgevoerd dat de non-inferiority toetst van een afwachtend beleid. Uit dit onderzoek blijkt dat het afwachtende beleid inderdaad niet leidt tot een slechtere overleving. Daarbij is het aantal adverse events en complicaties lager in de groep waar een afwachtend beleid wordt gevoerd (met lage bewijskracht). De meerjarenoverleving, toxiciteit, schoudermorbiditeit en de ziektevrije overleving zijn niet meegenomen. Overigens is deze studie nog gebaseerd op de oude TNM-7 classificatie, wat de geldende classificatie was ten tijde van de inclusie van de patiënten in de studie, niet op TNM 8. Het is lastig om dit goed te vertalen naar de nieuwe classificatie; de werkgroep concludeert dan ook dat dit een kennislacune is.

Tevens bleek een afwachtend beleid meer kosten-effectief (per persoon £1,492 en 0.08 QALYs per persoon). In een uitgebreidere studie naar kosten-effectiviteit (Fu, 2021) werden drie verschillende manieren van surveillance vergeleken met geplande nekdissectie, waarbij een PET-CT surveillance met herhaalde PET-scan na 6 maanden na chemoradiatie bij onduidelijke respons het meest kosten-effectief bleek. Er zijn geen studies beschikbaar die de haalbaarheid en aanvaardbaarheid van surveillance onderzochten.

Een vereiste voor het uitvoeren van een nekdissectie bij onvoldoende respons is de mogelijkheid om een PET-CT te maken. Uit de studie van Mehanna et al. blijkt dat er een hoge concordantie was tussen de beoordeling van de PET-CT door de (willekeurige) lokale specialist en de beoordeling door de ervaren

specialisten van de studie (92% voor respons van de primaire tumor en 97% voor de lymfkliermetastasen). Hieruit kan geconcludeerd worden dat het haalbaar is om de surveillance methode te implementeren in de kliniek.

Gezien beide methoden (een afwachtend beleid of een geplande nekdissectie na een chemoradiotherapie), gebaseerd op de huidige literatuur met enige onzekerheid, leiden tot een gelijke overleving, zouden de beide opties aan patiënten kunnen worden voorgelegd. Samen beslissen zal de acceptatie van patiënten maximaliseren. Daarbij is het wel goed om op te merken dat in Nederland het afwachtende beleid inmiddels vrijwel overal standaardpraktijk is. Er zijn geen duidelijke argumenten vóór een geplande nekdissectie, wat het voor de patiënt minder voor de hand liggend maakt om wel voor een geplande nekdissectie te kiezen.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er lijkt geen nadeel te zijn van het voeren van een afwachtend beleid kijkend naar de verschillende uitkomstmaten op basis van de huidige literatuur. Het aantal bijwerkingen en complicaties lijkt lager in de groep waar een afwachtend beleid wordt gevoerd.

De gradering van bewijs is laag en gebaseerd op één enkele studie, waardoor er geen sterke aanbeveling kan worden gedaan voor één van beide opties. Om deze reden is de keuze om wel of niet meteen een nekdissectie te plannen na chemotherapie een overweging die goed met de patiënt besproken kan worden. De aanbeveling is geformuleerd met de onderwerpen die in elk geval aan de patiënt voorgelegd kunnen worden.

Onderbouwing

Achtergrond

In de Nederlandse zorg bestaat er praktijkvariatie op het gebied van een halsklierdissectie bij patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben ondergaan. In sommige centra wordt als standaardprocedure een halsklierdissectie uitgevoerd, terwijl in andere centra een afwachtend beleid wordt gevoerd waarbij halsklierdissectie alleen wordt uitgevoerd indien dit uit responsevaluatie op basis van beeldvorming nodig blijkt te zijn. Er is geen consensus over wat de beste strategie is.

Conclusies

Overall survival (2 years) (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in little to no difference in overall survival compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Adverse events (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in less adverse events compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Recurrence (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in little to no difference in recurrence compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

- GRADE	No evidence was found regarding the effect of surveillance, where neck dissection is only performed based on PET-CT, on toxicity, shoulder mobility and disease-free survival, when compared with planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

Zoekvraag
Welke behandelstrategie is beter voor patiënten met een stadium N2/N3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben gehad: een geplande halsklierdissectie uitvoeren, of een afwachtend beleid voeren, waarbij de halsklierdissectie alleen wordt uitgevoerd indien dit na responsevaluatie nodig blijkt?

P: Patients who have undergone chemoradiation for a stage N2/3 hypopharynx, oropharynx or larynx carcinoma.
I: Chemoradiation + standard neck dissection.
C: Chemoradiation + neck dissection when residual is suspected after response evaluation.
O: Survival (3 to 5 years), disease free survival, recurrence, adverse events, toxicity, shoulder mobility, surgery complications.

Relevant outcome measures
The guideline development group considered survival (3 to 5 years), disease free survival, recurrence, and adverse events as critical outcome measures for decision making; and toxicity, shoulder mobility, and surgery complications as important outcome measures for decision making.

The guideline development group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as boundaries for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-free survival.
- 5% difference or more (absolute) or > 3% difference and HR< 0.7 in overall survival.

For the outcome measures adverse events, toxicity, shoulder mobility, and surgery complications no minimally clinically relevant difference was formulated.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 17th of February 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: suitability with the PICO, methodology (RCTs and SRs were included), studies in the English or Dutch language, and available full texts. Four studies were initially selected based on title and abstract screening. After reading the full text, three studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
One study was included in the analysis of the literature (Mehanna, 2016). Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature
Description of studies
Mehanna (2016) conducted a randomized controlled trial (non-inferiority study) in the UK assessing the non-inferiority of PET-CT guided surveillance that could lead to neck dissection, with planned neck dissection, in patients who received chemoradiotherapy as a primary treatment. In total, 564 patients participated in the trial, of which the randomization was 1:1. All patients were evaluated 12 weeks after chemoradiotherapy, either by CT or MRI (in the planned surgery group) or PET-CT (in the surveillance group). Incomplete or equivocal response in the lymph nodes led to a neck dissection within 4 weeks in the surveillance group. There were less neck dissections in the PET-CT–guided surveillance group compared to the planned surgery group (54 versus 221). The follow-up lasted for at least 24 months after randomization, and the outcomes that were measured were survival rate (primary endpoint), disease-specific mortality, mortality from other causes, adverse events, locoregional control, surgery complications, quality of life and cost-effectiveness.

Results
Survival (2 years)
3-to-5 year survival was not measured in the included study. However, the guideline development group decided to use the 2-year survival that was reported in the study. The 2-year overall survival rate was 84.9% (95% CI, 80.7 to 89.1) in the surveillance group and 81.5% (95% CI, 76.9 to 86.3) in the planned surgery group. The hazard ratio for death with surveillance as compared with planned surgery was 0.92 (95% CI, 0.65 to 1.32); this outcome slightly favored the surveillance group and met the prespecified definition of noninferiority (an overall survival rate that was no more than 10 percentage points below the estimated 75% 2-year overall

survival rate in patients in the planned surgery group).

Recurrence
Recurrence was measured as rate of locoregional control. The 2-year rate of locoregional control was 91.9% (95% CI, 88.5 to 95.3%) in the surveillance group and 91.4% (95% CI, 87.8 to 95.0%) in the planned-surgery group, with a RR of 1.00 (95% CI, 0.95 to 1.05).

Adverse events
A total of 282 serious adverse events occurred: 169 in the planned surgery group and 113 in the surveillance group (59.9% versus 40.1%, with a RR of 1.50 (95% CI, 1.26 to 1.78)).

Disease-free survival
This outcome was not measured in the included trial.

Toxicity
This outcome was not measured in the included trial.

Shoulder mobility
This outcome was not measured in the included trial.

Complications
A total of 22 surgical complications after neck dissection were noted in the surveillance group, as compared with 83 in the planned-surgery group, with a RR of 3.77 (95% CI, 2.43 to 5.86).

Level of evidence of the literature
Survival (2 years)
The level of evidence regarding the outcome survival started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies (1) and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Adverse events
The level of evidence regarding the outcome adverse events started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Recurrence
The level of evidence regarding the outcome adverse events started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Toxicity, shoulder mobility, disease-free survival
The study did not report on the outcome measures toxicity, shoulder mobility and disease-free survival and therefore GRADE could not be applied, and no conclusions could be drawn.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Recidief T2-T4

Uitgangsvraag

Wanneer en hoe is re-irradiatie in een curatieve setting mogelijk in een recidief hoofd-halscarcinoom na chemo-radiotherapie, wanneer salvage chirurgie niet meer mogelijk is?

Aanbeveling

Bespreek met de patiënt de nadelen van re-irradiatie van een hoofd-halsplaveiselcelcarcinoom wat betreft toxiciteit. Voorspellende factoren voor toxiciteit die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: dosis eerdere radiotherapie, eerdere chirurgie, tumorlokalisatie, leeftijd, en orgaan(dys)functie.

Bespreek bij patiënten met een nasofarynxcarcinoom de kans op overleving na re-irradiatie. Factoren die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: leeftijd, tumorstadium en EBV-concentratie in het bloed.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De werkgroep heeft een literatuuronderzoek verricht naar de prestatie van (multivariabele) modellen welke (de kans op) toxiciteit en overleving tijdens of na re-irradiatie voorspellen. Er werden twee gevalideerde modellen gevonden die overleving en toxiciteit voorspellen. Vanwege een zeer lage bewijskracht kan geen uitspraak worden gedaan over de prestatie van deze modellen. De zeer lage bewijskracht wordt voornamelijk veroorzaakt door beperkingen in de studieopzet ten aanzien van de ontwikkeling van de modellen en het ontbreken van externe validatie van de modellen. De werkgroep concludeert dan ook dat er een kennislacune bestaat omtrent het bestaan van beslissingsmodellen welke op basis van risicofactoren overleving en toxiciteit tijdens of na re-irradiatie bij patiënten, bij wie opereren geen mogelijkheid meer is, kunnen voorspellen.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Toxiciteit is een belangrijke uitkomst voor patiënten, waarbij de balans tussen toxiciteit en overleving een belangrijke afweging is. Toxiciteit geeft veel bijwerkingen, zoals necrose, mucositis, zwelling, slikproblemen, en pijn. Daarom moet met de patiënt worden besproken wat de nadelen kunnen zijn van re-irradiatie, en wat de eventuele voordelen zijn wat betreft overleving.

Kosten (middelenbeslag)
Re-irradiatie heeft geen grote impact op de kosten. Alternatieven van re-irradiatie zijn palliatieve opties, wanneer resectie niet meer mogelijk is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Vanwege de zeer lage bewijskracht van de gevalideerde modellen, kan er geen sterke aanbeveling worden gedaan welke factoren van belang zijn bij de keuze voor re-irradiatie. Het is belangrijk de voor- en nadelen met de patiënt te bespreken.

Onderbouwing

Achtergrond

Het doel van deze module is om de beste behandeling van een recidief hoofd-halscarcinoom na (chemo)radiotherapie als primaire behandeling dan wel adjuvant na resectie in beeld te brengen. Daarbij is het vooral van belang uit te zoeken wanneer re-irradiatie mogelijk is, als chirurgie niet meer mogelijk is, bij een recidief hoofd-halscarcinoom of tweede primaire tumor in een gebied dat eerder (chemo)radiotherapie gehad heeft. Daarbij zouden schade aan normale weefsels, overleving, toxiciteit, complicaties en kwaliteit van leven mogelijke uitkomsten kunnen zijn, en de factoren die bepalen of re-irradiatie nog mogelijk is, zouden type tumor, locatie tumor, reeds aanwezige postradiatie-effecten, tijdsinterval tot eerdere radiotherapie en patiëntgeschiedenis.

Conclusies

Toxicity: The level of evidence regarding the outcome measure toxicity started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (one level, no external validation) and imprecision (only one study with relatively low numbers of patients and events).

Overall survival: The level of evidence regarding the outcome measure started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (two levels, no external validation and different population).

Toxicity

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Ward, 2019, where dose of radiotherapy during first course, tumor site, organ dysfunction, any surgery, age and recurrent or second primary are selected as factors that predict toxicity after re-irradiation for head and neck squamous cell carcinoma. *Sources: (Ward, 2019)*

Overall survival

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Sun, 2022, where patient age, rT stage, and EBV DNA level are selected as factors that predict overall survival after re-irradiation for nasopharyngeal carcinoma. *Sources: (Sun, 2022)*

Samenvatting literatuur

Description of studies

Ward, 2019: From 9 institutions, 505 patients were included with recurrent or second primary (RSP) squamous carcinoma originating in a field previously irradiated to ≥ 40 Gy and treated with IMRT-based re irradiation to ≥ 40 Gy. A multivariable competing-risk model was fit to the actuarial risk of late toxicity with progression or death as the competing risk, using a backwards stepdown procedure. The final bootstrap optimized model was converted into a nomogram.

Sun, 2022: A prognostic model was established and validated for locally recurrent nasopharyngeal carcinoma (lrNPC) patients. In total, 531 patients from one center with lrNPC were retrospectively reviewed, including 271 patients from 2006 to 2012 as the training cohort and 260 patients from 2013 to 2016 as the validation cohort. Overall survival (OS) was the primary endpoint. Multivariate analysis was performed to select the significant prognostic factors (P < 0.05). A prognostic model for OS was derived by recursive partitioning analysis (RPA) combining independent predictors using the algorithm of optimized binary partition.

Results

Toxicity:
Ward, 2019: The final model included six clinical factors:

- Dose of radiotherapy during first course (continuous, per Gy) (HR 1.075 (95%CI 1.031 to 1.122)).
- Tumor site (oropharynx, larynx or lypopharynx versus other) (HR 1.575 (95%CI 0.984 to 2.519)).
- Organ dysfunction (yes versus no) (HR 3.029 (95%CI 1.919 to 4.783)).
- Any surgery (yes versus no) (HR 1.232 (95%CI 0.781 to 1.943)).
- Age (continuous, per year) (HR 0.977 (95%CI 0.955 to 0.998)).
- RSP (second primary versus recurrence) (HR 1.061 {95% CI 0.656 to 1.713)).

The final model demonstrated an average bootstrapped C-index of 0.698.

Overall survival:
Sun, 2022: The final model included 3 factors:

- Patient age (> 60 versus 60: hazard ratio (HR): 1.757, 95% confidence interval (CI): 1.181 to 2.615, P = 0.005).
- rT stage (rT2 versus rT1: HR: 1.725, 95% CI: 0.919 to 3.241, P = 0.090; rT3 versus rT1: HR: 2.439, 95% CI: 1.453 to 4.096, P = 0.001; rT4 versus rT1: HR: 5.007, 95% CI: 2.989 to 8.388, P < 0.001).
- EBV DNA level (detectable versus undetectable: HR: 1.825, 95% CI: 1.355 to 2.459, P < 0.001).

The study reported that re-irradiation could benefit patients in the low (P < 0.001) and intermediate-risk subgroups (P = 0.017), while no association between re-RT and survival benefit was found in the high-risk subgroup (P = 0.328).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the prognostic factors of successful re-irradiation in patients in a curative setting with a locoregional recurrent head and neck carcinoma after primary or adjuvant (chemo)radiotherapy, where salvage surgery is no longer possible?

P: (Patients) = Patients with a head and neck carcinoma that is recurring after primary or adjuvant (chemo)-radiotherapy, where salvage surgery is no longer possible.
I: (Intervention)= A model that predicts for which patients re-irradiation is successful, defined by intervention success, tissue damage, overall survival, toxicity, complications and quality of life.

C: (Comparison)= A different model/care as usual.
O: (Outcomes)= Predictive value of the model.
T:(Timing)= When in recurring head/neck carcinoma a treatment plan is determined.
S: (Setting)= Specialized care.

Relevant outcome measures
The guideline development group considered overall survival and toxicity as critical outcomes.

The working group defined the performance of the included models in Area Under the ROC Curve (AUC) as follows:

- 0.7 ≤AUC< 0.8: acceptable.
- 0.8 ≤AUC< 0.9: excellent.
- AUC≥ 0.9: outstanding.

Prognostic research: Study design and hierarchy
When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, the effectiveness of a clinical decision model is evaluated in a randomized clinical trial. Unfortunately, these studies are very rare. If not available, studies in which prediction models are developed and validated in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to studies that are not externally validated. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prediction models internally (e.g. bootstrapping or cross validation) can be used to answer the research question, but downgrading the level of evidence is necessary due to risk of bias and/or indirectness as it is not clear whether models perform sufficiently in target populations. The confidence in the results of unvalidated prediction models is very low. Therefore, such models will not be graded. This is also applicable for association models.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 14th of February 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 133 hits. Studies were selected based on the following criteria:

- Being a systematic review, randomized controlled trial (RCT) or observational study (cohort study).
- Reporting multivariable longitudinal association model or prediction model with outcome (mortality or complications periprocedural or within 30 days) as dependent variable and independent variables (patient characteristics) determined before the treatment plan was made.
- Models do not take independent variables into account that were determined after the treatment plan was made.

Four studies were initially selected based on title and abstract screening. After reading the full text, two studies were excluded (see the table with reasons for exclusion under the tab Methods) and two studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Larynxcarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Premaligne afwijkingen voor larynxcarcinoom

Uitgangsvraag

Op welke wijze dienen premaligne afwijkingen voor larynxcarcinoom behandeld te worden?

Aanbeveling

Behandel patiënten met een ernstige dysplasie/carcinoma in situ uitgaande van de ware stemplooien bij voorkeur met transorale laser microchirurgie (Microlarynx Chirurgie, MLC).

Overwegingen

Er is voor deze module geen systematische literatuursearch verricht. Het is aannemelijk dat onbehandelde ernstige dysplasie/carcinoma in situ uitgaande van de ware stemplooien bij ongeveer de helft van de patiënten zal leiden tot een conversie naar invasief carcinoom. Er bestaat derhalve een indicatie voor behandeling.

In een in 2021 gepubliceerd position paper van de European Laryngological Society wordt transorale laser microchirurgie (ook wel MicroLarynxChirurgie of MLC) als primaire behandelmodaliteit geadviseerd. Radiotherapie kan in bepaalde omstandigheden geïndiceerd zijn bijvoorbeeld bij multipele recidieven of multipele laesies of multipele aangedane gebieden van de larynx.

Er is geen rol voor medicatie bij de behandeling van larynxdysplasie.

Follow up van patiënten met larynxdysplasie is essentieel. De European Laryngological Society adviseert hiervoor te overwegen om patiënten te verdelen in laag of hoog riscio groepen met betrekking tot het ontwikkelen van een larynxcarcinoom. Aan de hand van deze risicostratificatie kan de frequentie en duur van de follow-up aangepast worden om zo onnodige follow-up en derhalve zorgkosten te voorkomen.

De follow-up kan verricht worden met dezelfde diagnostische modaliteiten als waarmee de primaire diagnose is gesteld.

Onderbouwing

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Behandeling Tis/T1 glottisch larynxcarcinoom

Uitgangsvraag

Hoe moeten Tis/T1 glottisch larynxcarcinomen worden behandeld: met radiotherapie of chirurgisch?

Aanbeveling

De behandeling van Tis-T1 larynxcarcinoom kan op twee manieren: laserchirurgie en radiotherapie. De werkgroep kan geen aanbevelingen geven over voorkeur voor radiotherapie of laserchirurgie omdat geen verschil is gevonden in oncologische en functionele uitkomsten.

Bespreek beide opties en ondersteun de patiënt bij het maken van een behandelkeuze waarbij de individuele patiëntkarakteristieken afgewogen dienen te worden.

Bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- Behandelduur:
  Laserchirurgie: De duur van de behandelingen zonder complicaties is één ingreep met een opname van één of twee dagen.
  Radiotherapie: De behandelduur varieert van 16 tot 33 behandelingen.
- Procedures:
  Laserchirurgie: opname en narcose.
  Radiotherapie: wordt poliklinisch verricht gedurende enkele weken.
- Korte en lange termijn complicaties en toxiciteit:
  Laserchirurgie: Er kunnen bloedingen, pijnklachten en ontstekingen optreden.
  Radiotherapie: Er kunnen vermoeidheid, huid- en slijmvliesreactie en slikklachten optreden.
- Kans op adjuvante behandeling: geen. Welk kan peroperatief blijken dat therapeutische laserchirurgie niet haalbaar is.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Eén RCT vergeleek laserchirurgie en radiotherapie, maar alleen op functionele uitkomsten (stemkwaliteit). De bewijskracht van deze studie is zeer laag. We zijn daarom onzeker of na de behandeling met radiotherapie de stemkwaliteit beter is, dan na laserchirurgie. Er werden geen studies gevonden waarin men verschillende typen chirurgische behandeling vergeleek. Omdat er bij deze vraag geen trials waren die de cruciale uitkomstmaten totale overleving of relapse-free survival onderzochten, is er gekeken naar geaggregeerd observationeel onderzoek (Ding, 2019). De individuele studies in deze review (die zijn gepubliceerd vanaf 2010) zijn beoordeeld (zie Evidence table). In geen van deze observationele studies corrigeerden de auteurs voor confounders, waardoor een verband tussen de interventies en uitkomsten zwakker of juist sterker kan zijn. Deze studies konden daarom niet bijdragen aan het formuleren van conclusies die dienen als basis voor richtlijnaanbevelingen.

Voor de cruciale uitkomstmaten *overall survival* en *relapse-free survival* zijn geen data beschikbaar uit RCT's. De reden voor de zeer lage bewijskracht van de functionele uitkomstmaat is dat er slechts één RCT met een klein aantal patiënten is gevonden. De overall bewijskracht is daarom zeer laag. Ook op de belangrijke uitkomsten is er geen data beschikbaar uit RCT's of observationeel onderzoek.

Mogelijke bijwerkingen van laserchirurgie zijn nabloeding of benauwdheid. De mogelijke bijwerkingen van radiotherapie zijn huid- en slijmvliesreacties, slikklachten en vermoeidheid. De kans op het optreden van complicaties erg klein. Er is een subgroep van patiënten (eigen dentitie en retrognathie, beperkte mondopening) bij wie laser chirurgie niet haalbaar is. Voor deze groep zal radiotherapie de enige goede behandeling zijn.

Belangrijk is verder te realiseren dat de techniek en het type laserbehandeling in de gepubliceerde studies kan verschillen en vaak niet goed omschreven is. Om dit in toekomstige studies te ondervangen is door European Laryngological Society een classificatie voor endoscopische chordectomie voorgesteld (Remacle, 2000; Remacle 2007).

RCT's die deze behandelmodaliteiten hebben getracht te vergelijken zijn gefaald omdat de behandelingen niet volledig gelijkwaardig zijn, de artsen gebiased zijn en de patiënten voorkeur hebben. Zij willen dus niet zomaar gerandomiseerd worden. Zie ook het artikel van Hamilton over de EaStER-trial (Hamilton, 2013).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Voor de patiënten zijn een goed oncologisch resultaat met een goede functionele uitkomst belangrijk. De belasting voor de patiënt is wel verschillend. Grofweg kan gesteld worden dat laserchirurgie een behandeling van 1 uur is in dagopname of met een opname van 1 nacht. Radiotherapie is een behandeling waarbij de patiënt 16 tot 33 keer behandeld zal worden en daarvoor naar het ziekenhuis moet komen.

Het is aannemelijk dat de kans op langdurigere en uiteindelijke preservatie van de larynx groter is als in eerste instantie behandeld wordt met laserchirurgie. Bij een recidief of 2e primaire tumor is het immers dan nog mogelijk om te behandelen met radiotherapie en is een laryngectomie niet de enige overgebleven optie (Schrijvers, 2009; Van Gogh, 2012).

Kosten (middelenbeslag)
Er zijn geen studies gevonden over kosteneffectiviteit van laserchirurgie versus radiotherapie. Goor (2007) lieten zien dat radiotherapie duurder is dan laserchirurgie, als de kosten voor de behandeling van mogelijke terugkeer van kanker worden meegenomen, terwijl de effecten voor beide behandelopties gelijk zijn. De werkgroep verwacht daarom dat deze aanbeveling wel een impact op de zorgkosten kan hebben.

Aanvaardbaarheid, haalbaarheid en implementatie
Beide behandelingen worden al langer toegepast in Nederland en zijn in de behandelprotocollen van de diverse hoofd-halscentra opgenomen. De beschikbaarheid van beide behandelingen is wijd verspreid in Nederland.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De behandeling van Tis-T1 glottisch larynxcarcinoom kan met radiotherapie of laserchirurgie. Uit de literatuur zijn er geen verschillen in overleving of functieverlies gevonden tussen de beide behandelmogelijkheden. Behandeling met laserchirurgie is wel goedkoper en heeft waarschijnlijk meer kans op langduriger behoud van de larynx.

Onderbouwing

Achtergrond

Glottische larynxcarcinomen ontstaan vaak in de stembanden. Mogelijke behandelingen zijn radiotherapie en chirurgische behandeling (open chirurgie of endolaryngeale/transorale chirurgie), of een combinatie van deze twee interventies. Het is onduidelijk wat de optimale behandelstrategie is wat betreft totale overleving, ziektevrije overleving, stemkwaliteit, kwaliteit van leven en (werk)participatie.

Conclusies

<u>Crucial outcome measures</u>
Overall survival

- **GRADE**	No conclusion can be drawn about the effect of treatment with laser surgery versus radiotherapy on overall survival on overall survival.

Relapse-free survival

- **GRADE**	No conclusion can be drawn about the effect of treatment with laser surgery versus radiotherapy on relapse-free survival on relapse-free survival.

Functional outcomes

Very low GRADE	*Expert-rated quality of voice* Laser surgery may increase voice breathiness and asthenia, and have no effect on overall voice quality, voice roughness and strain when compared with radiotherapy, but the evidence is very uncertain. *Self-rated quality of voice* Laser surgery may have no effect on self-rated hoarseness and may increase the impact of hoarseness on patients daily living activities two years after treatment, when compared with radiotherapy, but the evidence is very uncertain. *Videolaryngostroboscopic findings* Laser surgery may reduce sufficient glottal function at videolaryngostroboscopy performed two years after treatment, when compared with radiotherapy, but the evidence is very uncertain. *Sources: (Aaltonen, 2014)*

<u>Important outcome measures</u>

Larynx preservation, quality of life, secondary treatment, complications/adverse events, (work)participation

- GRADE	No conclusion can be drawn about the effect of treatment with laser surgery versus radiotherapy on larynx preservation, quality of life, secondary treatment, complications/adverse events, (work)participation

Samenvatting literatuur

<u>Description of studies</u>
Randomised controlled trials
The RCT performed by **Aaltonen (2014)** included male patients with histologically confirmed squamous cell carcinoma, limited to one mobile vocal cord, staged as T1aN0M0. Transoral laser surgery (TLS, tumour excision with a CO_2 laser) was compared with external beam radiation therapy (RT). The outcome was voice quality, which was assessed at baseline and 6 and 24 months after treatment and was measured in three ways: an expert-rated quality of voice, self-rated quality of voice, and videolaryngostroboscopic findings. In the study, 60 male patients were randomized to TLS (n=32, of which 31 were evaluated) or radiation therapy (n=28, of which 25 were evaluated). The follow-up period was 24 months. The median age was 69 years in the TLS group and 61 years in the RT group.

Observational studies
The systematic review by **Ding (2019)** included 18 studies in their analysis. Of them, seven were published after 2010 and met our PICO criteria. Since none of these observational studies corrected for confounding, these results do not contribute to the body of evidence and were not graded, but only described for informative purposes.

Overall survival at five years follow-up was reported in four studies and ranged from 86 % to 97% in the laser surgery group, and from 70% to 96% in the radiotherapy group. Relapse was reported in two studies (one study reported disease-free survival and one study reported local and regional recurrence). Functional outcomes were reported in six studies (three studies acoustic parameters, four studies voice handicap index, and one study Grade, Roughness, Breathiness, Asthenia, and Strain scale), and most studies reported worse functional outcomes in laser surgery patients, compared to radiotherapy patients. The results are summarized in the evidence table.

The retrospective cohort study by **Low (2016)** included patients with T1aN0 glottic squamous cell carcinoma (SCC) and was performed in Australia. Transoral laser microsurgery (TLM) was compared with RT on oncologic outcomes (overall survival and relapse-free survival). In total, 105 patients were included, of whom 53 were treated with TLM and 52 with RT. The mean age was 65.4 (sd 13.0) and 70.6 (sd 11.0) years, and 42/53 (79%) and 44/52 (85%) were men in the TLM and RT group, respectively. The mean follow-up was 3.58 (sd 2.41) years in the TLM group and 4.55 (sd 3.17) years in the RT group. They concluded that patients with T1aN0 glottic SCC treated with RT or TLM have similar survival outcomes.

The retrospective cohort study by **Kono (2016)** included patients with T1aN0M0 glottic cancer and was performed in Japan. Laser surgery (LS) was compared with RT, on functional outcomes (acoustic parameters, voice handicap index, and auditory-perceptual evaluation). Until July 2010, the laser was used in super pulse continuous mode with 4 to 5 W power (vaporization with defocused mode using laser surgery (LS-Vap)), and

from August 2010, the laser was used in super pulse continuous mode with 1 W power in focus (LS-Ex). In total 64 patients were included, of whom 37 were treated with LS and 27 with RT. The mean age was 69 (sd 9.8) and 69 (sd 9.8) years, and 33/37 (89%) and 22/27 (81%) were men in the TLM and RT group, respectively. The median follow-up period was 37 months. They concluded that early glottic cancer could be successfully treated by either RT or LS-Ex with equivalent posttherapeutic laryngeal function and quality of life.

The prospective cohort study by **Taylor (2013)** included patients with T1b squamous cell carcinoma (SCC) of the glottic larynx and was performed in Canada. TLS was compared with RT, on the oncologic outcomes (overall survival and disease-free survival), and functional outcomes (voice handicap index). In total, 63 patients were included, of whom 21 were treated with TLS and 42 with RT. The mean age was 64 and 69 years, and 18/21 (86%) and 39/42 (93%) were men in the TLM and RT group, respectively. Median follow-up was 34 months in both groups. They concluded that among patients with stage T1b SCC of the glottis oncological outcomes after TLM were at least equivalent to RT, and that voice quality was similar between the two groups.

The retrospective cohort study by **Remmelts (2013)** included patients with early stage (Tis-T2) glottic laryngeal carcinoma and was performed in the Netherlands. LS was compared with RT, on oncologic outcomes (overall survival), and functional outcomes (voice handicap index). In total, 248 patients were included, of whom 89 were treated with LS and 159 with RT. The mean age was 67 and 64 years, and 78/88 (88%) and 138/159 (87%) were men in the LS and RT group, respectively. The mean follow-up was 44 months in the LS group, and 48 months in the RT group. They concluded that oncological outcomes of both LS and RT are similar in T1a laryngeal cancer, and that numbers in this study were too small to allow any conclusions on oncological outcomes in stage T1b laryngeal cancer. According to subjective voice analysis outcomes were comparable in T1a lesions. For T1b lesions patients treated with LS had a statistically significantly higher percentage of voice deficiency (see details in the evidence tables).

The prospective cohort study by **Milovanovic (2013)** included patients with Tis and T1a glottic carcinoma and was performed in Serbia. TLM was compared with RT, on functional outcomes (acoustic parameters), and oncologic outcomes (overall survival). In total, 146 patients were included, of whom 72 were treated with TLM and 74 with RT. Mean age was 59.5 and 62.9 years, and 65/72 (90%) and 67/74 (91%) were men in the TLM and RT group, respectively. The follow-up ranged from 38 to 107 months. They concluded that, given that choice of treatment was also influenced by other factors, TLM was highly efficient and preferred choice of treatment for early glottic carcinoma in Serbia.

The prospective cohort study by **Van Gogh (2012)** included patients with T1aN0M0 glottic cancer and was performed in the Netherlands. Endoscopic laser surgery (LS) was compared with RT on functional outcomes (acoustic parameters). In total, 106 patients were included of whom 67 were treated with LS and 39 with RT. Mean age was 66 and 65 years, and 67/67 (100%) and 39/39 (100%) was men in the LS group and RT group, respectively. Median time of follow-up was comparable for patients in both groups and was maximum 24 months. They concluded that LS is the first treatment of choice in the treatment of selected cases of T1a glottic carcinomas with good functional and oncological results.

The retrospective cohort study by **Kerr (2012)** included patients with stage 1 or 2 glottic carcinoma and was

performed in Canada. TLM was compared with RT, on oncologic outcomes (overall survival), and functional outcomes (voice handicap index). In total, 243 patients were included of whom 143 were treated with TLM, and 91 with RT. Median age was 67 in both groups, and 123/143 (86%) and 82/91 (90%) were men in the TLM and RT group, respectively. Median follow-up was 28 months in the TLM and 32 months in the RT group. They concluded that TLM patients had poorer voice quality than RT patients (see details in the evidence tables). However, the authors argued that advantages of TLM in most patients outweighed the degree of voice handicap.

Results
None of the observational studies corrected for confounding and therefore their results did not contribute to the conclusions.

Overall survival at five years (crucial)
None of the studies reported on overall survival after a minimum follow-up duration of five years.

Relapse-free survival at five years (crucial)
None of the studies reported on relapse-free survival after a minimum follow-up duration of five years.

Functional outcomes (crucial)
1. Expert-rated quality of voice
Aaltonen (2014): The mean scores in expert-rated overall voice quality (G), voice roughness (R), and strain (S) remained similar between the groups during follow-up, but patients treated with TLS had a more breathy voice (B) than those who received radiation therapy (score 1.52 versus 0.28 (on a scale from 0 (normal) to 3 (extremely abnormal) 2 years after treatment, P<0.001). A statistically significant difference emerged also in asthenia (A) (0.74 versus 0.11; P=0.003), but in both groups the absolute value was under 1, suggesting limited clinical relevance of this finding. Breathiness and asthenia improved significantly with time in the radiation therapy group (from 1.17 at baseline to 0.28 2 years after treatment, P=0.001; and from 0.56 to 0.11, P=0.001, respectively) but not in the TLS group.

The degree of voice breathiness varied between groups. In the TLS group, 5/27 (19%) had no voice breathiness (score 0), the majority (20/27, 74%) had mildly or moderately breathy voice (score 1 or 2), and 2/27 (7%) had extremely breathy voice (score 3). In the RT group, the majority of patients (14/20, 70%) had no voice breathiness (score 0), 6/20 (30%) had mildly or moderately breathy voice (score 1 or 2), and none of the patients had extremely breathy voice (score 3).

2. Self-rated quality of voice
Aaltonen (2014): Self-rated hoarseness was judged similar between the groups (P=0.144). The self-reported quality of voice improved significantly from the baseline quality during follow-up in both groups (in the TLS group, the VAS-score decreased from 59.0 to 43.1, P=0.040; and in the RT group, from 53.1 to 35.4, P=0.026). Patients assigned to RT reported less impact of hoarseness on their daily living activities than did patients assigned to TLS (P=0.007).

3. Videolaryngostroboscopic findings

Aaltonen (2014): In comparison with the RT group, patients assigned to TLS had less sufficient glottal function at videolaryngostroboscopy performed two years after study entry. They had higher scores for irregular glottal closure (P=0.025), oval closure (P=0.005), and incomplete glottal closure (P=0.018).

Larynx preservation (important)
None of the studies reported on larynx preservation.

Quality of life (important)
None of the studies reported on quality of life.

Secondary treatment (important)
None of the studies reported on secondary treatment.

Complications/adverse events (important)
None of the studies reported on complications or adverse events.

(Work)participation (important)
None of the studies reported on (work)participation.

Certainty of the evidence
None of the observational studies corrected for confounding and therefore their results could not contribute to the conclusions. GRADE was applied to assess the certainty of the evidence originating from the RCT of Aaltonen (2014).

Crucial outcome measures
Overall survival and relapse-free survival at five years
None of the studies reported on the crucial outcome measures overall survival and relapse-free survival at five years, and therefore GRADE could not be applied, and no conclusions could be drawn.

Functional outcomes (voice quality)
The certainty of the evidence regarding functional outcomes started high as the evidence originated from an RCT, and was downgraded by three levels because of study limitations: one level for risk of bias (patients and assessors were not blinded); and two levels for very serious imprecision (only one study was included, with a very small sample size). Therefore, the certainty of the evidence was very low.

Important outcome measures
None of the studies reported on any of the important outcome measures (quality of life, secondary treatment, complications/adverse events, and (work)participation) and therefore GRADE could not be applied, and no conclusions could be drawn.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are the effects of radiotherapy compared to surgical treatment (open surgery/endolaryngeal surgery) in patients with Tis/T1 glottic laryngeal carcinomas?

P: patients with Tis/T1 glottic laryngeal carcinomas;
I: open surgery/endolaryngeal or transoral surgery;
C: radiotherapy;
O: overall survival at five years, disease-free survival at five years, voice quality, quality of life, secondary treatment, (work)participation.

Relevant outcome measures
The guideline development group considered overall survival, relapse-free survival and functional outcomes (voice quality) as crucial outcome measures for decision making; and quality of life, secondary treatment, complications/adverse events, and (work)participation as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Overall survival (defined as time from randomisation to death from any cause) with a minimum follow-up of 5 years.
Relapse-free survival	Relapse-free survival (time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence) with a minimum follow-up of 5 years.
Functional outcomes	Voice quality: self-rated (measured with an instrument such as the VHI-10), or expert-rated (measured with an instrument such as the GRBAS scale (grade, roughness, breathiness, asthenia, and strain)).
Larynx preservation	Laryngeal preservation rate.
Quality of life	Quality of life (overall or regarding a specific domain) as measured with a validated and reliable instrument such as the SF-36 or EORTC QLQ-C30.
Secondary treatment	Whether or not secondary (adjuvant) treatment is necessary.
Complications/adverse events	All negative effects related to the treatment (lethal, acute/serious, chronic).
(Work)participation:	Participation in school, work and/or informal care.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: a minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: statistically significant less complications/adverse events.
- Functional outcomes: statistically significant better functional outcomes.
- (Work)participation: statistically significant better (work)participation.

Search and select (Methods)

The guideline development group decided that the Cochrane review from Warner (2014) could be used as a base. After a more detailed investigation of the included study in this Cochrane review, the guideline development group decided that the interventions studied by Ogol'tsova (1990) were not relevant anno 2020, and therefore this study was excluded from the body of evidence. Literature was searched for studies published after the search date of Warner (September 2014). The databases Medline (via OVID) and Embase (via Embase.com) were searched for SRs and RCTs with relevant search term until July 10th, 2019. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1967 hits.

Studies were selected based on the following criteria: included patients with Tis/T1 glottic larynx carcinoma, compared radiotherapy with open or endolaryngeal surgery, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and written in English language.

Eight studies were initially selected based on title and abstract screening. After reading the full texts and thorough assessment of the included studies, seven studies were excluded (see the table with reasons for exclusion under the tab Methods). Through the SR of Huang (2017) one RCT (Aaltonen, 2014) was included. No other, more recent, RCTs were found. Therefore, in addition to this RCT, the guideline development group decided to select the most recent SR of observational studies that could answer the PICO (Ding, 2019). The comparative observational studies described in this SR were added to the body of evidence and described in the summary of literature.

Data-synthesis

Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis) separately. A priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:

- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results

One RCT (Aaltonen, 2014) and seven comparative observational studies were included in the analysis of the literature. They all compared laser surgery with radiation therapy (RT). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table. No studies were found that compared open surgery with radiotherapy.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Behandeling van Tis/T1 supraglottische larynxcarcinomen

Uitgangsvraag

Op welke wijze dienen Tis/T1 supraglottisch larynxcarcinomen behandeld te worden?

Aanbeveling

Aanbeveling-1
Behandel patiënten met Tis/T1 supraglottisch larynxcarcinoom bij voorkeur met radiotherapie. Overweeg een horizontale laryngectomie of een endoscopische behandeling indien:

- de kans op adjuvante radiotherapie laag is;
- de tumor goed bereikbaar is;
- voldoende behoud van functies mogelijk lijkt te zijn.

Aanbeveling-2
Ondersteun patiënten die in aanmerking komen voor zowel radiotherapie als chirurgie bij het maken van een behandelkeuze waarbij de individuele patiënt- en tumorkarakteristieken dienen te worden afgewogen.

Bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:

- Behandelduur:

De duur van de behandelingen zonder complicaties is bij chirurgie één tot enkele dagen.
Voor RT is de behandeling poliklinisch en de behandelduur vijf tot zeven weken.

- Overblijvende behandelopties:

Na radiotherapie is doorgaans geen radiotherapie meer mogelijk voor een recidief of tweede primaire tumor in het bestraalde gebied.
Na chirurgie is radiotherapie en soms ook nog hernieuwde chirurgie mogelijk.

- Procedures:

Een dergelijke operatie wordt onder narcose verricht.

- Korte en lange termijn complicaties en toxiciteit:

Bij chirurgie kunnen bloedingen, pijnklachten en ontstekingen optreden. Als lange termijn effect kunnen slikklachten ontstaan waarvoor in ernstige gevallen logopedische sliktraining of een blijvende gastrostomie nodig kan zijn.
Bij radiotherapie kunnen heesheid en slikklachten optreden. Zes weken na radiotherapie verdwijnen deze klachten in het algemeen. De kans op radionecrose of een secundaire tumor door de radiotherapie is zeer klein.

- Voor primaire chirurgie bestaat een kans op een adjuvante behandeling met radiotherapie.

- De kans op genezing is bij beide behandelopties gelijk.

Overwegingen

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten hebben onderzocht van horizontale supraglottische laryngectomie in vergelijking met endoscopische behandeling of radiotherapie, voor patiënten met een Tis/T1 supraglottisch larynxcarcinoom.

De meest uitgebreide review is van der Woerd (2018). Deze review werd gevonden in de search maar voldeed niet aan alle criteria. Het gaat om een systematische review naar functionele uitkomsten bij patiënten met een T1 (43%) of T2 (57%) supraglottische tumor, die radiotherapie (n=320) of orgaansparende chirurgie (n=320) ondergingen. Onder de tien geïncludeerde studies waren zes retrospectieve cohort studies en vier case series, in veel gevallen ging het om data van meer dan tien jaar oud. Wegens heterogeniteit en onvolledige rapportage van functionele uitkomsten voor de verschillende behandelopties kon geen voorkeur voor één van beide modaliteiten worden uitgesproken. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ter onderbouwing van een aanbeveling.

Expert opinion: In de meeste instituten in Nederland en Noord-Europa worden patiënten met een Tis / T1 supraglottisch carcinoom behandeld met primaire radiotherapie met een lokale controle > 90% en goed functioneel resultaat. In een systematische review van Sanabria (2020) werd de incidentie van occulte lymfekliermetastasen per tumorlokatie en tumorstadium gerapporteerd. In 19 studies werd data gerapporteerd voor supraglottische tumoren. In een subgroepanalyse van studies met daarin tenminste 75% van de patiënten met een T1/T2 tumor werd een incidentie van 18,4% (95%BI 11,8% tot 25,0%) occulte metastasen gerapporteerd. Er was aanzienlijke variatie; de hoogst gerapporteerde incidentie was 48,2% terwijl drie studies een incidentie lager dan 12% rapporteerden. Deze variatie kon niet goed worden verklaard. Het advies van de auteurs van de review luidt om bij T1-T2 cN0 supraglottische tumor level IIa-III bilateraal te bestralen.

Mutlu (2014) voerde een retrospectieve studie uit onder 118 patiënten die een chirurgische behandeling met daarbij een nek dissectie hadden ondergaan. Bij 11 van de 38 patiënten (28,9%) met een supraglottische tumor (tumorstadium niet gespecificeerd) werden occulte lymfeklier metastasen aangetroffen. Bij twee van de 19 patiënten (10,5%) met een T1 tumor (supraglottisch, glottisch of transglottisch) werden occulte metastasen aangetroffen.

Bij primaire tumor > 4 cm is deze kans verhoogd. Het lijkt daarom aan te bevelen electieve bestraling van de halsklierstations level IIA-III af te laten hangen van het tumor volume, op basis van de literatuur zijn geen exacte maten aan te geven.

Transorale laser chirurgie dan wel horizontale supraglottische laryngectomie via een externe benadering is een alternatief in geselecteerde casus. Selectiecriteria betreffen onder andere voldoende marge naar de stembanden en een goede longfunctie. Bij endoscopische chirurgie moet de tumor goed bereikbaar zijn. Dit hangt onder andere af van de mondopening, dentitie en lokale anatomie.

Bij deze tumoren dient zoveel mogelijk gestreefd te worden naar een behandeling met één modaliteit, chirurgie of radiotherapie. Indien het risico op adjuvante radiotherapie hoog is kan het beste gekozen worden voor primaire radiotherapie. Tevens moet afhankelijk van lokalisatie, grootte en uitbreiding ingeschat worden met welke behandeling het slikken, spreken en ademen zonder tracheotomie zo goed mogelijk behouden kunnen blijven. Patiënten dienen dus goed geselecteerd te worden voor één van deze behandelingen. De behandeling zal dan dus ook geïndividualiseerd zijn.

Samengevat is primaire chirurgie een alternatief bij kleine craniaal gelegen epiglottische tumoren bij patiënten met een goede long- en slikfunctie waarbij het risico op adjuvante radiotherapie laag is en voldoende behoud van functies mogelijk lijkt te zijn. Deze voor- en nadelen moeten worden besproken met de individuele patiënt en afgewogen worden bij het gezamenlijk nemen van een beslissing over de in te zetten behandeling.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Het belangrijkste doel voor de patiënt is een hoge kans op locoregionale genezing van de tumor (bij Tis/ T1 supraglottisch larynxcarcinoom > 90%) met een goed functioneel resultaat, goede slikfunctie en spraak. Radiotherapie wordt poliklinisch toegepast in 25 tot 35 fracties in 5 tot 7 weken. De meeste klachten betreffen slikklachten en heesheid en ontstaan tijdens de radiotherapie en voorbijgaand in de periode 6 weken na de bestraling. Chirurgie is een eenmalige ingreep met een paar dagen ziekenhuis opname. Bij chirurgie kunnen bloedingen, pijnklachten en ontstekingen optreden. Als lange termijn effect kunnen slikklachten ontstaan waarvoor in ernstige gevallen logopedische sliktraining of een blijvende gastrostomie nodig kan zijn. Bij een deel van de patiënten zal nog postoperatieve radiotherapie volgen; in een retrospectieve studie van Dyckhoff (2021) kregen 7 van de 31 patiënten (22,6%) met een T1 supraglottisch larynxcarcinoom adjuvante radiotherapie na transorale laser chirurgie. Goede selectie van patiënten is dan ook noodzakelijk.

Kosten (middelenbeslag)
Er bestaan geen studies over een kostenvergelijking tussen de therapeutische opties.
Wat betreft de primaire behandeling is de vergelijking tussen een kortdurende klinische opname met een operatie onder narcose (chirurgie) versus een poliklinische behandeling 5 dagen per week gedurende 5 tot 7 weken. Daarnaast zullen na alle behandelingen nog kosten gemaakt worden voor revalidatie vanwege klachten van slikken en spreken.

Aanvaardbaarheid, haalbaarheid en implementatie
Behandeling van Tis/ T1 supraglottische carcinomen is voorbehouden aan de bij de NWHHT aangesloten HH centra. Een horizontale supraglottische laryngectomie wordt ook binnen de NWHHT centra in Nederland maar beperkt toegepast. Het kan een reden zijn om deze patiënten te verwijzen naar een centrum met expertise op dit gebied.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Aanbeveling-1

Er is onvoldoende wetenschappelijke literatuur om conclusies te kunnen trekken over de rol van horizontale supraglottische laryngectomie in vergelijking met endoscopische behandeling of radiotherapie voor patiënten met een Tis/T1 supraglottisch larynxcarcinoom. In de meeste instituten worden deze patiënten behandeld met primaire radiotherapie, met goed resultaat. Op basis van expert opinie wordt aanbevolen om patiënten bij voorkeur met radiotherapie te behandelen, waarbij transorale laser chirurgie of horizontale supraglottische laryngectomie in geselecteerde gevallen overwogen kunnen worden.

Aanbeveling-2
Er zijn geen vergelijkende studies wat betreft het effect van chirurgische behandeling en behandeling met radiotherapie op locoregionale genezing en functionele uitkomsten. Indien chirurgische behandeling overwogen wordt, bespreek de verschillende behandelopties en de voor- en nadelen van deze opties met de patiënt en beslis samen welke behandeling het meest geschikt is voor de patiënt.

Onderbouwing

Achtergrond

In de literatuur worden drie verschillende behandelingsopties als geaccepteerde behandeling voor het T1 supraglottisch larynxcarcinoom besproken: radiotherapie, endoscopische behandeling (meestal met CO_2 laser) en horizontale supraglottische laryngectomie. Welke van deze opties, of combinatie van opties, de beste kans op herstel of minste kans op recidief geeft is niet duidelijk.

Conclusies

No studies were selected that reported on the crucial and important outcome measures. Therefore, GRADE could not be applied, and no conclusions about the three treatment options for patients with Tis/T1 supraglottic laryngeal carcinomas could be drawn.

Samenvatting literatuur

No studies were found that reported on the crucial and important outcome measures.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of horizontal supraglottic laryngectomy versus endoscopic treatment or radiotherapy for patients with a Tis/T1 supraglottic laryngeal carcinoma?

P: patients with a Tis/T1 supraglottic laryngeal carcinoma;
I: horizontal supraglottic laryngectomy;
C: radiotherapy or endoscopic treatment;
O: 5-year survival, 5-year recurrence of disease, dysphagia (SwalQoL and swallowing tests: video-based swallowing research, assessing penetration scores), eating and drinking, voice quality, breathing (dyspnea), feeding tube, tracheotomy.

<u>Relevant outcome measures</u>
The guideline development group considered recurrence free (local and regional) survival and dysphagia as

critical outcome measures for decision making; and disease free survival and permanent feeding tube, eating and drinking, voice quality, breathing (dyspnea) and tracheotomy as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7
- Relapse-free survival: HR< 0.7

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms for RCTs and systematic reviews until March 11th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 660 hits.

Studies were selected based on the following criteria:

- the study design was a systematic review (SR) or randomized controlled trial (RCT);
- written in English language;
- included patients with a Tis/T1 supraglottic laryngeal carcinoma;
- compared horizontal supraglottic laryngectomy with radiotherapy or endoscopic treatment;
- reported at least one of the outcomes of interest.

Seven studies were initially selected based on title and abstract screening. After reading the full text, all seven studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
No studies were included in the analysis of the literature.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Behandeling T3 larynx

Uitgangsvraag

Wat is de rol van radiotherapie ten opzichte van chirurgie bij patiënten met een T3 larynxcarcinoom?

Aanbeveling

Overweeg bij patiënten met een functionele larynx bij aanvang van de behandeling een larynxsparend beleid.

Voor patiënten tot en met 70 jaar met een WHO 0-1:

- Overweeg geaccelereerde radiotherapie dan wel chemoradiatie bij uitgebreide halsstatus.
- Overweeg het tumorvolume mee te laten wegen bij keuze tussen primaire radiotherapie en chemoradiatie, waarbij een groter volume van de tumor een indicatie kan zijn om chemotherapie toe te voegen (mogelijke afkappunten zijn > 3,5 cc voor glottische tumoren en > 6 cc voor supraglottische tumoren).

Voor patiënten ouder dan 70 jaar en/of een WHO>1:

- Overweeg geaccelereerde radiotherapie.

Overweeg bij een disfunctionele larynx een primaire TLE met postoperatieve (chemo)radiatie in plaats van een larynxsparend beleid. Dit in verband met slechte functionele resultaten voor deze groep met primaire (chemo)radiatie.

Bespreek de behandelopties, te weten primaire (chemo)radiotherapie met een salvage laryngectomie bij een lokaal recidief/residu dan wel primaire laryngectomie met afhankelijk van de pathologie uitslag gevolgd door (chemo)radiotherapie, en ondersteun de patiënt bij het maken van een behandelkeuze waarbij de individuele patiëntkarakteristieken afgewogen dienen te worden.

Voordeel van primaire (chemo)radiatie is behoud van de natuurlijke stem in +/- 70% van de patiënten.

Bespreek de volgende belangrijke voor- en nadelen van de interventies indien van toepassing op de patiënt:
- **Behandelduur:**

  - De duur van de behandelingen zonder complicaties is bij chirurgie gemiddeld twee tot drie weken gevolgd door gemiddeld vijf tot zeven weken (chemo-)radiatie.
  - Voor radiotherapie is de behandeling poliklinisch en de behandelduur vijf tot zeven weken.

- **Overblijvende behandelopties:**

  - Na radiotherapie is doorgaans geen radiotherapie meer mogelijk voor een recidief of tweede primaire tumor in het bestraalde gebied.
  - Na chirurgie is hernieuwde chirurgie zelden nog mogelijk.

- **Procedures:**

- Een dergelijke operatie wordt onder narcose verricht.

- **Korte en lange termijn complicaties en toxiciteit:**

  - Bij chirurgie kunnen bloedingen, pijn en ontstekingen optreden. Als lange termijn effect kunnen slikklachten, voornamelijk als gevolg van stenosering, optreden. Voor deze klachten kan logopedische sliktraining nodig zijn.
  - Bij radiotherapie kunnen heesheid en slikklachten optreden. Zes weken na radiotherapie verbeteren deze klachten in het algemeen, maar kunnen ook persisteren. Voor deze klachten kan logopedische/ergotherapeutische sliktraining of een blijvende gastrostomie nodig zijn.
  - De kans op een disfunctionele larynx is reëel bij (chemo)radiotherapie, wat een indicatie kan zijn voor een permanente tracheotomie of zelfs een laryngopharyngectomie, met name wanneer tevens ondanks intensieve logopedische training ernstige slik- en stemklachten blijven bestaan. De kans op radionecrose of een secundaire tumor door de radiotherapie is zeer klein.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De systematische zoekactie in Medline en Embase resulteerde in drie RCT's (Wolf, 1991; Richard, 1993; Bhalavat, 2003).

Voor alle drie de cruciale uitkomstmaten (lokale controle, locoregionale controle en overleving) werden resultaten gerapporteerd. Eén studie rapporteerde zowel lokale als locoregionale controle. In de radiotherapie groep werd lokale controle gerapporteerd voor 20/27 patiënten (74%) en locoregionale controle voor 24/27 patiënten (88%), terwijl voor alle 28 patiënten in de chirurgie groep lokale en locoregionale controle werd gerapporteerd. Gezien de kleine aantallen patiënten is het lastig om hier conclusies aan te verbinden. Overleving werd in alle drie de RCT's gerapporteerd. Twee studies rapporteerden geen klinisch relevant verschil tussen de groepen, terwijl de derde studie een slechtere overleving in de radiotherapie groep rapporteerde (2-jaarsoverlevingpercentages van 69% versus 84%).

Voor drie van de zes belangrijke uitkomstmaten (ziektevrije overleving, het behoud van de larynx en toxiciteit/complicaties) werden resultaten gerapporteerd. Ziektevrije overleving werd in alle drie de RCT's gerapporteerd, deze was in alle gevallen slechter in de radiotherapie groep (waarbij in twee gevallen op basis van de curve bepaald werd dat het verschil groter was dan 5% en één studie 5-jaars overleving percentages rapporteerde van 50% voor radiotherapie en 80% voor chirurgie). Behoud van de larynx werd ook in alle drie de studies gerapporteerd, het ging daarbij om het percentage patiënten in de radiotherapie groep die uiteindelijk geen totale laryngectomie hoefden te ondergaan. Dit betrof 64%, 42% en 60% van de patiënten. Toxiciteit werd in alle studies vermeld, dit was echter lastig te vergelijken omdat het om twee heel verschillende interventies gaat waarvoor een verschillend profiel aan bijwerkingen en complicaties werd gezien. Voor overleving zonder terugkeer van de kanker, kwaliteit van leven en functie van de larynx werden geen resultaten gerapporteerd.

De bewijskracht voor alle uitkomstmaten was zeer laag. Er werd afgewaardeerd wegens een risico op bias omdat de randomisatie en allocatie niet beschreven waren, omdat één van de studies voortijdig stopgezet was wegens een sterke patiëntvoorkeur voor behandeling met radiotherapie, en omdat er in één studie sprake bleek van misclassificatie (T3 waar de patiënt geclassificeerd had moeten worden als T4). Voor overleving was er sprake van inconsistentie, waarbij twee studies geen verschil vonden in overleving, terwijl één studie een slechtere overleving liet zien voor radiotherapie. Ook werd er afgewaardeerd voor indirectheid omdat in één studie de resultaten voor zowel T3 als T4 tumoren werden gerapporteerd en omdat in één studie bij alle patiënten sprake was van larynxhelftstilstand. Tenslotte ging het om studies met kleine patiëntaantallen (in twee studies ging het om minder dan 40 patiënten per arm) wat leidde tot brede betrouwbaarheidsintervallen. Alles bij elkaar genomen is er op basis van deze drie studies nog veel onzekerheid of de geschatte effecten ook het werkelijke effect weergeven. De bewijskracht is dusdanig laag dat er helaas geen conclusie worden getrokken over de aan- of afwezigheid van klinisch relevante verschillen tussen de twee groepen. De keuze tussen radiotherapie of chirurgie zal gemaakt moeten worden op basis van de overwegingen van zorgprofessionals en patiënten, zoals hieronder beschreven.

De gerandomiseerde studies werden verricht voor 2000. Inductiechemotherapie was toen de trend, maar wordt voor het T3 larynxcarcinoom niet meer gegeven. De trend is nu cisplatin gecombineerde chemoradiatie. De gegeven radiotherapie was suboptimaal: geen gebruik van Intensity Modulated RadioTherapy (IMRT) of Volumetric-Modulated Arc Therapy (VMAT), geen beeldgeleide radiotherapie, alleen standaardfractionering. Daardoor zijn de resulaten van deze drie RCT's maar van beperkte waarde voor de huidige praktijk. Vandaar dat hieronder ook observationele studies worden beschreven.

In een meta-analyse van Tang (2018) werden resultaten van 15 studies met cumulatief 6208 patiënten met T3-T4 larynxcarcinoom geanalyseerd. TLE werd uitgevoerd bij n=2696, niet chirurgische behandeling bij 3592 patiënten. Voor de subgroep met T3 carcinoom was de algehele overleving niet verschillend tussen de twee therapie opties. De niet-chirurgische behandeling was niet opgesplitst naar radiotherapie en chemoradiatie.

In de National Cancer Database werden 2622 patiënten met een T3N0 larynxcarcinoom geanalyseerd, 657 behandeld met chirurgie (met adjuvante (chemo)radiatie), 1965 met (chemo)radiatie, waarvan 570 met geaccelereerde radiotherapie (Ko, 2017). Alleen data van de algehele overleving waren beschikbaar. Er was geen verschil in voor bekende confounders gecorrigeerde 5-jaars algehele overleving tussen chirurgie en (chemo)radiotherapie, eveneens niet tussen chemoradiatie en radiotherapie alleen. Nadeel van deze studie is dat selectiebias een rol zal hebben gespeeld, en dat er geen data bekend zijn van de ziektevrije overleving. Zo kan de eventuele meerwaarde in locoregionale controle van geaccelereerde radiotherapie ten opzichte van conventioneel eenmaal dagelijkse radiotherapie, dan wel chemoradiatie niet worden aangetoond. In een vervolgpublicatie van de National Cancer Database uit 2019 (Bates, 2019) werden alle T3 patiënten geanalyseerd, 1044 behandeld met chirurgie en 6525 met chemoradiatie. De resultaten waren gelijk aan die in de studie van Ko (2017).

Geaccelereerde radiotherapie voor hoofd-halsplaveiselcelcarcinoom kan leiden tot een 10% hogere lokale controle ten opzichte van een standaard schema. Dit werd aangetoond in de DAHANCA studie (Overgaard, 2003) en bevestigd in een tweede internationale gerandomiseerde studie (IAEA-ACC) (Overgaard, 2010). Het voordeel van geaccelereerde radiotherapie werd gezien voor o.a. het larynxcarcinoom en marginaal voor T3-

T4 tumoren. Alhoewel er dus geen gerandomiseerde studies bestaan voor alleen het T3 larynxcarcinoom wordt dit schema in Nederland vaak gebruikt als alternatief voor chemoradiatie bij gevorderde larynxcarcinomen.

Met betrekking tot de rol van het volume van de tumor en de effectiviteit van primaire radiotherapie of chemoradiatie is de literatuur niet eenduidig. Twee Amerikaanse studies hebben een indicatie gegeven van het tumorvolume waarboven de kans op lokale controle met primaire radiotherapie duidelijk afnam. De studie van Pameijer (1997) onder 42 patiënten met glottische tumoren gaf aan dat radiotherapie met name effectief was bij patiënten met een tumorvolume tot 3,5 cm^3. De studie van Mancuso (1999) onder 63 patiënten met een supraglottische tumor gaf aan dat radiotherapie met name effectief was bij patienten met een tumorvolume tot 6 cm^3. Dit betreft echter oude data, waarbij geen geaccelereerde radiotherapie werd toegepast.
In de ARCON studie werden 345 patiënten met uitgebreide T2-T4 larynxcarcinoom ingesloten (Janssens, 2014). Van de 345 gerandomiseerde patiënten hadden er 143 een T3 larynxcarcinoom. In deze studie werd geaccelereerde radiotherapie (64 tot 68 Gy in 5 ½ week) +/- Nicotinamide en carbogeen gegeven. In deze studie werd geen relatie gezien tussen tumorvolume en lokale controle. In een publicatie uit Utrecht (Van Bockel, 2013) onder 150 patiënten die behandeld waren met geaccelereerde radiotherapie werd wel een relatie gezien tussen tumorvolume en lokale controle. Echter een duidelijke afkapwaarde werd niet gevonden.

Op basis van deze studies kan gesteld worden dat er voor het T3 larynxcarcinoom een relatie lijkt te bestaan tussen tumorvolume en kans op lokale controle met standaard gefractioneerde radiotherapie, onduidelijk is of dit ook geldt voor geaccelereerde radiotherapie. Overweeg bij de keuze voor primaire radiotherapie voor het T3 larynxcarcinoom een geaccelereerd schema. Geaccelereerde radiotherapie leidt tot meer acute toxiciteit, maar geen toename in late toxiciteit (DAHANCA). Overweeg het tumor volume mee te laten wegen bij de keuze tussen primaire radiotherapie en chemoradiatie.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Naast lokale controle en ziektevrije overleving is het aannemelijk dat kwaliteit van leven, behoud van zelfstandigheid (Festen, 2021) en functie van de larynx van belang zijn voor patiënten. Het doel van de behandeling van T3 larynxtumoren is naast oncologische controle dan ook om orgaansparend te werk te gaan. Er zijn geen studies gevonden waarin (chemo-)radiotherapie versus chirurgie met postoperatieve (chemo)radiatie wordt onderzocht met betrekking tot de kwaliteit van leven en larynxfunctie. Bij gelijke oncologische resultaten zou een voordeel van primaire (chemo-) radiotherapie kunnen zijn dat patiënten hun normale spreekfunctie behouden, wat de kwaliteit van leven voor patiënten vergroot. In een deel van deze patiënten zal de in opzet larynxsparende behandeling resulteren in een disfunctionele larynx en/of een lokaal recidief (rond de 25%). Voor deze patiënten geldt dat zij tracheotomie afhankelijk worden, dan wel alsnog een laryngopharyngectomie moet ondergaan. Een studie op basis van data van alle patiënten die in Nederland tussen 1991 en 2010 gediagnosticeerd zijn met een hypofarynx carcinoom liet zien dat na vijf jaar een salvage/functionele TLE was verricht bij 7% van de patiënten die met radiotherapie alleen waren behandeld en bij 4% van de patiënten die met chemoradiatie waren behandeld (Petersen, 2018b). Het is echter onduidelijk welke waarde patiënten hechten aan deze voor- en nadelen omdat dit nooit is onderzocht.

Het is dus belangrijk alle risico's en mogelijke complicaties mee te nemen, en alle voor- en nadelen met een patiënt te bespreken. Hiervoor kan een hulpmiddel zoals een keuzehulp worden gebruikt, er is een keuzehulp ontwikkeld die momenteel geëvalueerd wordt (Petersen, 2019).

Het streven is om een patiënt met zo min mogelijk verschillende modaliteiten te hoeven behandelen. De voorkeur bij primaire radiotherapie gaat uit naar geaccelereerde radiotherapie. Chemoradiotherapie bestaat uit twee modaliteiten, maar heeft de voorkeur bij klieren groter dan 3 cm en/of extranodale groei, gezien de hogere regionale controle ten opzichte van radiotherapie alleen. Gezien de toxiciteit van de behandeling dienen patiënten in principe niet ouder dan 70 jaar te zijn en een WHO 0 tot 1 te hebben om in aanmerking te komen voor chemoradiatie. Bij een deel van de patiënten zal salvage chirurgie nodig zijn. Het uitvoeren van een totale laryngectomie na chemoradiatie kan leiden tot complicaties. Er is een meta-analyse beschikbaar waarin een overzicht van deze complicaties wordt gegeven, gebaseerd op 50 studies waarin 3292 patiënten zijn geïncludeerd. Bij een salvage laryngectomie was het risico op een complicatie 67,5%, waarbij een faryngocutane fistel de meest voorkomende complicatie was (28,9%). Hierbij werd geen significant verschil gevonden in faryngocutane fistels tussen een salvage laryngectomie na radiotherapie alleen (233/1048) of na chemoradiatie (243/820) (Hasan, 2017). In een Amerikaanse studie werd de incidentie van postoperatieve complicaties vergeleken tussen patiënten die een salvage totale laryngectomie hadden ondergaan (n=70) en patiënten die een primaire totale laryngectomie hadden ondergaan (n=113) (Ganly, 2005). Een salvage laryngectomie na chemoradiotherapie was geassocieerd met frequentere postoperatieve lokale complicaties dan een primaire laryngectomie (44,7% versus 24,8%). Dit betreft vooral wondgenezingsproblemen, met name de ontwikkeling van een faryngocutane fistel (12,4% versus 31,6%). Voor een salvage laryngectomie na radiotherapie alleen werden geen significante verschillen gevonden met een primaire laryngectomie wat betreft lokale complicaties (21,9%) en faryngocutane fistels (15,6%). Primaire chemoradiatie is een onafhankelijke voorspeller voor lokale wondgenezingsproblemen en faryngocutane fistel (Ganly, 2005).

Ook zal niet bij iedereen nog een operatie mogelijk zijn, bijvoorbeeld in verband met verdere groei van de tumor, hoewel aanvankelijk chirurgie nog een optie was.

Bij primaire chirurgie zal bij de grote meerderheid een indicatie zijn voor adjuvante radiotherapie met of zonder chemotherapie. Bij primair (chemo-)radiatie zal de behandeling beperkt kunnen worden tot één of twee modaliteiten. Primaire chirurgie heeft de voorkeur indien er sprake is van een disfunctionele larynx voor aanvang van de therapie, zoals ernstige slikklachten en/of stridor. Dit omdat dan verwacht mag worden dat deze functies onvoldoende terugkeren.

Kosten (middelenbeslag)
Er is een studie over kosten gepubliceerd (Davis, 2005). Het gaat om een Amerikaanse modelleringsstudie waarvoor data werden gebruikt uit trials, case-series, meta-analyses en Medicare diagnosis related group reimbursement rates. De studie is uitgevoerd vanuit het perspectief van een 'health care payer'. Deze studie suggereert dat chirurgie ongeveer 3000 dollar goedkoper is dan radiotherapie. Belangrijke kanttekeningen zijn dat deze studie ongeveer 20 jaar geleden is uitgevoerd, gebaseerd op studies die nog langer geleden zijn uitgevoerd, waarbij het kans op een lokaal recidief (dus extra kosten voor salvage chirurgie) hoger was dar met de recente (chemo)radiotherapie.

Aanvaardbaarheid, haalbaarheid en implementatie
Er wordt geen effect verwacht van de aanbeveling op de gezondheidsgelijkheid. Ook worden er geen belemmerende factoren verwacht op het gebied van implementatie van de interventies.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De behandeling van T3 larynxcarcinoom kan plaatsvinden met primaire (chemo)radiatie en met primaire totale laryngectomie afhankelijk van de pathologie uitslag gevolgd door radiotherapie dan wel chemoradiatie. De werkgroep kan op basis van de literatuur geen voorkeur aangeven voor primaire chemoradiatie of primaire totale laryngectomie met postoperatieve (chemo-)radiatie. TLE heeft als voordeel een mogelijk betere overleving, maar als nadeel verlies van de normale spraak en het feit dat nagenoeg alle patiënten alsnog aanvullend (chemo)radiatie krijgen. Het voordeel van larynxsparend beleid is behoud van de natuurlijke stem bij ongeveer 70% van de patiënten. Om deze reden wordt vaak gekozen voor (chemo)radiatie. Daarentegen brengt een salvage laryngectomie (na (chemo)radiatie) mogelijk een hoger risico op wondgenezingsproblemen (onder andere fistels) met zich mee in vergelijking met een primaire laryngectomie en is dit ook niet altijd meer mogelijk.
Op basis van de RCT's en observationele studies lijkt de algehele overleving voor chemoradiatie, geaccelereerde radiotherapie en chirurgie gelijk. De werkgroep is van mening dat patiënten door de verschillende complicatie- en toxiciteitspatronen die ontstaan wegens de aard van de interventies een voorkeur voor één van de drie interventies kunnen hebben. De werkgroep acht het daarom belangrijk dat de voor- en nadelen van de mogelijke interventies besproken worden.

Het voordeel van primaire geaccelereerde radiotherapie is dat volstaan kan worden met één modaliteit, met waarschijnlijk een lagere toxiciteit. Vergelijkende studies naar de meerwaarde van chemoradiotherapie ten opzichte van geaccelereerde radiotherapie bij het T3 larynxcarcinoom ontbreken. In verband met de toxiciteit van chemoradiatie komen in principe alleen patiënten tot en met 70 jaar en een WHO 0 tot 1 hier voor in aanmerking. De halsklierstatus (klieren groter dan 3 cm, extranodale groei) en het tumorvolume (> 3,5 cc voor glottische tumoren en > 6 cc voor supraglottische tumoren) vormen een indicatie om de radiotherapie te combineren met chemotherapie.

Er is een voorkeur voor primaire TLE bij een disfunctionele larynx voor aanvang van de therapie.

Onderbouwing

Achtergrond

In 1988 werd door de NWHHT een retrospectieve studie verricht naar resultaten van 511 patiënten met een T3 plaveiselcelcarcinoom van de larynx, behandeld van 1975 tot 1984. De verhouding totale laryngectomie (TLE) ten opzichte van primaire radiotherapie was 60% versus 40% respectievelijk. De 6-jaarsoverleving was voor primaire radiotherapie gelijk aan primaire TLE, maar beter bij TLE gevolgd door postoperatieve radiotherapie (Terhaard, 1992). De lokale controle na drie jaar met primaire radiotherapie was 53%, echter er was een significante dosis-respons relatie (Terhaard, 1991).

Een enquête bij de hoofd-halscentra in Nederland (Doornaert, 2015) toonde overeenkomsten maar ook

verschillen in de behandeling van T3 larynxcarcinomen. De belangrijkste behandelopties voor het T3 larynxcarcinoom zijn chirurgie dan wel conventionele radiotherapie (35 x 2 Gy in 7 weken), geaccelereerde radiotherapie, chemoradiatie en radiotherapie met cetuximab. Welke van deze behandelopties de beste kans geeft op overleving, kwaliteit van leven, locoregionale controle, larynxsparing en kans op complicaties is niet geheel duidelijk. Met name niet bij gevorderde leeftijd (70+), comorbiditeit, een groot tumorvolume en reeds ernstig verminderde larynxfunctie (uitend in ernstige kortademigheid en slikklachten), mannelijk geslacht of verminderde mobiliteit van de stemband.

In de studie van Petersen (2018a) werd een predictiemodel ontwikkeld voor vijfjaarsoverleving bij gevorderd larynxcarcinoom (T3 en T4). De C-index van het model was echter laag (0,59) en de behandelmodaliteit (chirurgie of radiotherapie) bleek geen voorspellende waarde te hebben voor de vijfjaarsoverleving.

Conclusies

Local control (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy on local control when compared with surgery in patients with a T3 laryngeal carcinoma *Sources: (Bhalavat, 2003)*

Locoregional control (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy on locoregional control when compared with surgery in patients with a T3 laryngeal carcinoma *Sources: (Bhalavat, 2003)*

Overall survival (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy on overall survival when compared with total laryngectomy in patients with a T3 laryngeal carcinoma *Sources: (Wolf, 1991; Richard, 1993; Bhalavat, 2003)*

Disease-free survival (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy on disease-free survival when compared with total laryngectomy in patients with a T3 laryngeal carcinoma *Sources: (Wolf, 1991; Richard, 1993; Bhalavat, 2003)*

Recurrence-free survival, quality of life, (a/dys)functional larynx (tube feeding, tracheotomy) (important outcomes)

No GRADE	
	Sources: -

Larynx preservation (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy on larynx preservation when compared with total laryngectomy in patients with a T3 laryngeal carcinoma
	Sources: (Wolf, 1991; Richard, 1993; Bhalavat, 2003)

Acute and late toxicity and complications (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy on acute and late toxicity and complications when compared with total laryngectomy in patients with a T3 laryngeal carcinoma
	Sources: (Wolf, 1991; Richard, 1993; Bhalavat, 2003)

Samenvatting literatuur

Description of studies
Wolf (1991) performed a multi-institutional, randomized controlled trial in the United States. Patients with biopsy-proved, previously untreated stage III or IV squamous carcinoma of the larynx according to classification system of AJCC, were included. Patients with a T1N1 carcinoma, unresectable cancer, distant metastases, previous radiation therapy to head or neck or previous cancer, were excluded. In total 332 patients were included, 166 were randomly assigned to induction chemotherapy and radiotherapy and 166 to surgical resection and radiotherapy. Induction chemotherapy consisted of cisplatin (100 mg/m^2) given as rapid intravenous infusion followed by continuous 24-hour intravenous infusion of fluorouracil (1000 mg/m^2 per day) for five days. Chemotherapy was repeated on day 22 and 43. After the second cycle, patients with a partial or complete response received a third cycle of chemotherapy followed by definitive radiotherapy. Patients who did not achieve at least a partial response underwent surgery and postoperative radiotherapy.

Radiotherapy consisted of 6600 to 7600 cGy to the primary tumor site. Doses to the nodes varied according to initial node size. All areas presumed to be at risk for microscopic disease received at least 5000 to 5040 cGy. In total, there were 31 patients (10%) classified with a T1 or T2 tumor, 216 patients (65%) with a T3 tumor and 85 patients (25%) with a T4 tumor. Of the patients with a T3 tumor, 107 (49%) received induction chemotherapy and radiotherapy and 109 patients (51%) underwent a surgical resection of the larynx. There were no significant baseline differences between groups. Median follow-up was 33 months (range 11 to 62). Outcome measures included overall survival, disease-free survival, larynx preservation and toxicity and complications.

Richard (1998) performed a multi-institutional, randomized controlled trial in France. Patients with a biopsy-proven squamous cell carcinoma of the larynx classified as T3, N0, N2, N2 a or b, considered for total laryngectomy, were included. Patients with a T1N1 carcinoma, unresectable cancer, distant metastases, previous radiation therapy to head or neck or previous cancer, were excluded. In total 68 patient were

included, 36 were randomly assigned to chemotherapy followed by either radiotherapy or by total laryngectomy and 32 patients were assigned to treatment by total laryngectomy followed by radiotherapy. Chemotherapy consisted of cisplatin (100 mg/m^2) given as rapid intravenous infusion followed by continuous 24-hour intravenous infusion of fluorouracil (1000 mg/m^2 per day) for five days. The second cycle of chemotherapy was administered on day 22 and the third cycle on day 43. Tumour response was assessed by laryngoscopy before the start of the third cycle. In case of tumour progression, the third cycle of chemotherapy was omitted and surgery was performed. Median follow-up was 8.3 years. Outcome measures included overall survival, disease-free survival, larynx preservation and toxicity and complications.

Bhalavat (2003) performed a randomized controlled trial in India. Patients with a T3/T4 squamous carcinoma of the supraglottic larynx and ipsilateral early nodal disease (N0-2b) and a good general condition were included. Patients aged above 70 or with bilateral nodal disease at presentation or in stridor were excluded. In total, 72 patients were included in the study, 33 were randomly assigned to the radical radiation therapy with salvage surgery group and 39 patients were assigned to the radical surgery with post-operative radiation group. Radical surgery included total laryngectomy, near-total laryngectomy or laryngopharyngectomy with or without nodal dissection. Post-operative radiation started within 4 to 6 weeks from surgery. In the radical radiation therapy group, salvage radical surgery was offered for residual/recurrent lesions. In total, there were 55 patients (86%) classified with T3 stage tumor and 9 patients (14%) with T4 stage tumor. In the intervention group 28 patients (84%) and in the control group 27 patients (81%) were classified with T3 stage tumor. There were no significant baseline differences between groups. Minimum follow-up was two years. Outcome measures included local control, locoregional control, overall survival, disease-free survival, larynx preservation and toxicity and complications.

Results
1.   Local control
One study reported local control (Bhalavat, 2003). Bhalavat (2003) reported local control in 20/27 patients (74%) in the radiotherapy group and 28/28 patients (100%) in the surgical group.

2.   Locoregional control
One study reported locoregional control (Bhalavat, 2003). Bhalavat (2003) reported locoregional control in 24/27 patients (88%) in the radiotherapy group and 28/28 patients (100%) in the surgical group.

3.   Overall survival
Three studies reported overall survival. Two studies found no clinically relevant difference in overall survival between the radiotherapy and surgical group (Wolf, 1991; Bhalavat, 2003).

Wolf (1991) reported a two-year survival rate of 68 percent (95%CI 60 to 76) in the radiotherapy group and 68 percent (95% CI 60 to 75) in the surgical group (p=0.9864).

Richard (1998) reported a two-year survival rate in the radiotherapy group of 69 percent and in the surgical group of 84 percent (p=0.006).

Bhalavat (2003) reported, in a sub-analysis for T3 staged patients, a five-year overall survival rate of 75 percent in the radiotherapy group and 75 percent in the surgical group (RR 1.04 (95%CI 0.42 to 2.56)).

4. Disease-free survival
All three studies reported disease-free survival.

Wolf (1998) reported that disease-free survival seemed to be worse in the radiotherapy group compared with the surgery group (p=0.1195). No further information was provided in the text, but the graph shows that up to about 27 months, the difference between the groups was less than 5%, while from 27 months up to 63 months, there was a difference of more than 5% in favour of the surgery group.

Richard (1993) found a clinically relevant difference in disease-free survival between the radiotherapy group and the surgical group in favor of the surgical group (P=0.02). No further information was given in the text, but the graph shows that from about 12 months up to 120 months, the difference in disease-free survival between the groups is more than 5%.

Bhalavat (2003) reported, in a sub-analysis for T3 staged patients, five-year disease free survival rates of 50 percent in the radiotherapy group and 80 percent in the surgical group

5. Recurrence-free survival
No studies reported recurrence-free survival.

6. Quality of life
No studies reported quality of life.

7. (a/dys)functional larynx (tube feeding, tracheotomy)
No studies reported data on (a/dys)functional larynx.

8. Larynx preservation
Three studies reported data on larynx preservation (Wolf, 1991; Richard, 1993; Bhalavat, 2003).

Wolf (1991) reported larynx preservation in the radiotherapy group of 64 percent.

Richard (1993) reported larynx preservation in the radiotherapy group of 42 percent. Bhalavat (2003) reported larynx/vocal preservation in the radiotherapy group of 60 percent.

9. Acute and late toxicity and complications
Three studies reported acute and late toxicity and complications.

Wolf (1991) reported one death in the radiotherapy group (0,6%) and 12 cases (7%) of toxicity necessitating to discontinue chemotherapy. Wolf (1991) also reported 63 cases of grade two mucositis in the primary radiotherapy group (38%) and 40 cases who received adjuvant radiotherapy following surgery (24%) (RR=1.57 95%CI 1.19 to 2.08).

Richard (1993) reported 3 cases (8%) with grade three or four toxicity in the radiotherapy group.

Bhalavat (2003) reported one post-operative death (3%) and seven other post-operative complications (18%) in the surgery group. There were no deaths or other post-operative complications reported in the radiotherapy group.

<u>Level of evidence of the literature</u>
The level of evidence regarding the outcome measure **local control** was downgraded by three levels because of study limitations (-1; Risk of Bias regarding allocation sequence generation and misclassification bias) and number of included patients (-2; Imprecision due to low sample size and small amount of events in a single study). Publication bias was not assessed.

The level of evidence regarding the outcome measure **locoregional control** was downgraded by three levels because of study limitations (-1; Risk of Bias regarding allocation sequence generation and misclassification bias) and number of included patients (-2; Imprecision due to low sample size and small amount of events in a single study). Publication bias was not assessed.

The level of evidence regarding the outcome measure **overall survival** was downgraded by four levels because of study limitations (-1; Risk of Bias regarding allocation sequence generation, study stopped prematurely and misclassification bias), conflicting results (-1; inconsistency because one study showed worse overall survival in the radiotherapy group and two studies showed no difference), applicability (-1; Bias due to indirectness because one study reported T3 and T4 staged tumors and one study reported patients with 100 percent vocal cord fixation); number of included patients (-1; imprecision because of confidence intervals crossing the boundary of clinical relevance). Publication bias was not assessed.

The level of evidence regarding the outcome measure **disease-free survival** was downgraded by three levels because of study limitations (-1; Risk of Bias regarding allocation sequence generation and concealment, study stopped prematurely and misclassification bias), applicability (bias due to indirectness because one study reported T3 and T4 staged tumors and one study reported patients with 100 percent vocal cord fixation), number of included patients (-1; Imprecision due to low sample size and small amount of events). Publication bias was not assessed.

The level of evidence regarding the outcome measure **larynx preservation** was downgraded by three levels because of study limitations (-1; Risk of Bias regarding allocation sequence generation and concealment, study stopped prematurely and misclassification bias); applicability (bias due to indirectness because one study reported T3 and T4 staged tumors and one study reported patients with 100 percent vocal cord fixation), number of included patients (-1; Imprecision due to low number of included patients). Publication bias was not assessed.

The level of evidence regarding the outcome measure **acute and late toxicity and complications** was downgraded by three levels because of study limitations (-1; Risk of Bias regarding allocation sequence generation, study stopped prematurely and misclassification bias), applicability (-1; Bias due to indirectness

because two studies reported T3 and T4 staged tumors and one study reported patients with 100 percent vocal cord fixation); number of included patients (-1; imprecision because of low sample size and confidence intervals including the possibility of a negative effect). Publication bias was not assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the benefits and risks of primary radiotherapy compared with total laryngectomy for patients with a T3 laryngeal carcinoma?

P: Patients with a T3 laryngeal carcinoma.
I: Primary radiotherapy (conventional/ accelerated/ chemoradiation/ radiotherapy with targeted treatment).
C: Surgery (total laryngectomy).
O: Local control, locoregional control, survival (OS, DFS, RFS), quality of life, (a/dys)functional larynx (tube feeding, tracheotomy), larynx preservation, acute and late toxicity and complications.

Relevant outcome measures
The guideline development group considered local control, locoregional control, and overall survival as critical outcome measures for decision making; and disease-free survival, recurrence-free survival, quality of life, (a/dys)functional larynx (tube feeding, tracheotomy), larynx preservation, acute and late toxicity and complications as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as:

- Local control and locoregional control: 0.8 or 1.25 as borders for risk or odds ratios.
- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Recurrence-free survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Quality of life: a difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- (a/dys)functional larynx (tube feeding, tracheotomy): statistically significant difference.
- Larynx preservation: statistically significant difference.
- Acute and late toxicity/complications: statistically significant difference in grade ≥3 adverse event rate.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until February 23, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 695 hits (101 SRs and 594 RCTs). Studies were selected based on the following criteria: (1) study only included patients with a T3 laryngeal carcinoma or included a subgroup analysis for patients with a T3 laryngeal carcinoma; (2) a direct comparison between radiotherapy and surgery was made; (3) SR, RCT; (4) full-text English language publication. The systematic reviews were screened first, 13 studies

were initially selected based on title and abstract screening. After reading the full-text paper, all 13 reviews were excluded (see the table with reasons for exclusion under the tab Methods). The review by Luo (2015) was excluded because most studies did not make a direct comparison between radiotherapy and surgery, however, this review identified three relevant RCTs: Wolf (1991), Richard (1998) and Bhalavat (2003). The review by Tang was excluded because only retrospective studies were included, however, a comprehensive search was performed in Medline, Embase and the Cochrane library in October 2016. We therefore decided to only screen RCTs that were published from 2016 onwards. Two studies were initially selected based on title and abstract screening. After reading the full-text paper, both studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results

Three RCTs (Wolf, 1991; Richard, 1998; Bhalavat, 2003) were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Primaire Behandeling N3 hypofarynx, orofarynx- en larynxcarcinoom

Uitgangsvraag

Welke volgorde van behandelmodaliteiten heeft de voorkeur bij patiënten met een N3 hypofarynx, orofarynx- en larynxcarcinoom: Eerst een halsklierdissectie gevolgd door (chemo)radiotherapie, of (chemo)radiotherapie gevolgd door een halsklierdissectie wanneer nodig?

Aanbeveling

Op basis van de huidige literatuur, praktijkkennis en patiëntenvoorkeuren kan geen aanbeveling gedaan worden welke volgorde van behandeling, chemoradiatie gevolgd door een halsklierdissectie dan wel een halsklierdissectie gevolgd door chemoradiatie, de voorkeur verdient.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De systematic reviews die werden gevonden bij deze uitgangsvraag (Elicin, 2016 en Gupta, 2004) vergeleken steeds een halsklierdissectie met daarna chemoradiotherapie versus chemoradiotherapie alleen. Beide studies zijn gebaseerd op de oude TNM-7 classificatie. Bij de vergelijkingen die we hebben gevonden werd er geen halsklierdissectie meer gedaan na de chemoradiotherapie. Om deze reden is het niet mogelijk om op basis van de literatuur tot een eenduidige conclusie te komen welke volgorde van interventies beter is.

Echter, wanneer na chemoradiotherapie een afwachtend beleid wordt gevoerd lijkt dit geen negatieve invloed op de overleving te hebben in vergelijking met wanneer aansluitend een halsklierdissectie wordt verricht (zie module 13.4).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Er zijn geen studies verricht die het verschil voor patiënten tussen de verschillende volgorde van behandeling vergelijken. Echter het starten met de (chemo)radiatie kan als nadeel hebben dat een salvage halsklierdissectie een hoger risico geeft op complicaties. Het starten met een halsklierdissectie heeft als nadeel dat de behandeling van de primaire tumor vertraging op kan lopen.

Kosten (middelenbeslag)
Er zijn geen studies verricht die het verschil in kosten tussen de verschillende volgorden van behandeling vergelijken.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Omdat er geen studies zijn gevonden die het verschil in volgorde van behandelingen hebben vergeleken, en er ook geen duidelijke voorkeur lijkt te zijn vanuit de praktijk of de patiënten, kan er op dit moment geen aanbeveling worden gedaan voor één van de opties.

Onderbouwing

Achtergrond

Een inventarisatie in Nederland door de Richtlijnencommissie van de NWHTT leerde dat bij het larynxcarcinoom het beleid ten aanzien van de N3 hals zeer verschillend was tussen de verschillende centra. Wanneer de N3 lymfekliermetastase op voorhand resectabel is worden óf de primaire tumor en hals behandeld met (chemo)radiatie en afhankelijk van de responsevaluatie (maar met een hoge kans hierop) een salvage halsklierdissectie verricht, óf eerst een halsklierdissectie verricht en vervolgens de primaire tumor en de hals behandeld met (chemo)radiatie. Het is aannemelijk dat dit verschil ook aanwezig is bij andere primaire tumoren die vaak primair met (chemo)radiatie behandeld worden. Het starten met de (chemo)radiatie heeft als nadeel dat het residu van de N3 lymfekliermetastase irresectabel geworden kan zijn en een salvage halsklierdissectie een hoger risico heeft op complicaties. Het starten met een halsklierdissectie heeft als nadeel dat de behandeling van de primaire tumor vertraagd wordt door de halsklierdissectie.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question: Which order of interventions is preferred for N3 hypopharynx, oropharynx and larynx carcinoma patients: Up-front neck dissection followed by (chemo)-radiotherapy, or (chemo)-radiotherapy followed by neck dissection if necessary?

P: = N3 hypopharynx, oropharynx and larynx carcinoma.
I: = Up-front neck dissection followed by (chemo)-radio therapy.
C: = (Chemo)-radio therapy followed by neck dissection if necessary.
O: = Overall survival (3 to 5 year follow up), disease free survival, disease specific survival, recurrence, morbidity, surgery complications, adverse events.

Relevant outcome measures
The guideline development group considered overall survival, disease free survival and recurrence as a critical outcome measure for decision making; the group considered morbidity, surgery complications, and adverse events as an important outcome measure for decision making.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) or >3% and HR< 0.7 in overall survival.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 17th of February 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: methodology (RCT's and SR's were included), suitability with the PICO. Two studies were initially selected based on title and abstract screening. After reading the full text, both studies were excluded (see the table with reasons for exclusion under the tab Methods).

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Halsklierdissectie N3 patiënten

Uitgangsvraag

Is, voor patiënten met een stadium N2/N3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben gehad, een geplande halsklierdissectie een betere optie dan een afwachtend beleid voeren, waarbij de halsklierdissectie alleen wordt uitgevoerd indien dit na responsevaluatie nodig blijkt?

Aanbeveling

Bespreek met patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom de twee mogelijke opties na behandeling met chemoradiatie: 1) hoe dan ook een nekdissectie plannen, of 2) de respons op chemoradiatie evalueren middels PET-CT en bij onvoldoende of onduidelijke respons pas een nekdissectie verrichten.

Benoem dat:

- een afwachtend beleid niet tot een slechtere overleving lijkt te leiden;
- een afwachtend beleid niet lijkt te leiden tot meer recidief;
- een afwachtend beleid resulteert in minder chirurgische complicaties.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Om de vraag te beantwoorden of het beter is een afwachtend beleid op basis van een responsevaluatie met PET-CT te voeren of een nekdissectie te plannen na een chemoradiotherapie bij patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom, is een onderzoek uitgevoerd dat de non-inferiority toetst van een afwachtend beleid. Uit dit onderzoek blijkt dat het afwachtende beleid inderdaad niet leidt tot een slechtere overleving. Daarbij is het aantal adverse events en complicaties lager in de groep waar een afwachtend beleid wordt gevoerd (met lage bewijskracht). De meerjarenoverleving, toxiciteit, schoudermorbiditeit en de ziektevrije overleving zijn niet meegenomen. Overigens is deze studie nog gebaseerd op de oude TNM-7 classificatie, wat de geldende classificatie was ten tijde van de inclusie van de patiënten in de studie, niet op TNM 8. Het is lastig om dit goed te vertalen naar de nieuwe classificatie; de werkgroep concludeert dan ook dat dit een kennislacune is.

Tevens bleek een afwachtend beleid meer kosten-effectief (per persoon £1,492 en 0.08 QALYs per persoon). In een uitgebreidere studie naar kosten-effectiviteit (Fu, 2021) werden drie verschillende manieren van surveillance vergeleken met geplande nekdissectie, waarbij een PET-CT surveillance met herhaalde PET-scan na 6 maanden na chemoradiatie bij onduidelijke respons het meest kosten-effectief bleek. Er zijn geen studies beschikbaar die de haalbaarheid en aanvaardbaarheid van surveillance onderzochten.

Een vereiste voor het uitvoeren van een nekdissectie bij onvoldoende respons is de mogelijkheid om een PET-CT te maken. Uit de studie van Mehanna et al. blijkt dat er een hoge concordantie was tussen de beoordeling van de PET-CT door de (willekeurige) lokale specialist en de beoordeling door de ervaren

specialisten van de studie (92% voor respons van de primaire tumor en 97% voor de lymfkliermetastasen). Hieruit kan geconcludeerd worden dat het haalbaar is om de surveillance methode te implementeren in de kliniek.

Gezien beide methoden (een afwachtend beleid of een geplande nekdissectie na een chemoradiotherapie), gebaseerd op de huidige literatuur met enige onzekerheid, leiden tot een gelijke overleving, zouden de beide opties aan patiënten kunnen worden voorgelegd. Samen beslissen zal de acceptatie van patiënten maximaliseren. Daarbij is het wel goed om op te merken dat in Nederland het afwachtende beleid inmiddels vrijwel overal standaardpraktijk is. Er zijn geen duidelijke argumenten vóór een geplande nekdissectie, wat het voor de patiënt minder voor de hand liggend maakt om wel voor een geplande nekdissectie te kiezen.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er lijkt geen nadeel te zijn van het voeren van een afwachtend beleid kijkend naar de verschillende uitkomstmaten op basis van de huidige literatuur. Het aantal bijwerkingen en complicaties lijkt lager in de groep waar een afwachtend beleid wordt gevoerd.

De gradering van bewijs is laag en gebaseerd op één enkele studie, waardoor er geen sterke aanbeveling kan worden gedaan voor één van beide opties. Om deze reden is de keuze om wel of niet meteen een nekdissectie te plannen na chemotherapie een overweging die goed met de patiënt besproken kan worden. De aanbeveling is geformuleerd met de onderwerpen die in elk geval aan de patiënt voorgelegd kunnen worden.

Onderbouwing

Achtergrond

In de Nederlandse zorg bestaat er praktijkvariatie op het gebied van een halsklierdissectie bij patiënten met een stadium N2/3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben ondergaan. In sommige centra wordt als standaardprocedure een halsklierdissectie uitgevoerd, terwijl in andere centra een afwachtend beleid wordt gevoerd waarbij halsklierdissectie alleen wordt uitgevoerd indien dit uit responsevaluatie op basis van beeldvorming nodig blijkt te zijn. Er is geen consensus over wat de beste strategie is.

Conclusies

Overall survival (2 years) (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in little to no difference in overall survival compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Adverse events (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in less adverse events compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Recurrence (critical outcome measure)

Low GRADE	Surveillance, where neck dissection is only performed based on PET-CT, may result in little to no difference in recurrence compared to planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

- GRADE	No evidence was found regarding the effect of surveillance, where neck dissection is only performed based on PET-CT, on toxicity, shoulder mobility and disease-free survival, when compared with planned neck dissection in patients with stage N2/3 hypopharynx, oropharynx or larynx carcinoma who have received chemoradiotherapy. *Sources: (Mehanna, 2016)*

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

Zoekvraag
Welke behandelstrategie is beter voor patiënten met een stadium N2/N3 hypofarynx-, orofarynx- of larynxcarcinoom die als primaire behandeling chemoradiatie hebben gehad: een geplande halsklierdissectie uitvoeren, of een afwachtend beleid voeren, waarbij de halsklierdissectie alleen wordt uitgevoerd indien dit na responsevaluatie nodig blijkt?

P: Patients who have undergone chemoradiation for a stage N2/3 hypopharynx, oropharynx or larynx carcinoma.
I: Chemoradiation + standard neck dissection.
C: Chemoradiation + neck dissection when residual is suspected after response evaluation.
O: Survival (3 to 5 years), disease free survival, recurrence, adverse events, toxicity, shoulder mobility, surgery complications.

Relevant outcome measures
The guideline development group considered survival (3 to 5 years), disease free survival, recurrence, and adverse events as critical outcome measures for decision making; and toxicity, shoulder mobility, and surgery complications as important outcome measures for decision making.

The guideline development group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as boundaries for clinical decision-making for risk or odds ratios of neck recurrence.
- 5% difference or more (absolute) and HR< 0.7 in disease-free survival.
- 5% difference or more (absolute) or > 3% difference and HR< 0.7 in overall survival.

For the outcome measures adverse events, toxicity, shoulder mobility, and surgery complications no minimally clinically relevant difference was formulated.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 17th of February 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 287 hits. Studies were selected based on the following criteria: suitability with the PICO, methodology (RCTs and SRs were included), studies in the English or Dutch language, and available full texts. Four studies were initially selected based on title and abstract screening. After reading the full text, three studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results

One study was included in the analysis of the literature (Mehanna, 2016). Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

Mehanna (2016) conducted a randomized controlled trial (non-inferiority study) in the UK assessing the non-inferiority of PET-CT guided surveillance that could lead to neck dissection, with planned neck dissection, in patients who received chemoradiotherapy as a primary treatment. In total, 564 patients participated in the trial, of which the randomization was 1:1. All patients were evaluated 12 weeks after chemoradiotherapy, either by CT or MRI (in the planned surgery group) or PET-CT (in the surveillance group). Incomplete or equivocal response in the lymph nodes led to a neck dissection within 4 weeks in the surveillance group. There were less neck dissections in the PET-CT–guided surveillance group compared to the planned surgery group (54 versus 221). The follow-up lasted for at least 24 months after randomization, and the outcomes that were measured were survival rate (primary endpoint), disease-specific mortality, mortality from other causes, adverse events, locoregional control, surgery complications, quality of life and cost-effectiveness.

Results

Survival (2 years)

3-to-5 year survival was not measured in the included study. However, the guideline development group decided to use the 2-year survival that was reported in the study. The 2-year overall survival rate was 84.9% (95% CI, 80.7 to 89.1) in the surveillance group and 81.5% (95% CI, 76.9 to 86.3) in the planned surgery group. The hazard ratio for death with surveillance as compared with planned surgery was 0.92 (95% CI, 0.65 to 1.32); this outcome slightly favored the surveillance group and met the prespecified definition of noninferiority (an overall survival rate that was no more than 10 percentage points below the estimated 75% 2-year overall

survival rate in patients in the planned surgery group).

Recurrence
Recurrence was measured as rate of locoregional control. The 2-year rate of locoregional control was 91.9% (95% CI, 88.5 to 95.3%) in the surveillance group and 91.4% (95% CI, 87.8 to 95.0%) in the planned-surgery group, with a RR of 1.00 (95% CI, 0.95 to 1.05).

Adverse events
A total of 282 serious adverse events occurred: 169 in the planned surgery group and 113 in the surveillance group (59.9% versus 40.1%, with a RR of 1.50 (95% CI, 1.26 to 1.78)).

Disease-free survival
This outcome was not measured in the included trial.

Toxicity
This outcome was not measured in the included trial.

Shoulder mobility
This outcome was not measured in the included trial.

Complications
A total of 22 surgical complications after neck dissection were noted in the surveillance group, as compared with 83 in the planned-surgery group, with a RR of 3.77 (95% CI, 2.43 to 5.86).

<u>Level of evidence of the literature</u>
Survival (2 years)
The level of evidence regarding the outcome survival started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies (1) and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Adverse events
The level of evidence regarding the outcome adverse events started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Recurrence
The level of evidence regarding the outcome adverse events started at high as evidence originated from an RCT, and was downgraded by 2 levels due to the limited number of studies and included patients (imprecision). Publication bias could not be assessed, as there was only one study included. The certainty of the evidence was graded as low.

Toxicity, shoulder mobility, disease-free survival
The study did not report on the outcome measures toxicity, shoulder mobility and disease-free survival and therefore GRADE could not be applied, and no conclusions could be drawn.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Dosering cisplatin lokaal gevorderde tumoren

Uitgangsvraag

Welke dosering van cisplatin heeft de voorkeur in combinatie met radiotherapie bij de definitieve behandeling van lokaal gevorderde hoofd-halstumoren?

Aanbeveling

Geef patiënten tot en met 70 jaar met een locoregionaal vergevorderd plaveiselcelcarcinoom van het hoofdhalsgebied (Stadium III-IV) die een indicatie hebben voor chemoradiatie bij voorkeur concomitante chemotherapie met cisplatin (100 mg/m2 op dag 1, 22 en 43) in combinatie met conventioneel gefractioneerde radiotherapie (voorbeeld 70 Gy in zeven weken).

Op basis van bijvoorbeeld ingeschat toxiciteitsrisico kan een wekelijks (40 mg/m^2) schema een te verdedigen alternatieve optie zijn.

Overwegingen

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>
Onze systematische zoekactie in Medline en Embase resulteerde in acht RCT's (Mashhour, 2020; Sahoo, 2017; Noronha, 2018; Rawat, 2016; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012). In vier van deze RCT's werden (ook) patiënten geïncludeerd die adjuvant behandeld werden (Mashhour, 2020; Noronha, 2018; Kiyota, 2022; Tsan, 2012).

Voor beide cruciale uitkomsten (overleving en terugkeer van de kanker) werden resultaten gerapporteerd. Overleving werd gerapporteerd in vijf studies, één studie rapporteerde een slechtere overleving in de groep die wekelijks 40 mg/m^2 cisplatin kreeg, vergeleken met driewekelijks cisplatin. Het ging hierbij echter om zeer kleine aantallen patiënten die waren overleden en een ongelijke grootte van de studiearmen (10/25 versus 9/31). Eén studie rapporteerde een betere overleving in de groep die wekelijks 40 mg/m2 cisplatin kreeg in de adjuvante setting, vergeleken met driewekelijks cisplatin.

Terugkeer van de kanker werd op twee verschillende manieren gerapporteerd: het wel of niet bereiken van een complete respons op de behandeling of locoregionale controle. Informatie over het bereiken van een complete respons was beschikbaar in vijf studies. Eén studie liet zien dat de frequentie van complete respons hoger was in de groep die wekelijks cisplatin kreeg (Nanda, 2020, 81% versus 75%; 40 mg/m^2, 100% definitieve behandeling).
Twee studies lieten geen verschil zien (Mashhour, 2020, 30 mg/m^2, 50% adjuvant behandeld en 50% definitief; Rawat, 2016, 35 mg/m2, 100% definitieve behandeling). Twee studies lieten zien dat de frequentie van complete respons lager was in de groep die wekelijks cisplatin kreeg (Sahoo, 2017, 72% versus 86%; 30 mg/m^2, 100% definitieve behandeling; Nair, 2017, 75% versus 90%, 40 mg/m2, 100% definitieve behandeling). Locoregionale controle werd gerapporteerd in zes studies. In drie studies was de frequentie van locoregionale controle lager in de groep die wekelijks cisplatin kreeg, waarbij het in twee studies ging om een zeer klein aantal patiënten waarbij de kanker terugkeerde (4/29 versus 2/31 en 13/30 versus 8/30). In één van deze studies werd een dosering van 40 mg/m^2 gebruikt in de definitieve setting en in de overige twee

studies werd in de definitieve of adjuvante setting een dosering van 30 mg/m^2 gebruikt. In één studie was de frequentie van locoregionale controle hoger in de groep die wekelijks 40 mg/m^2 cisplatin kreeg in de adjuvante setting, vergeleken met driewekelijks cisplatin.

Ook voor alle belangrijke uitkomsten (ziektevrije overleving, kwaliteit van leven en bijwerkingen) werden resultaten gerapporteerd. Ziektevrije overleving werd in vier studies gerapporteerd. Eén studie (40 mg/m^2) liet een slechtere 2-jaars overleving zien in de wekelijkse behandelgroep (53% versus 65%), twee studies (30 mg/m^2 en 40 mg/m^2) lieten geen verschil zien en in één studie (40 mg/m^2) was het niet mogelijk om te bepalen of het verschil klinisch relevant was, de mediane ziektevrije overleving was echter vrijwel gelijk tussen de groepen (26,4 maanden versus 27,4 maanden).

Bijwerkingen werden in alle studies gerapporteerd. De frequentie acute bijwerkingen van graad 3 of hoger lag in één studie (30 mg/m^2) lager in de wekelijkse behandelgroep (72% versus 85%; p=0.006), terwijl in een andere studie (40 mg/m2) geen verschil werd gevonden in de frequentie van bijwerkingen van graad 3 of hoger (81% versus 80%; p=0.87), maar wel in de frequentie van graad 4 bijwerkingen (8% versus 19%; p=0.017). Een andere studie analyseerde de frequentie van niet-hematologische bijwerkingen van graad 3 of hoger,
waarbij een lagere frequentie werd gerapporteerd in de wekelijkse behandelgroep (57% versus 77%). In sommige studies werd voor afzonderlijke niet-hematologische bijwerkingen van graad 3 of hoger een lagere frequentie in de wekelijkse groep gerapporteerd, bijvoorbeeld een verschil in de frequentie van dysfagie (63% versus 26%), maar dit werd niet consistent in alle studies teruggezien. Voor hematologische bijwerkingen werd in de meerderheid van de studies geen verschil in bijwerkingen van graad 3 of hoger tussen de groepen gerapporteerd.

Kwaliteit van leven werd in één studie gerapporteerd, waarbij zowel de scores voor de Trial Outcome Index (een combinatie van drie subschalen) als de scores voor vijf subschalen werden gerapporteerd. Scores op de Trial Outcome Index lagen op alle vier de meetmomenten wat lager (wat een lagere kwaliteit van leven inhoudt) in de wekelijkse behandelgroep. Alleen op het laatste meetmoment, drie maanden na het afronden van de behandeling, ging het om een klinisch relevant verschil tussen de groepen (9.7 punten verschil op een schaal van 0 tot 96). Voor de subschalen werd een wisselend beeld gezien.

De bewijskracht voor alle uitkomstmaten was zeer laag. Er werd afgewaardeerd wegens een risico op bias omdat de randomisatie en allocatie niet beschreven waren, omdat er niet geblindeerd was (voor de uitkomst kwaliteit van leven) en omdat één van de studies voortijdig stopgezet was wegens tegenvallende inclusie. Daarnaast werd in twee gevallen afgewaardeerd voor inconsistentie wegens verschillen in gerapporteerde effecten tussen de studies. Voor alle uitkomsten werd afgewaardeerd wegens indirectheid, omdat vier studies (ook) patiënten includeerden die in de adjuvante setting behandeling werden met chemoradiatie en omdat zeven van de acht studies waren uitgevoerd in Azië. Daarnaast ging het in zes van de acht studies om kleine patiëntaantallen (range 30 tot 71) wat leidde tot brede betrouwbaarheidsintervallen waardoor afgewaardeerd werd wegens imprecisie.

Uit de geïncludeerde studies bleek dat patiënten die wekelijks cisplatin kregen over het algemeen een lagere cumulatieve dosis ontvingen vergeleken met patiënten die driewekelijks cisplatin kregen. In twee

Nederlandse retrospectieve studies werd voor patiënten waarbij dosisbeperkende toxiciteit optrad een minder goede overleving gerapporteerd (Bril, 2022; Wendrich, 2017).

In de literatuursamenvatting zijn alleen RCT's geïncludeerd. De RCT's zijn over het algemeen relatief klein en hebben hun beperkingen. Er zijn diverse niet-gerandomiseerde studies verschenen die zich met name op een vergelijking van toxiciteit hebben gericht. Hieruit komen aanwijzingen naar voren dat het wekelijks toedienen van cisplatin (40 mg/m^2) tot minder (renale) toxiciteit zou kunnen leiden (Bauml, 2019; Driessen, 2016; Espeli, 2012; Ho, 2008). Daarnaast werd er één RCT geëxcludeerd omdat deze was uitgevoerd onder patiënten met een nasofarynxcarcinoom (Lee, 2016). Deze kleine RCT uit Korea suggereerde dat een wekelijkse dosis van 40 mg/m^2 niet inferieur zou zijn aan driewekelijkse toediening van cisplatin.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Het doel van het toedienen van cisplatin in een wekelijks schema in plaats van een driewekelijks schema is het verminderen van toxiciteit, zonder duidelijke afname van de effectiviteit. Er is geen onderzoek gedaan naar de waarden en voorkeuren van patiënten wat betreft deze twee doseringsschema's. Uit een meta-analyse van 107 RCT's naar de effecten van chemotherapie bij hoofd-halstumoren (Lacas, 2021) bleek dat met het toenemen van de leeftijd het effect van het toevoegen van cisplatin aan radiotherapie afneemt, waarbij er in de leeftijdsgroep boven de 70 jaar geen positief effect is op overleving en dit positieve effect in de leeftijdsgroep 60-69 ook aanzienlijk lager is dan in de groep jonger dan 50 jaar. Het is goed om te realiseren dat in de studies ook selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van het wekelijkse doseringsschema ten opzichte van het driewekelijkse schema. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht dat de aanbeveling geen relevante impact heeft op de zorgkosten.

Aanvaardbaarheid, haalbaarheid en implementatie
Patiënten bezoeken het ziekenhuis dagelijks voor de radiotherapie, daarom is de belasting van wekelijkse ten opzichte van driewekelijkse toediening wat minder groot. .

In Nederland is de hoofd-halsoncologie gecentreerd in 8 werkgroepen, waardoor een hoge mate van expertise is gewaarborgd. Voor sommige patiënten betekent dit langere reistijden wat een belasting kan zijn. Er zijn geen aanwijzingen dat dit de therapie trouw ten nadele beïnvloedt. In het algemeen is in de centra sprake van voldoende capaciteit, hoewel er binnen financiële kaders spanningen op kunnen treden. Gezien de zeer goede onderlinge samenwerking binnen een groot team, waarvan de samenstelling en benodigde expertise is vastgesteld in de SONCOS-normen, is de kwaliteit gewaarborgd. De centra worden regelmatig gevisiteerd. Alle patiënten worden besproken binnen het multidisciplinaire overleg (MDO), waarbij ook de behandelaar aanwezig is. Hierna vindt overleg plaats met de patiënt, waarbij op basis van de adviezen uit het MDO met aandacht voor de eigen voorkeur van de patiënt een beleid wordt vastgesteld.

De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Concomitante chemotherapie met cisplatin (100 mg/m^2 dag 1,22 en 43) in combinatie met conventioneel gefractioneerde radiotherapie (voorbeeld 70 Gy in zeven weken) wordt beschouwd als de standaard in de definitieve behandeling van het plaveiselcelcarcinoom van het hoofd-halsgebied. Op basis van de beschikbare literatuur is het onzeker of het wekelijkse schema tenminste net zo effectief is als het driewekelijkse schema met minder bijwerkingen.

Retrospectieve studies geven aanwijzingen dat de wekelijkse toediening gepaard zou kunnen gaan met minder (met name nefro-)toxiciteit. Een studie met dezelfde behandeling, maar voor een andere indicatie (nasofarynxcarcinoom) suggereerde dat wekelijkse toediening in een dosis van 40 mg/m^2 niet inferieur is aan driewekelijkse toediening. De weging van argumenten voor en tegen de ene dan wel de andere behandeling dient besproken te worden met patiënten.

Onderbouwing

Achtergrond

Bij de definitieve behandeling van lokaal gevorderde hoofdhals-tumoren leidt chemoradiatie met cisplatin tot betere uitkomsten dan radiotherapie alleen. Van oudsher wordt een driewekelijks schema gebruikt met een dosering van 100 mg/m^2 cisplatin op dag 1, 22 en 43 van de radiotherapie. Echter, dit gaat gepaard met aanzienlijke toxiciteit (in het bijzonder renale toxiciteit). In Nederland krijgt tegenwoordig ongeveer de helft van de patiënten cisplatin toegediend in een wekelijks schema, waarbij vaak een dosis van 40 mg/m^2 wordt gegeven. Er zijn ook studies gedaan met een lagere wekelijkse dosis van bijvoorbeeld 30 of 35 mg/m^2. De vraag is echter of een wekelijks doseringsschema even effectief is als het driewekelijkse schema en minder toxiciteit geeft.

Conclusies

Overall survival (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on overall survival when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Noronha, 2018; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Recurrence (complete tumour response) (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on recurrence (complete tumour response) when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Mashhour, 2020; Sahoo, 2017; Rawat, 2016; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Recurrence (locoregional control) (critical outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on recurrence (locoregional control) when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Mashhour, 2020; Kiyota, 2022; Noronha, 2018; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Disease-free survival (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on disease-free survival when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Noronha, 2018; Kiyota, 2022; Nanda, 2019; Nair, 2017)*

Adverse events (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on adverse events when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Mashhour, 2020; Sahoo, 2017; Noronha, 2018; Rawat, 2016; Kiyota, 2022; Nanda, 2019; Nair, 2017; Tsan, 2012)*

Quality of life (important outcome)

Very low GRADE	The evidence is very uncertain about the effect of weekly cisplatin concurrent with definitive radiotherapy on quality of life when compared with three-weekly cisplatin concurrent with definitive radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Sources: (Tsan, 2012)*

Samenvatting literatuur

Samenvatting literatuur

Description of studies

Eight randomized controlled trials were included. Different doses of cisplatin (30, 35, or 40 mg/m^2) were used in the weekly treatment arms. Studies are grouped according to the dose provided. This clinical question is focused on patients treated with definitive chemoradiation. Four studies (also) included patients who received cisplatin in adjuvant setting (Mashhour, 2020; Noronha, 2018; Kiyota, 2022; Tsan, 2012). Most studies included patients with a carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, however the study of Nanda (2019) only included patients with an oropharyngeal carcinoma and Tsan (2012) only included patients with an oral cavity carcinoma. One study was performed in Egypt, the other seven studies were conducted in Asia.

30 mg/m^2

Mashhour (2020) conducted a randomized controlled trial in Egypt. Patients with a locally advanced head and neck squamous cell carcinoma, aged between 18 to 70 years, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were eligible. Patients were treated with adjuvant (52%) or definitive (48%) intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=30) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=30). Both groups received cisplatin concurrently with intensity modulated radiation therapy. Radiotherapy was given in a total dose of 70Gy in 33 fractions, delivered five days a week. Treatment compliance in terms of completing all planned cycles was higher in the weekly treatment group, where 70% of patients received at least six cycles of weekly chemotherapy with minor dose reductions because of toxicity. In the group receiving cisplatin every three weeks, 60% of patients completed three cycles of treatment and 40% received only two cycles. However, the median cumulative cisplatin dose was lower in the weekly treatment group (170 mg/m^2 versus 200 mg/m^2). In the weekly treatment group, 46% of patients received at least 200 mg/m^2, while in the three-weekly treatment group 75% received at least 200 mg/^{2}. Outcome measures included tumour response, locoregional control, and treatment toxicities. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

Sahoo (2017) conducted a randomized controlled trial at a regional cancer centre in India. Patients with advanced stage squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx, aged between 18 and 70 years, with an ECOG performance status ≤ 2 were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=15) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=15). External beam radiotherapy was delivered to a dose of 66 Gy in a conventional fractionation schedule. Treatment compliance in terms of completing all planned cycles was 67% in the weekly treatment arm (six cycles) and 47% in the three-weekly treatment arm (three cycles). Completion of 66 Gy radiotherapy was 87% in the weekly treatment group and 80% in the three-weekly treatment group. Outcome measures included tumour response, locoregional control, and acute and late toxicity. Toxicities were assessed using the Radiation Therapy Oncology Group Acute Radiation Morbidity Criteria.

Noronha (2018) conducted a randomized controlled trial at an academic oncology hospital in India. Patients with locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx or metastatic cervical lymphadenopathy of unknown primary, aged between 18 and 70 years, with an ECOG

performance status ≤ 2 were eligible. Patients were treated with adjuvant (93%) or definitive (7%) intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 30 mg/m^2 weekly (n=150) or at a planned dose of 100 mg/m2 every three weeks (on days 1, 22, and 43) (n=150). External beam radiotherapy in a conventional fractionation schedule was delivered to a dose of 70 Gy in 35 fractions for patients receiving definitive treatment, and a dose of 60 Gy for patients receiving adjuvant treatment. Treatment compliance in terms of completing the planned chemoradiation was 89% in the weekly treatment arm and 94% in the three-weekly treatment arm. The chemotherapy dose was reduced in 9% of patients in the weekly treatment arm and 8% of patients in the three-weekly treatment arm, while dosing was delayed for 25% in the weekly arm and 28% in the three-weekly arm. The median cumulative cisplatin dose was 210 mg/m^2 in the weekly arm and 300 mg/m^2 in the three-weekly arm. Outcome measures included overall survival, tumour response, locoregional control, progression-free survival and acute and chronic toxicity. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (version 4.03).

35 mg/m^2
Rawat (2016) conducted a randomized controlled trial at a single centre in India. Patients with locally advanced (stage III – IV B) squamous cell carcinoma of the head and neck, aged between 18 and 65 years were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 35 mg/m2 weekly (n=30) or at a planned dose of 100 mg/m^2 every three weeks (on days 1, 22, and 43) (n=30). Radiotherapy was given in a total dose of 70 Gy in 35 fractions. Treatment compliance in terms of completing all planned chemotherapy cycles was 90% in the weekly arm and 79% in the three-weekly arm. Mean cisplatin dose received was lower in the weekly arm as compared with the three-weekly arm (292 mg/m^2 versus 438 mg/m^2).
The mean dose of radiotherapy received was comparable between the arms (69.86 Gy versus 69.22 Gy). Radiotherapy had to be interrupted for 17% of patients in the weekly arm and 34% of patients in the three-weekly arm. Outcome measures included tumour response and toxicity. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Toxicity was assessed using the CTCAE version 4.03.
40 mg/m^2

Kiyota (2022) conducted a randomized controlled non-inferiority trial in 28 centres in Japan. Patients with postoperative high-risk locally advanced squamous cell carcinoma of the head and neck, aged between 20 and 75 years, with an ECOG performance score of 0 or 1 were eligible. All patients received treatment with adjuvant intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=129) or at a planned dose of 100 mg/m^2 every three weeks (n=132). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. The median number of chemotherapy cycles received was 6 (IQR 5 to 7) in the weekly arm and 3 (IQR 3 to 3) in the three-weekly arm. The median cumulative cisplatin dose was lower in the weekly treatment group (239 mg/m^2 [IQR 199 to 277] versus 280 mg/m^2 [IQR 250 to 299]). The median total radiotherapy dose was 66 Gy in both groups (IQR 66 to 66). Outcome measures included overall survival, relapse-free survival, local relapse-free survival, and adverse events. Toxicity was assessed using the CTACE version 4.0.

Nanda (2019) conducted a randomized controlled trial at a single centre in India. Patients with locally advanced oropharyngeal carcinoma, aged between 20 and 70 years, with a Karnofsky performance score > 70

were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=39) or at a planned dose of 100 mg/m^2 every three weeks (n=31). Radiotherapy was given in a total dose of 70 Gy in 35 fractions. The median number of chemotherapy cycles received was five in the weekly arm and two in the three-weekly arm. The median cumulative cisplatin dose was lower in the weekly treatment group (272 mg/m^2 versus 303 mg/m^2). Fewer patients in the weekly treatment group as compared with the three-weekly group received at least 200 mg/m^2 cisplatin (89% versus 97%). In the weekly arm, 54% of patients discontinued chemotherapy beyond four cycles, mostly because of toxicity. All patients received the planned radiation dose of 70 Gy. Outcome measures included overall survival, tumour response, locoregional control, disease-free survival, and toxicities. Tumour response was evaluated according to the WHO criteria. Toxicity was assessed using the Radiation Therapy Oncology Group criteria for radiotherapy-induced acute toxicities, and Common Toxicity Criteria for chemotherapy-induced toxicity.

Nair (2017) conducted a randomized controlled trial at a regional cancer centre in India. Patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx or larynx, aged between 18 and 70 years, with an ECOG performance status 0 or 1 were eligible. All patients received treatment with definitive intent. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=25) or at a planned dose of 100 mg/m^2 every three weeks (n=31). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. Treatment compliance in terms of completing all planned chemotherapy cycles was 63% in the weekly treatment group (six cycles) and 35% in the three-weekly treatment group (three cycles). The mean cumulative cisplatin dose was slightly lower in the weekly treatment group (339 mg/m^2 versus 357 mg/m^2). All patients completed radiation apart from one patient who died during treatment. Outcome measures included overall survival, locoregional control, tumour response, disease-free survival, and toxicities. Tumour response was evaluated using RECIST criteria. Toxicity was assessed using the Radiation Therapy Oncology Group criteria for radiotherapy-induced toxicities, and Common Terminology Criteria version 4 for chemotherapy-induced toxicity.

Tsan (2012) conducted a randomized controlled trial at a single centre in Taiwan. Patients with high-risk oral cavity squamous cell carcinoma, aged between 18-70 years, with an ECOG performance status 0 to 2 were eligible. All patients received treatment with adjuvant intent. The trial aimed to recruit 371 patients but the trial was stopped after recruiting only 55 patients (of which 50 were randomized) over 30 months. Patients were randomly assigned (1:1) to receive either cisplatin at a planned dose of 40 mg/m^2 weekly (n=24) or at a planned dose of 100 mg/m^2 every three weeks (n=26). Radiotherapy was given in a total dose of 66 Gy in 33 fractions. The mean cumulative doses of cisplatin and radiotherapy were comparable between the groups. However, fewer patients in the weekly treatment group received at least 200 mg/m^2 cisplatin (63% versus 89%). Outcome measures included (preliminary) overall survival, (preliminary) locoregional recurrence-free survival, quality of life (Chinese version of the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) questionnaire) and adverse events. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results

No meta-analysis was performed because of clinical and methodological heterogeneity, but the results for overall survival and locoregional recurrence are shown in Figures 13.9.1 and 13.9.2 to provide more insight in the effects found.

30 mg/m^2

Overall survival

Noronha (2018) observed 60 deaths in the weekly treatment arm (40%) and 53 deaths in the three-weekly treatment arm (35%). Median overall survival was 39.5 months in the weekly treatment arm, while median overall survival was not reached in the three-weekly treatment arm (HR 1.14 (95%CI 0.79 to 1.65; p=0.48).

Recurrence (tumour response)

Mashhour reported tumour response, a complete response was seen in 77% of patients receiving weekly cisplatin and 76% of patients receiving three-weekly cisplatin. A partial response was seen in 13.2% of patients receiving weekly cisplatin and 12.6% of patients receiving three-weekly cisplatin. Two months after treatment, stable disease was observed in 4.6% of patients in the weekly treatment group and 4.1% of patients in the three-weekly treatment group.

Sahoo (2017) reported that after a median follow-up of seven months, complete response was achieved by 73% of patients in the weekly arm and 86% of patients in the three-weekly arm (not statistically significant).

Recurrence (locoregional control)

Mashhour (2020) reported that after a median follow-up of 24 months, locoregional control rates were 57.6% in the weekly treatment group and 72.8% in the three-weekly treatment group (HR 1.78; p=0.015).

Noronha (2018) reported that the 2-year locoregional control rate was 58.5% in the study arm receiving weekly cisplatin and 73.1% in the group receiving three-weekly cisplatin (HR 1.76 (95%CI 1.11 to 2.79; p=0.014).

Disease-free survival

In the trial by Noronha (2018), the estimated median progression-free survival was 17.7 months (95%CI 0.42 to 35.05) in the weekly treatment arm and 28.6 months (95%CI 15.9 to 41.3) in the three-weekly treatment arm (HR 1.24 (95%CI 0.89 to 1.73); p=0.21).

Quality of life

Quality of life was not reported in any of the RCTs using a dose of 30 mg/m^2.

Adverse events

Mashhour (2020) reported non-haematological and haematological adverse events. For non-haematological adverse events, acute toxicities grade ≥ 3 were observed less frequently in the weekly treatment group (56.6%) compared with the three-weekly treatment group (76.6%) (p=0.007). No statistically significant differences were found for individual grade ≥ 3 toxicities, including mucositis (53% in the weekly cisplatin

group versus 47% in the three-weekly cisplatin group), dysphagia (47% versus 67%) , nausea/vomiting (13% versus 20%), xerostomia (17% versus 20%), dermatitis (13% versus 10%), and laryngeal oedema (17% versus 17%).

For haematological adverse events, grade $\geq$ 3 leukopenia (20% versus 37%; p<0.05) and neutropenia (10% versus 20%; p<0.05) occurred less frequently in the weekly cisplatin group compared with the three-weekly cisplatin group. No differences were found between the frequency of grade $\geq$ 3 anemia (17% versus 30%) and thrombocytopenia (3% versus 10%) in the weekly and three-weekly treatment groups.

Sahoo (2017) reported that grade 3 mucositis and vomiting were less frequent in the weekly cisplatin arm compared with the three-weekly cisplatin arm (53% versus 40%; p=0.729) and (20% versus 7%; p=0.360). In contrast, grade 3 dermatitis was more frequent in the weekly arm compared with the three-weekly arm (27% versus 7%; p=0.360). The frequencies of grade 3 dysphagia, anemia, and leukopenia were (almost) similar between the arms (0% versus 7%, 7% versus 7%, 13% versus 7%). The frequency of late toxicities (xerostomia and skin fibrosis) was comparable between the study arms.

Noronha (2018) reported acute (within 90 days from the start of treatment) and chronic (more than 90 days from the start of treatment) toxicities. For acute toxicities, any acute toxicity grade $\geq$ 3 was observed in 72% of patients receiving weekly cisplatin and 85% of patients receiving three-weekly cisplatin (p=0.006). Toxicities that occurred less frequently in the weekly treatment group included vomiting (1% versus 7%; p=0.019), infection (21% versus 34%; p=0.015), deafness (5% versus 13%; p=0.013), hyponatremia (23% versus 52%; p<0.001), leukopenia (3% versus16%; p<0.001), neutropenia (1% versus 13%; p<0.001), febrile neutropenia (1% versus 6%; p=0.019), and lymphocytopenia (72% versus 89%; p=0.001). No differences between the weekly and three-weekly treatment group were observed in the frequency of mucositis, dysphagia, odynophagia, xerostomia, dysgeusia, dermatitis, diarrhoea, fatigue, weight loss, hoarseness, hypertension, hypokalemia, transaminase elevation, anemia and thrombocytopenia. There were no patients experiencing $\geq$ 3 neuropathy or renal dysfunction.

For chronic toxicities, any chronic toxicity grade $\geq$ 3 was observed in 10% of patients receiving weekly cisplatin and 14% of patients receiving three-weekly cisplatin (p=0.55). The only toxicity that occurred less frequency in the weekly treatment group was deafness (4% versus 16%; p=0.004). No differences between the weekly and three-weekly treatment group were observed in the frequency of mucositis, dysphagia, odynophagia, infection, xerostomia, subcutaneous, trismus, and hypertriglyceridemia. There were no patients experiencing $\geq$ 3 dysgeusia, skin toxicity, hypothyroidism, or thromboembolic events.

35 mg/m^2
Overall survival
Rawat (2016) did not report on overall survival.

Recurrence (tumour response)
Rawat (2016) reported that three months after treatment completion, complete response was 67% in the group receiving weekly cisplatin and 62% in the group receiving three-weekly cisplatin. Partial responses were received in 33% of patients receiving weekly treatment and 38% of patients receiving three-weekly treatment. No statistically significant differences were found between the arms (p=0.20).

Recurrence (locoregional control)
Rawat (2016) did not report on locoregional control.

Disease-free survival
Rawat (2016) did not report on disease-free survival.

Quality of life
Rawat (2016) did not report on quality of life.

Adverse events
For non-haematological toxicities, Rawat (2016) reported that the frequency of grade 3 mucositis (70% versus 76%; p=0.20) was similar between the groups, while the frequency of grade 3 vomiting was lower in the group receiving weekly treatment (20% versus 35%; p=0.03). For haematological toxicities, no differences were found for grade 3 anemia (33% versus 31%; p=0.22) and thrombocytopenia (7% versus10%; p=0.32), while grade 3 neutropenia was less frequent in the group receiving weekly treatment (27% versus 55%; p=0.02). Rawat (2016) also reported on a number of other toxicities. For acute renal toxicity, only mild toxicity was observed, while for significant weight loss, hyponatremia and hypomagnesemia it was not clear whether the frequencies involved grade 3 toxicity.

<u>*40 mg/m^2*</u>
Overall survival

Kiyota (2022) reported estimated 2-year and 3-year survival rates of 77.7% and 71.6% in the weekly treatment arm and 74.5% and 59.1% in the three-weekly treatment arm. The hazard ratio was 0.69 (99.1%CI 0.37 to 1.27; one-sided p-value for non-inferiority=0.0027). Since the upper limit of the confidence interval was below the prespecified threshold of 1.32, the authors concluded that weekly treatment is non-inferior with regard to survival.

Nanda (2020) reported that median overall survival was 35.4 months in the weekly treatment group and 32.9 months in the three-weekly treatment group (p=0.303). The two-year and five-year survival rates were 55% and 42% in the weekly treatment group and 58% and 32% in the three-weekly treatment group (not statistically significant, no p-value provided).

Nair (2017) reported two-year survival rates of 61% in the weekly treatment arm and 71% in the three-weekly treatment arm (p=0.610).

Tsan (2012) reported preliminary overall survival after a median follow-up of 12 months. In each group, six patients had died. One-year overall survival rates were 72% in the weekly treatment group and 79% in the three-weekly treatment group (p=0.978).

Recurrence (tumour response)
Nanda (2020) reported that complete response was seen in 81% of patients receiving weekly treatment and

75% of patients receiving three-weekly treatment. Partial responses were seen in 14% of patients receiving weekly treatment and 13% of patients receiving three-weekly treatment. Eight weeks after completion of treatment, stable disease was 5% in the weekly treatment group and 4% in the three-weekly treatment group.

Nair (2017) reported that complete responses were observed in 75% of patients in the weekly treatment arm and 90% of patients in the three-weekly arm. Partial response rates were 12% and 6%. Twelve weeks after completion of treatment, two patients in each arm (8% versus 6%) had residual disease.

Recurrence (locoregional control)
Kiyota (2022) reported recurrences in 29% of patients receiving weekly treatment and 39% of patients received three-weekly treatment.

Nanda (2020) observed locoregional relapses in 14% of patients receiving weekly treatment and 6% of patients receiving three-weekly treatment. Three months after completion of treatment, stable or progressive disease was observed in 29% of patients in the weekly treatment group and 42% of patients in the three-weekly treatment group.

Nair (2017) reported that two patients in the weekly treatment group developed local recurrence and one patient developed lung metastasis (13%), while four patients in the three-weekly treatment group developed local recurrence (13%). In the weekly treatment group, three patients developed a second primary tumour (in the esophagus or tongue) (13%), while in the three-weekly group two patients developed a second primary tumour in the esophagus (6%). Two-year locoregional control rates were 63% in the weekly cisplatin arm and 61% in the three-weekly cisplatin arm.

Tsan (2012) reported preliminary locoregional recurrence-free survival after a median follow-up of 12 months. In the weekly arm, 9 patients had experienced a recurrence while in the three-weekly arm, 8 patients had experienced a recurrence. One-year locoregional recurrence-free survival rates were 60% in the weekly treatment group and 71% in the three-weekly treatment group (p=0.806).

Disease-free survival
Kiyota (2022) reported hazard ratios of 0.71 (95%CI 0.48 to 1.06) for relapse-free survival and 0.73 (95%CI 0.47 to 1.13) for local relapse-free survival.

Nanda (2020) reported that median progression-free survival was 26.4 months in the weekly treatment group and 27.4 months in the three-weekly treatment group (p=0.953).

Nair (2017) reported that two-year disease-free survival rates were 53% in the weekly arm and 65% in the three-weekly arm (p=0.674).

Adverse events

Kiyota (2022) reported no difference in the proportion of patients experiencing at least one grade ≥ 3 event (81.1% versus 79.8%; p=0.87), while fewer patients in the weekly group experienced a grade 4 event (8.2%

versus 18.6%; p=0.017). For haematological adverse events, there were no differences in the frequency of grade ≥ 3 events (64.8% versus 61.2%; p=0.06) and grade 4 events (7.4% versus 14.7%; p=0.07). Specific grade ≥ 3 adverse events that were reported to be lower in the weekly treatment group included neutropenia (35% versus 49%) and infection (7% versus 12%).

Nanda (2020) observed no statistically significant differences in the frequency of grade ≥ 3 radiation toxicities and haematological toxicities between the two groups. Radiation toxicities included mucositis (32% versus 29%; p=1.00), dysphagia (46% versus 32%; p=0.27), dermatitis (14% versus 19%; p=0.73), larynx (11% versus 10%; p=1.00), and nausea/vomiting (7% versus 0%; p=0.22). Haematological toxicities included anemia (0% versus 3%; p=1.00), leukopenia (25% versus 13%; p=0.32), neutropenia (18% versus 7%; p=0.24), and thrombocytopenia (0% versus 3%; p=1.00).

Nair (2017) reported a lower frequency of grade ≥ 3 dysphagia (63% versus 26%; p<0.05) in the weekly cisplatin group. No other statistically significant differences were reported in the frequency of grade ≥ 3 non-haematological and haematological toxicities between the two groups. Non-haematological toxicities included mucositis (54% versus 52%; p>0.05), and dermatitis (13% versus3%; p>0.05). Haematological toxicities included anemia (4% versus 0%; p>0.05), neutropenia (8% versus 3%; p>0.05), and thrombocytopenia (no grade 3 adverse events observed). No grade ≥ 3 renal toxicity was observed.

Tsan (2012) reported that overall, more grade ≥ 3 toxicities were observed in the weekly group (92%) compared with the three-weekly group (81%) (p=0.02). For non-haematological toxicities, mucositis was reported more frequency in the weekly treatment group (75%) compared with the three-weekly group (39%) (p=0.012). The frequencies of the following toxicities were comparable between the groups: pharyngitis (54% versus 54%; p=1.0), stomatitis (54% versus 54%; p=1.0), laryngeal edema (4% versus 12%; p=0.611), dermatitis (8% versus 8%; p=1.0), and nausea/vomiting (21% versus 12%; p=0.456).

For haematological toxicities, no differences were observed between the groups for anemia (4% versus 4%; p=1.0), leukopenia (13% versus 0%; p=0.103), neutropenia (4% versus 0%; p=0.480), and thrombocytopenia (0% versus 0%).

Quality of life
Tsan (2012) reported results for five subscales of the FACT H&N questionnaire and the Trial Outcome Index (TOI) which is a combined scale for the subscales physical well-being, functional well-being and the head and neck subscale. Higher scores represent better QoL. It was not reported how many patients completed the questionnaires at each time point.

For the physical well-being scale (range 0 to 28), lower scores were seen in the weekly treatment group at week 2 (difference of 4.5 points between the groups), week 4 (5.7 points), at the end of radiotherapy (7.8 points) and follow-up after three months (4.3 points). For the social well-being scale (range 0 to 28), higher scores were seen in the weekly treatment group at week 4 (difference of 2.9 points between the groups), at the end of radiotherapy (5.7 points), and follow-up after three months (5 points). Emotional well-being scores were comparable between the groups at all time points. Functional well-being scores (range 0 to 28) were only different between the groups at three months follow-up, with lower scores seen in the weekly treatment

group (3.3 points difference between the groups). Scores on the head and neck subscale were comparable between the groups at all time points. TOI scores (range 0 to 96) were only different between the groups at three months follow-up, with lower scores seen in the weekly treatment group (difference 9.7 points).

<u>Level of evidence of the literature</u>
All studies were RCTs, therefore the level of evidence started at 'high' for all outcome measures.

The level of evidence was downgraded for all outcomes because most (7/8) studies were conducted in Asia (India, Taiwan, and Japan), while it has been described that head and neck cancers in Asian countries have a different etiology and molecular biology. Publication bias was not assessed because of the low number of studies found.

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by four levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one trial was stopped prematurely); applicability (-1; bias due to indirectness because three studies were conducted among patients who were treated (mainly) with adjuvant intent and all studies were conducted in Asia); and number of included patients (-2; imprecision because of wide confidence intervals including the possibility of a negative effect, no effect, and a positive effect). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>recurrence (tumour response)</u> was downgraded by five levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); conflicting results (-1; inconsistency because two studies showed worse tumour response rates, two studies showed no effect and one study showed better tumour response rates); applicability (-1; bias due to indirectness because in one study 52% of patients were treated with adjuvant intent and most studies were conducted in Asia); and number of included patients (-2; imprecision because of the low sample sizes). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>recurrence (locoregional control)</u> was downgraded by five levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one trial was stopped prematurely); conflicting results (-1; inconsistency because three studies showed worse locoregional control, two studies showed no effect, and one study showed better locoregional control); applicability (-1; bias due to indirectness because four studies were conducted among patients who were treated (mainly) with adjuvant intent and most studies were conducted in Asia); and number of included patients (-2; imprecision because of wide confidence intervals including the possibility of a negative effect, no effect, and a positive effect). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by three levels because of conflicting results (-1; inconsistency because one study showed worse DFS and two showed no difference); applicability (-1; bias due to indirectness because two studies were conducted among patients who were treated (mainly) with adjuvant intent and all studies were conducted in Asia); and number of included patients (-1; imprecision because of confidence intervals including the possibility of a negative effect and no effect (and a positive effect)). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology and one study was stopped prematurely); applicability (-1; bias due to indirectness because four studies were conducted among patients who were treated (mainly) with adjuvant intent and most studies were conducted in Asia); and number of included patients (-1; imprecision because of the low number of patients included in individual studies). Publication bias was not assessed.

The level of evidence regarding the outcome measure <u>quality of life</u> was downgraded by five levels because of study limitations (-2 risk of bias because of incomplete reporting of study methodology, lack of blinding, and study stopped prematurely); applicability (-1; bias due to indirectness because the study was conducted among patients who were treated with adjuvant intent and was conducted in Asia); number of included patients (-2; imprecision because of the low sample size in a single study). Publication bias was not assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the benefits and risks of weekly versus three-weekly cisplatin concurrent with definitive radiotherapy for patients with locally advanced head and neck squamous cell carcinoma?

P: Patients with locally advanced head and neck squamous cell carcinoma.
I: Weekly cisplatin concurrent with definitive radiotherapy.
C: Three-weekly cisplatin concurrent with definitive radiotherapy.
O: Overall survival, recurrence (tumour response and locoregional control), disease-free survival, quality of life, adverse events.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and recurrence as critical outcome measures for decision making; and disease-free survival, adverse events, and quality of life as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically important difference as follows:

- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Tumour response: absolute difference > 5% in complete response rates
- Local recurrence: 0.8 or 1.25 as borders for risk or odds ratios.
- Locoregional control: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Progression-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Adverse events: statistically significant difference in grade ≥ 3 adverse event rate.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 12 November 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 534 hits (60 SRs and 474 RCTs). Studies were selected based on the following criteria: (1) patients with a locally advanced squamous cell carcinoma in the head and neck region; (2) comparison between radiotherapy combined with weekly or three-weekly cisplatin; (3) systematic review or randomized controlled trial; (4) full-text English language publication. Studies including only patients with nasopharyngeal cancer were excluded.

24 studies were initially selected based on title and abstract screening. After reading the full text, 17 studies were excluded (see the table with reasons for exclusion under the tab Methods) and seven studies were included. The working group identified an additional RCT that was published after the search date. This RCT was also included in the summary of literature. We cannot exclude the possibility that other relevant reviews or RCTs were published after the search date.

Results

Eight original studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Alternatief voor cisplatin bij chemoradiatie

Uitgangsvraag

Wat is de rol van systemische therapie in aanvulling op definitieve radiotherapie bij patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied bij wie cisplatin is gecontra-indiceerd?

Aanbeveling

Bespreek met patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied bij wie cisplatin gecontra-indiceerd is de alternatieven voor cisplatin in aanvulling op definitieve radiotherapie, te weten cetuximab, carboplatin of carboplatin in combinatie met 5-FU, en wijs daarbij op de voor- en nadelen van deze alternatieven.

Op basis van prospectief onderzoek kan geen aanbeveling worden gedaan voor patiënten boven de 70 jaar.

Overwegingen

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>
Onze systematische zoekactie in diverse databases resulteerde in 13 relevante studies die resultaten rapporteren van 9 verschillende RCT's.

1. RT + cetuximab
In totaal hadden 3 van de 13 studies betrekking op de vergelijking tussen radiotherapie en cetuximab enerzijds en alleen radiotherapie anderzijds (Bonner, 2006; Curran, 2007 en Bonner, 2010). Deze studies rapporteerden resultaten van een en dezelfde trial. Er werden klinisch relevante verschillen gevonden voor totale overleving (cruciale uitkomstmaat) op 3 en 5 jaar en progressievrije overleving (belangrijke uitkomstmaat) op 2 en 3 jaar, ten faveure van bioradiotherapie. Er werd geen klinisch relevant verschil gevonden voor kwaliteit van leven (belangrijke uitkomstmaat). Van de acute bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) traden een acné-achtige huiduitslag, infusiereacties en anemie statistisch significant vaker op bij patiënten die behandeld werden met radiotherapie en cetuximab, vergeleken met patiënten die alleen radiotherapie kregen. Het percentage patiënten met een late bijwerking van graad 3 of hoger verschilde niet tussen de behandelgroepen. Een subgroepanalyse liet zien dat voor totale overleving patiënten met een orofarynxtumor mogelijk het meeste baat hebben bij de toevoeging van cetuximab aan radiotherapie. Het percentage patiënten met een lokaal recidief (cruciale uitkomstmaat) werd niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege de actieve rol van de studiesponsor bij het verzamelen en analyseren van de data), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was) en imprecisie (vanwege het geringe aantal deelnemers en het feit dat de 3 studies betrekking hadden op slechts 1 RCT). Inconsistentie en publicatiebias konden niet beoordeeld worden.

2. RT + carboplatin
Eveneens 3 van de 13 studies hadden betrekking op de vergelijking tussen radiotherapie en carboplatin enerzijds en alleen radiotherapie anderzijds (Fountzilas, 2004; Jeremic, 1997 en Ruo Redda, 2010). Deze

studies rapporteerden resultaten van 3 verschillende trials. Er werd een klinisch relevant verschil gevonden voor totale overleving (cruciale uitkomstmaat) op 1, 2, 3 en 4 jaar, ten faveure van chemoradiotherapie, maar niet voor totale overleving op 10 jaar. De studies toonden conflicterende resultaten voor totale overleving op 5 jaar: 2 studies (n = 79 en n = 106) lieten wel een klinisch relevant verschil zien, terwijl in 1 studie (n = 164) geen klinisch relevant verschil werd gevonden. Voor ziektevrije overleving (belangrijke uitkomstmaat) werd een klinisch relevant verschil gevonden op 3 jaar, ten faveure van chemoradiotherapie, maar niet op 5 en 10 jaar. Voor geen van de acute en late bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) werd een eenduidig klinisch relevant verschil gevonden. Het percentage patiënten met een lokaal recidief (cruciale uitkomstmaat), progressievrije overleving en kwaliteit van leven werden niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege onvolledige rapportage, verschillen in patiëntkenmerken tussen de behandelarmen in een studie en het vroegtijdig stoppen van een trial), inconsistentie (vanwege conflicterende resultaten), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was) en imprecisie (vanwege het geringe aantal deelnemers per studie). Inconsistentie kon niet beoordeeld worden voor ziektevrije overleving, en publicatiebias kon in het geheel niet beoordeeld worden.

3. RT + carboplatin and 5-FU
De resterende 7 studies hadden betrekking op de vergelijking tussen radiotherapie gecombineerd met carboplatin en 5-FU enerzijds en alleen radiotherapie anderzijds (Bourhis, 2012; Calais, 1997; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001 en Semrau, 2006). Deze studies rapporteerden resultaten van 5 verschillende trials. Er werd een klinisch relevant verschil gevonden voor totale overleving (cruciale uitkomstmaat) op 1, 2, 3 en 5 jaar, ten faveure van chemoradiotherapie. Voor het percentage patiënten met een lokaal recidief (cruciale uitkomstaat) en ziektevrije overleving (belangrijke uitkomstmaat) op 2, 3 en 5 jaar werd eveneens een klinisch relevant verschil gevonden, ten faveure van chemoradiotherapie, maar niet voor progressievrije overleving (belangrijke uitkomstmaat). Voor geen van de acute bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) werd een eenduidig klinisch relevant verschil gevonden. Voor de late bijwerkingen van graad 3 of hoger (belangrijke uitkomstmaat) gold dat late slikproblemen en permanente sondevoeding vaker werden gezien bij patiënten die behandeld waren met hypergefractioneerde, geaccelereerde radiotherapie in combinatie met 5-FU, vergeleken met alleen radiotherapie; dit verschil was klinisch relevant. Kwaliteit van leven werd niet gerapporteerd in de studies. De bewijskracht voor de cruciale en belangrijke uitkomstmaten was laag tot zeer laag. Er werd afgewaardeerd voor studiebeperkingen (vanwege onvolledige rapportage, verschillen in patiëntkenmerken tussen de behandelarmen in een studie en het vroegtijdig stoppen van 2 trials), inconsistentie (vanwege conflicterende resultaten), indirectheid (vanwege het feit dat de studiepopulatie niet bestond uit patiënten bij wie cisplatin gecontra-indiceerd was en het gebruik van verschillende radiotherapeutische regimes) en imprecisie (vanwege het geringe aantal deelnemers per studie). Inconsistentie kon niet beoordeeld worden voor het percentage patiënten met een lokaal recidief en ziekte- en progressievrije overleving, en publicatiebias kon in het geheel niet beoordeeld worden.

Op basis van de resultaten van de studie van Mehanna (2019) lijkt het toevoegen van cetuximab aan definitieve radiotherapie niet van waarde te zijn voor patiënten met een gevorderd HPV-positief orofarynxcarcinoom. De studie van Mehanna (2019) is in deze module overigens geëxcludeerd omdat er

alleen patiënten met een gevorderd HPV-positief orofarynxcarcinoom zijn geïncludeerd. Voor deze patiëntenpopulatie is een aparte module beschikbaar (RLDB: link invoegen naar module 'Behandeling HPV-positieve orofarynx tumoren'). Daarnaast wordt in de studie van Mehanna (2019) en ook de studie van Gillison (2019) geen vergelijking gemaakt tussen radiotherapie en cetuximab met alleen radiotherapie, maar wordt radiotherapie en cetuximab vergeleken met radiotherapie met cisplatin. Op basis van de huidige literatuur kan geen uitspraak gedaan worden over de rol van carboplatin met of zonder 5-FU als alternatief voor cetuximab.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Curran (2007) vonden geen statistisch significant, maar wel een beperkt klinisch relevant verschil in kwaliteit van leven tussen patiënten die behandeld werden met radiotherapie en cetuximab en patiënten die alleen radiotherapie kregen, ten nadele van de patiënten die met cetuximab werden behandeld. Er is geen onderzoek gedaan naar kwaliteit van leven bij de andere schema's. Vanwege de beperkte literatuur op dit gebied kan de werkgroep geen uitspraak doen over de waarden en voorkeuren van patiënten.

Het doel van het toevoegen van cetuximab of carboplatin met of zonder 5-FU aan definitieve radiotherapie is het verbeteren van de locoregionale controle, zonder duidelijke toename van de toxiciteit. Dit laatste is met name ook voor de patiënt van belang, omdat het hier een kwetsbare groep patiënten betreft. Uit een meta-analyse van 107 RCT's naar de effecten van chemotherapie bij hoofd-halstumoren (Lacas, 2021) bleek dat met het toenemen van de leeftijd het effect van het toevoegen van cisplatin aan radiotherapie afneemt, waarbij er in de leeftijdsgroep boven de 70 jaar geen positief effect is op overleving en dit positieve effect in de leeftijdsgroep 60-69 al weer aanzienlijk lager is dan in de groep jonger dan 50 jaar. Het is goed om te realiseren dat in de studies ook selectie heeft plaatsgevonden, bijvoorbeeld op basis van leeftijd en de aan- of afwezigheid van ernstige comorbiditeit. Met de patiënt moet duidelijk gecommuniceerd worden wat met de huidige behandelopties bereikt kan worden, en tegen welke prijs. Op basis hiervan en de eigen doelen van de patiënt kan een gewogen beslissing worden genomen.

Kosten (middelenbeslag)
Extra kosten voor de patiënt zijn het regelmatig bezoeken van het ziekenhuis voor de behandelingen. Ook de bijwerkingen kunnen leiden tot extra kosten, zoals de kosten van medicatie vanwege huiduitslag, de kosten die gepaard gaan met een eventuele infectie of bloeding en de kosten van mogelijke extra ziekenhuisopnames. De meeste van deze kosten zijn verzekerd, maar dit betekent kosten voor de samenleving en voor familie en relaties. Gezien de onzekerheid die bestaat over de gunstige effecten is het moeilijk aan te geven of dit de (extra) middelen waard is? Een kosten-batenanalyse ontbreekt in de literatuur.

Gezien de langere overleving bij HPV-positieve patiënten met een orofarynxcarcinoom zou bij deze groep adjuvante therapie meer van waarde kunnen zijn. Anderzijds zal bij oudere patiënten (> 75 jaar) met een 'WHO performance status' > 2 gezien de bijwerkingen meer terughoudendheid moeten worden betracht.

De werkgroep heeft geen informatie gevonden over de kosteneffectiviteit van de-escalatiestrategieën. De werkgroep heeft dit aspect daarom niet meegewogen bij het formuleren van de aanbeveling. De werkgroep verwacht dat de aanbeveling geen relevante impact heeft op de zorgkosten.

Aanvaardbaarheid, haalbaarheid en implementatie
In Nederland is de hoofd-halsoncologie gecentreerd in 8 werkgroepen, waardoor een hoge mate van expertise is gewaarborgd. Voor sommige patiënten betekent dit langere reistijden wat een belasting kan zijn. Er zijn geen aanwijzingen dat dit de therapietrouw ten nadele beïnvloedt. In het algemeen is in de centra sprake van voldoende capaciteit, hoewel er binnen financiële kaders er spanningen op kunnen treden. Gezien de zeer goede onderlinge samenwerking binnen een groot team, waarvan de samenstelling en benodigde expertise is vastgesteld in de SONCOS-normen, is de kwaliteit gewaarborgd. De centra worden regelmatig gevisiteerd. Alle patiënten worden besproken binnen het multidisciplinaire overleg (MDO), waarbij ook de behandelaar aanwezig is. Hierna vindt uitgebreid verleg plaats met de patiënt, waarbij op basis van de adviezen uit het MDO en de eigen voorkeur van de patiënt een beleid wordt uitgestippeld.

De werkgroep is van mening dat de aanbeveling aanvaardbaar is voor zowel zorgverleners als patiënten. De werkgroep verwacht dat het uitvoeren van de aanbeveling haalbaar en implementeerbaar is. De aanbeveling sluit aan bij de huidige werkwijze in de praktijk.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Op basis van de huidige literatuur kan geen zekere uitspraak gedaan worden over een goed alternatief voor cisplatin bij patiënten bij wie cisplatin gecontra-indiceerd is. In de voorgaande richtlijn werd cetuximab genoemd als alternatief voor patiënten bij wie cisplatin gecontra-indiceerd is. Op basis van recente studies (Gillison (2019) en Mehanna (2019)) is twijfel gerezen over de toegevoegde waarde van cetuximab aan radiotherapie in de behandeling van patiënten met een gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied, hoewel in deze studies met name patiënten met een HPV-positief orofarynxcarcinoom waren geïncludeerd. Voor patiënten met een gevorderd HPV-positief orofarynxcarcinoom lijkt het toevoegen van cetuximab aan definitieve radiotherapie niet van waarde te zijn, zie ook de module 'Behandeling HPV-positieve orofarynx tumoren').
Deze onzekerheid wat betreft het beste alternatief voor cisplatin dient besproken te worden met deze patiënten. Er kan gekozen worden voor een van de in deze richtlijnmodule besproken alternatieven, maar dan moet het risico op toegenomen toxiciteit worden afgewogen tegen de onzekere voordelen.

Onderbouwing

Achtergrond

Patiënten met een lokaal gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied kunnen in opzet curatief behandeld worden met radiotherapie. Het toevoegen van cisplatin aan deze behandeling leidt bij patiënten van 70 jaar of jonger en een 'WHO performance status' van 0 of 1 tot een betere lokale controle en overleving, maar gaat ook gepaard met meer toxiciteit. Met het toenemen van de leeftijd neemt het effect van het toevoegen van chemotherapie aan radiotherapie af, waarbij er bij patiënten boven de 70 jaar geen positief effect op overleving is gerapporteerd. Bij een deel van de patiënten is behandeling met cisplatin gecontra-indiceerd vanwege bijvoorbeeld cardiovasculaire problemen of nierinsufficiëntie. Mogelijke behandelalternatieven voor deze patiënten zijn cetuximab, carboplatin of carboplatin én 5-fluoro-uracil (5-FU). Het toxiciteitsprofiel van deze geneesmiddelen is weliswaar anders dan dat van cisplatin, maar het is onduidelijk hoe effectief deze middelen zijn en welk middel de voorkeur heeft.

Conclusies

1. RT + cetuximab
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. Sources: (Bonner, 2006; Bonner, 2010)

Local recurrence

- GRADE	No evidence was found regarding the effect of radiotherapy combined with cetuximab on local recurrence in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Disease-free survival

- GRADE	No evidence was found regarding the effect of radiotherapy combined with cetuximab on disease-free survival in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Progression-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on progression-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. Sources: (Bonner, 2006)

Quality of life

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on quality of life when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. Sources: (Curran, 2007)

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with cetuximab on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. Sources: (Bonner, 2006)

2. RT + carboplatin
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Fountzilas, 2004; Jeremic, 1997; Ruo Redda, 2010)*

Local recurrence

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on local recurrence in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on disease-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Ruo Redda, 2010)*

Progression-free survival

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on progression-free survival in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Quality of life

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin on quality of life in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Fountzilas, 2004; Jeremic, 1997; Ruo Redda, 2010)*

3. RT + carboplatin and 5-FU
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on overall survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012; Calais, 1999; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001; Semrau, 2006)*

Local recurrence

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on local recurrence when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: Calais, 1999; Denis, 2004)*

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on disease-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Calais, 1999; Denis, 2004; Olmi, 2003)*

Progression-free survival

Low GRADE	The evidence suggests that radiotherapy combined with carboplatin and 5-FU results in little to no difference in progression-free survival when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012)*

Quality of life

- GRADE	No evidence was found regarding the effect of radiotherapy combined with carboplatin and 5-FU on quality of life in patients with a locally advanced squamous cell carcinoma in the head and neck region.

Adverse events

Very low GRADE	The evidence is very uncertain about the effect of radiotherapy combined with carboplatin and 5-FU on adverse events when compared with radiotherapy alone in patients with a locally advanced squamous cell carcinoma in the head and neck region. *Sources: (Bourhis, 2012; Calais, 1999; Denis, 2004; Chitapanarux, 2013; Olmi, 2003; Staar, 2001; Semrau, 2006)*

Samenvatting literatuur

Description of studies

1. Radiotherapy + cetuximab

Bonner (2006), Curran (2007) and Bonner (2010) report on a multicenter, randomized controlled phase 3 trial that was conducted at 73 academic centers in the US and 14 other countries, including the Netherlands. Patients with previously untreated, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 60, and normal bone marrow, hepatic and renal function. Patients were randomly assigned (1:1) to receive high-dose radiotherapy and cetuximab (n = 211), or high-dose radiotherapy alone (n = 213). Investigators were required to select 1 of 3 radiotherapy-fractionation regimens (concomitant boost, once daily, or twice daily) before randomization. The final review of radiotherapy revealed that the mean and median doses for the 3 regimens did not differ between the 2 treatment groups. Administration of cetuximab was initiated 1 week before radiotherapy at a loading dose of 400 mg/m^2 over a period of 120 minutes, followed by weekly 60-minute infusions of 250 mg/m^2 for the duration of radiotherapy. The primary outcome measure was the duration of locoregional control, which was not of our interest. Secondary outcome measures of our interest included overall survival, progression-free survival, quality of life and safety. Quality of life was assessed using two validated, multidimensional instruments, namely the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC QLQ Head and Neck Cancer-Specific Module (H&N35). Acute toxic effects were assessed through the eighth week after treatment using the criteria of the Radiation Therapy Oncology Group (RTOG). Late toxic effects of radiotherapy were assessed thereafter using the criteria of the RTOG/EORTC.

2. Radiotherapy + carboplatin

Fountzilas (2004) conducted a multicenter, randomized controlled phase 3 trial at 5 hospitals in Greece, Romania and Germany. Patients aged ≥ 18 years with biopsy-proven, previously untreated, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow, hepatic and renal function, and adequate cardiovascular, pulmonary, nutritional and mental status. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy and carboplatin (n = 38), standard fractionated radiotherapy and cisplatin (n = 45) or standard fractionated radiotherapy alone (n = 41). The treatment group of patients who received standard fractionated radiotherapy and cisplatin is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 70 Gy at 1.8 Gy per fraction per day, 5 days per week. Carboplatin was administered at an AUC of 7 on days 2, 22 and 42. The primary outcome measure was the overall survival at 3 years. The authors also report the overall survival at 5 years, the median overall survival, and safety. Acute toxic effects were assessed using the criteria of the RTOG.

Jeremic (1997) conducted a single-center, randomized controlled trial in Yugoslavia. Patients aged > 18 years with histologically confirmed, previously untreated, unresectable, non-metastatic, stage III or IV, measurable squamous cell carcinoma of the head and neck were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 50, adequate bone marrow, hepatic and renal function, and no serious concomitant disease. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy and carboplatin (n = 53), standard fractionated radiotherapy and cisplatin (n = 53) or standard fractionated

radiotherapy alone (n = 53). The treatment group of patients who received standard fractionated radiotherapy and cisplatin is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 70 Gy at 1.8 Gy per fraction per day, 5 days per week. Carboplatin was intravenously administered 45-60 minutes before the irradiation as a bolus at a daily dose of 25 mg/m^2. The primary outcome measure was the overall survival at 3 years. The authors also report the overall survival at 1 year, 2 years, 4 years and 5 years, and safety. Acute and late toxic effects of radiotherapy were assessed using the criteria of the RTOG and RTOG/EORTC, respectively. Toxic effects of chemotherapy were assessed using the criteria of the ECOG. The trial was prematurely stopped before the planned accrual of 85 patients per treatment group was reached, because the chief investigator had to leave the department.

Ruo Redda (2010) conducted a multicenter, randomized controlled phase 3 trial at 6 centers in Italy. Patients aged 18-70 with biopsy-proven, previously untreated, stage III or IV, non-metastatic, measurable, unresectable squamous cell carcinoma of the head and neck were eligible. Criteria for eligibility also included an ECOG performance status $\leq$ 2, adequate bone marrow, hepatic and renal function, adequate nutritional and liquid intake, and no serious concomitant disease. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy and carboplatin (n = 82), or standard fractionated radiotherapy alone (n = 82). Radiotherapy was given in a total dose of 70 Gy at 2 Gy per fraction per day, 5 days per week. Carboplatin was intravenously administered 45-60 minutes before the irradiation as a bolus at a daily dose of 45 mg/m^2 on day 1-5 of the 1st, 3rd, 5th and 7th week of the combined treatment (total dose: 900 mg/m^2). The primary outcome measure was the locoregional recurrence-free survival, which was not of our interest. Secondary outcome measures of our interest included overall survival, disease-free survival, and safety. Acute toxic effects were assessed using the criteria of the World Health Organization (WHO). Late toxic effects were assessed using the criteria of the RTOG/EORTC.

3. Radiotherapy + carboplatin and 5-FU
Bourhis (2012) conducted a multicenter, randomized controlled phase 3 trial at 22 centers in France and Belgium (GORTEC 99-02 trial). Patients with histologically confirmed, previously untreated, stage III or IV, non-metastatic, squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible. Criteria for eligibility also included an ECOG performance status $\leq$ 2, adequate bone marrow, hepatic and renal function, no history of other cancer in the previous 5 years, and no clinically significant cardiac disease. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 279), accelerated radiotherapy plus carboplatin and 5-FU (n = 280) or very accelerated radiotherapy alone (n = 281). Patients allocated to receive standard fractionated radiotherapy received a total dose of 70 Gy in 7 weeks: 5 fractions of 2 Gy per week, with spinal cord exclusion at 40 Gy. These patients also received 3 cycles of 4 days of carboplatin 70 mg/m² per day plus 5-FU 600 mg/m² per day on day 1 to 4, day 22-25, and day 43-46. Patients allocated to receive accelerated radiotherapy received a total dose of 70 Gy in 6 weeks: 5 fractions of 2 Gy per week until 40 Gy, with spinal cord exclusion at 40 Gy, followed by 1.5 Gy per fraction twice daily for 5 days per week for the remaining 30 Gy. These patients also received 2 cycles of 5 days of carboplatin 70 mg/m² per day and 5-FU 600 mg/m² per day on day 1 to 5 and day 29 to 33. Patients allocated to receive very accelerated radiotherapy alone received a total dose of 64.8 Gy in 3.5 weeks: 1.8 Gy per fraction twice daily for 5 days per week, with spinal cord exclusion at 34.2 Gy. The primary outcome measure was progression-free survival, defined as the time between randomisation and the first of the

following events: locoregional progression or relapse, distant relapse, or death from any cause (or the last follow-up contact for patients who did not have any of these events). Secondary outcome measures of our interest included overall survival and safety. Acute toxic effects of radiotherapy and chemotherapy occurring during treatment or within 3 months after the end of treatment were assessed using the criteria of the RTOG and WHO. Late toxic effects occurring more than 3 months after the end of treatment were assessed using the criteria of the RTOG/EORTC.

Calais (1999) and Denis (2004) report on a multicenter, randomized controlled phase 3 trial that was conducted at university hospitals, cancer centers, and private hospitals in France (GORTEC 94-01 trial). Patients aged < 75 years with previously untreated, non-metastatic, stage III or IV, squamous cell carcinoma of the oropharynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 60, and normal bone marrow and renal function. Patients were excluded if they had lost more than 20% of their body weight, if they had previously undergone treatment for this disease or any other cancer, except basal cell carcinoma of the skin, or if they had synchronous primary lesions. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 113), or standard fractionated radiotherapy alone (n = 109). Radiotherapy was given in a total dose of 70 Gy in 35 fractions at 2 Gy per fraction per day, 5 days per week. In the intervention group, patients received 3 cycles of chemotherapy during the 1st, 4th, and 7th week of radiotherapy. Chemotherapy consisted of carboplatin (i.v. bolus of 70 mg/m^2 per day for 4 days) and 5-FU (600 mg/m^2 per day infused continuously in 24 hours for 4 days). The primary outcome measure was the overall survival at 3 years. The authors also report the median overall survival, overall survival at 5 years, disease-free survival at 3 and 5 years, local recurrence rate, and safety. Acute toxic effects were assessed using the criteria of the EORTC. Late toxic effects were assessed using the criteria of the National Cancer Institute (NCI) and RTOG/EORTC.

Chitapanarux (2013) conducted a single-center, randomized controlled phase 3 trial at a university hospital in Thailand. Patients aged 18-75 years with previously untreated, stage III or IV, non-metastatic, squamous cell carcinoma of the head and neck, excluding the nasopharynx, nasal cavity, paranasal sinuses and salivary glands, were eligible. Criteria for eligibility also included an ECOG performance status ≤ 1 and adequate organ system function. Patients were randomly assigned (1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 48) or hybrid accelerated radiotherapy alone (n = 37). Patients allocated to receive standard fractionated radiotherapy received a total dose of 66 Gy in 6.5 weeks: 5 fractions of 2 Gy per week, with spinal cord exclusion at 40 Gy. These patients also received 3 cycles of 4 days of carboplatin 70 mg/m² per day plus 5-FU 600 mg/m² per day on day 1 to 4, day 22-25, and day 43-46. Patients allocated to receive hybrid accelerated radiotherapy received a total dose of 70 Gy in 6 weeks: 5 fractions of 2 Gy per week until 40 Gy, with spinal cord exclusion at 40 Gy, followed by a first daily fraction of 1.8 Gy and a second daily fraction of 1.2 Gy for 5 days per week for the remaining 30 Gy. The primary outcome measure was the locoregional control rate, which was not of our interest. Secondary end points of our interest included overall survival and safety. Acute toxic effects of radiotherapy and chemotherapy were assessed using the criteria of the NCI. Late toxic effects were assessed using the criteria of the RTOG/EORTC. Due to slow inclusion, the trial was prematurely stopped before reaching the planned accrual of 106 patients.

Olmi (2003) conducted a multicenter, randomized controlled phase 3 trial at 18 centers in Italy (ORO 93-01 trial). Patients aged < 70 years with histologically confirmed, previously untreated, stage III or IV, non-

metastatic, epidermoid tumors of the oropharynx were eligible. Criteria for eligibility also included a Karnofsky performance score ≥ 70 or an ECOG performance status ≤ 1, adequate bone marrow, hepatic, renal, cardiac and pulmonary function, no previous tumors, except adequately treated in situ carcinoma of the cervix and basal cell carcinoma of the skin, and no psychosis or active infectious disease. Patients were excluded if they had a T1N1 or T2N1 lesion. Patients were randomly assigned (1:1:1) to receive standard fractionated radiotherapy plus carboplatin and 5-FU (n = 64), split-course hyperfractionated accelerated radiotherapy alone (n = 65) or standard fractionated radiotherapy alone (n = 63). The treatment group of patients who received split-course hyperfractionated accelerated radiotherapy alone is not relevant for the current clinical question and is, therefore, disregarded in the summary of the literature. Radiotherapy was given in a total dose of 66-70 Gy in 33-35 fractions in 6.5-7 weeks at 2 Gy per fraction per day, 5 days per week. In the intervention group, patients received 3 cycles of chemotherapy. The first 2 cycles were given in the 1st and 5th week of radiotherapy, whereas the last cycle was given in the 9th week, therefore, after the radiotherapy was finished. Chemotherapy consisted of carboplatin (bolus of 75 mg/m^2 per day infused in 30 minutes for 4 days) and 5-FU (1000 mg/m^2 infused continuously in 96 hours for 4 days). The authors report the overall and disease-free survival at 2 year, and safety. Acute toxic effects of radiotherapy occurring within 90 days from the start of treatment were assessed using the criteria of the RTOG. Acute toxic effects of chemotherapy were assessed using the criteria of the WHO. Late toxic effects of radiotherapy occurring after 90 days from the start of treatment were assessed using the criteria of the RTOG. Due to slow inclusion, the trial was prematurely stopped before reaching the planned accrual of 260 patients.

Staar (2001) and Semrau (2006) report on a multicenter, randomized controlled phase 3 trial that was conducted at 5 centers in Germany. Patients with histologically confirmed, previously untreated, unresectable, non-metastatic, stage III or IV, squamous cell carcinoma of the oro- or hypopharynx were eligible. Criteria for eligibility also included an ECOG performance status ≥ 60, adequate bone marrow and renal function, and no history of a prior malignancy. Patients were randomly assigned (1:1) to receive hyperfractionated accelerated radiotherapy plus carboplatin and 5-FU (n = 113), or hyperfractionated accelerated radiotherapy alone (n = 127). Radiotherapy was given in a total dose of 69.9 Gy in 38 days, using a concomitant boost regimen: 5 fractions of 1.8 Gy per week in week 1-3, followed by a first daily fraction of 1.8 Gy and a second daily fraction of 1.5 Gy for 5 days per week in week 4-5.5. In the intervention group, patients received 2 cycles of chemotherapy during the 1st and 5th week of radiotherapy. Chemotherapy consisted of carboplatin (i.v. bolus of 70 mg/m^2 per day for 4 days) and 5-FU (600 mg/m^2 per day infused continuously for 4 days). The primary outcome measure was survival with local control at 1 year, which was not of our interest. The authors also report overall survival at 1, 2 and 5 years, and safety. Acute toxic effects were assessed using the criteria of the RTOG. Late toxic effects were assessed using the criteria of the RTOG/EORTC.

Results

1. Radiotherapy + cetuximab

Overall survival

Bonner (2006) found that the median duration of overall survival was 49.0 months (95%CI: 32.8-69.5) among patients treated with high-dose radiotherapy and cetuximab and 29.3 months (95%CI: 20.6-41.4) among those treated with high-dose radiotherapy alone (HR 0.74; 95%CI: 0.57 to 0.97). The overall survival rate at 3 years was 55% in the intervention group versus 45% in the control group. In the same study population, Bonner (2010) found that the overall survival rate at 5 years was 46% among patients treated with high-dose

radiotherapy and cetuximab and 36% among those treated with high-dose radiotherapy alone (HR 0.73; 95%CI: 0.56 to 0.95). Based on a subgroup analysis, cetuximab seemed to provide the most benefit for patients with an oropharyngeal tumor (n = 253). Although effect estimates and corresponding 95%-confidence intervals are not reported, the forest plot shows a statistically significant HR < 0.60, favoring the addition of cetuximab. For patients with a laryngeal or hypopharyngeal tumor, the HR did not reach the threshold for a minimal clinically important difference (i.e. HR < 0.7).

Progression-free survival
Bonner (2006) found that the median duration of progression-free survival was 17.1 months among patients treated with high-dose radiotherapy and cetuximab and 12.4 months among those treated with high-dose radiotherapy alone (HR 0.70; 95%CI: 0.54 to 0.90). The progression-free survival rates 2 and 3 years were 46% and 42%, respectively, in the intervention group versus 37% and 31%, respectively, in the control group (p-value for log-rank test = 0.04 for the comparison at 3 years, whereas no p-value is reported for the comparisor at 2 years).

Quality of life
Curran (2007) found a small, albeit statistically non-significant, absolute difference of less than 10 points in the mean global health status score (EORTC QLQ-C30) at baseline between patients treated with high-dose radiotherapy and cetuximab and patients treated with high-dose radiotherapy alone. At all visits up to and including month 12, the mean score of patients treated with high-dose radiotherapy and cetuximab was a few points higher compared with patients treated with radiotherapy alone (with higher scores representing better quality of life). The line graph shows that patients in both treatment groups had a global health score of approximately 60 at baseline. Scores decreased during treatment and had returned to baseline levels by month 12. For functional and symptom scale scores, also no statistically significant differences were found between treatment groups.

Adverse events
Bonner (2006) reported adverse events that occurred in at least 10% of patients in either treatment, regardless of the cause. The prevalence of grade $\geq$ 3 acute toxic effects did not differ significantly between patients treated with high-dose radiotherapy and cetuximab and patients treated with high-dose radiotherapy alone, except for acneiform rash (17% versus 1%; p < 0.001) and infusion reactions (3% versus 0%; p = 0.01) and anemia (1% versus 6%; p = 0.006). Severe late toxic effects related to radiotherapy were reported in about 20% of the patients in each treatment group. The sites most commonly affected were the esophagus, salivary glands, larynx, mucous membranes, subcutaneous tissues, bone, and skin. For late toxic effects, no absolute numbers or percentages per treatment group are reported.

Local recurrence and disease-free survival
No data were reported for these outcome measures.

2. RT + carboplatin
Overall survival
Fountzilas (2004) found that the median duration of overall survival was 24.5 months (range: 0.2 to 79.9) among patients treated with standard fractionated radiotherapy and carboplatin and 12.2 months (range: 1.2

to 81.7) among those treated standard fractionated radiotherapy alone (p-value for log-rank test = 0.0064). Patients treated with standard fractionated radiotherapy and carboplatin had a non-statistically significant higher overall survival than patients treated with standard fractionated radiotherapy alone (adjusted HR 0.57; 95%CI: 0.31 to 1.04). The overall survival rates at 3 and 5 years were 42% and 38%, respectively, in the intervention group versus 17.5% and 9%, respectively, in the control group.

Jeremic (1997) found that the median duration of overall survival was 30 months among patients treated with standard fractionated radiotherapy and carboplatin and 16 months (range: 1.2 to 81.7) among those treated standard fractionated radiotherapy alone (p = 0.0064). Patients in the intervention group had higher overall survival rates at 1, 2, 3, 4 and 5 years, compared with the control group: 76%, 55%, 47%, 31% and 29% versus 57%, 35%, 27%, 17% and 15%, respectively (p-value for log-rank test = 0.019).

Ruo Redda (2010) found that patients treated with standard fractionated radiotherapy and carboplatin had higher overall survival rates at 3, 5 and 10 years, compared with those treated with standard fractionated radiotherapy alone: 28.9%, 9% and 5.5% versus 11.1%, 6.9% and 6.9%, respectively (p-value for log-rank test = 0.02).

Disease-free survival
Ruo Redda (2010) found that patients treated with standard fractionated radiotherapy and carboplatin had higher disease-free survival rates at 3, 5 and 10 years, compared with those treated with standard fractionated radiotherapy alone: 28.9%, 9% and 5.5% versus 11.1%, 6.9% and 6.9%, respectively (p-value for log-rank test = 0.09).

Adverse events
Fountzilas (2004) found that the prevalence of grade $\geq$ 3 acute toxic effects did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone, except for thrombocytopenia (26% versus 0%; p = 0.0004), and nausea and vomiting (16% versus 0%; p = 0.0107).

Jeremic (1997) found that the prevalence of grade $\geq$ 3 acute non-hematological toxic effects, including mucositis, xerostomia, esophagitis, nausea and vomiting, and nephrotoxicity, did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone. Grade $\geq$ 3 acute hematological toxic effects, including leukopenia (11% versus 0%; p = 0.012) and thrombocytopenia (8% versus 0%; p = 0.041), occurred more frequently in patients treated with standard fractionated radiotherapy and carboplatin. The prevalence of grade $\geq$ 3 late toxic effects, including bone toxicity, skin toxicity and subcutaneous tissue fibrosis, was similar between treatment groups.

Ruo Redda (2010) found that the prevalence of grade $\geq$ 3 acute toxic effects, including mucositis, anemia, leukopenia and thrombocytopenia, did not differ significantly between patients treated with standard fractionated radiotherapy and carboplatin and patients treated with standard fractionated radiotherapy alone. The prevalence of grade $\geq$ 3 late toxic effects was similar between treatment groups, except for severe neck

fibrosis, which occurred more frequently in patients treated with radiotherapy and carboplatin (7 versus 3 cases). One patient treated with radiotherapy and carboplatin developed mandibular bone necrosis. No radiation myelitis or toxic-related death was observed in either treatment group.

Local recurrence, progression-free survival and quality of life
No data were reported for these outcome measures.

3. RT + carboplatin and 5-FU
Overall survival
Bourhis (2012) found that the overall survival rate at 3 years was 42.6% (95%CI: 37.0 to 48.5) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU (arm A), 39.4% (95%CI: 33.8 to 45.3) among patients treated with accelerated radiotherapy combined with carboplatin and 5-FU (arm B), and 36.5% (95%CI: 31.1 to 42.3) among patients treated with very accelerated radiotherapy alone (arm C). Resultantly, the HRs and corresponding 95%-confidence intervals are as follows: arm A versus C: HR 0.81; 95%CI: 0.67 to 0.99; arm B versus C: HR 0.87; 95%CI: 0.72 to 1.06; and arm B versus A: HR 1.05; 95%CI: 0.86 to 1.29).

Calais (1999) found that after a median follow-up of 35 months (range: 12 to 56) the median duration of overall survival was 29.2 months among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 15.4 months among those treated with standard fractionated radiotherapy alone. The overall survival rate at 3 years was 51% (95%CI: 39 to 68) in the intervention group versus 31% in the control group (p-value for log-rank test = 0.02). In the same study population, Denis (2004) found that after a median follow-up of 5.5 years (range: 4 to 7.2) the median duration of overall survival was 20 months among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 13 months among those treated with standard fractionated radiotherapy alone. The overall survival rate at 5 years was 22.4% in the intervention group versus 15.8% in the control group (p-value for log-rank test = 0.05).

Chitapanarux (2013) found that the overall survival rate at 5 years was 76.1% (95%CI: 57.8 to 7.3) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 63.5% (95%CI: 42.0 to 78.8) among patients treated with hybrid accelerated radiotherapy alone (p-value for log-rank test = 0.05).

Olmi (2003) found that the overall survival rate at 2 years was 51% among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 40% among patients treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.129).

Staar (2001) found that the overall survival rates at 1 and 2 years for all tumor types was 66% (95%CI: 57 to 75) and 48% (95%CI: 38 to 58), respectively, among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, and 60% (95%CI: 51 to 69) and 39% (95%CI: 30 to 48), respectively, among patients treated with hyperfractionated accelerated radiotherapy alone (p-value for log-rank test = 0.1139). For patients with an oropharyngeal tumor (n = 178), the overall survival rate at 1 year was 68% in the intervention group versus 57% in the control group (95%CI: ± 10; p-value for log-rank test = 0.0091). For patients with a hypopharyngeal tumor (n = 62), the overall survival curves did not differ significantly between treatment groups. In the same study population, Semrau (2006) found that the overall

survival rate at 5 years for all tumor types was 25.6% (95%CI: 15.8 to 35.4) among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, and 15.8% (95%CI: 9.1 to 22.4) among patients treated with hyperfractionated accelerated radiotherapy alone (p-value for log-rank test = 0.016). For patients with an oropharyngeal tumor (n = 178), the overall survival rate at 5 years was 26.1% (95%CI: 14.3 to 37.8) in the intervention group versus 13.0% (95%CI: 5.3 to 20.6) in the control group (p-value for log-rank test = 0.008). For patients with a hypopharyngeal tumor (n = 62), the overall survival curves did not differ significantly between treatment groups (22.2% versus 22.2%; p-value for log-rank test = 0.722).

Local recurrence
Calais (1999) found that after a median follow-up of 35 months (range: 12 to 56) the local recurrence rate was lower among patients treated with standard fractionated combined with carboplatin and 5-FU, compared with patients treated with standard fractionated radiotherapy alone (33% versus 51%; risk ratio (RR) 0.64; 95%CI: 0.47 to 0.89). In the same study population, Denis (2004) found that after a median follow-up of 5.5 years (range: 4 to 7.2) the local recurrence rate remained lower among patients treated with standard fractionated combined with carboplatin and 5-FU (41% versus 58%; RR 0.71; 95%CI: 0.54 to 0.93).

Disease-free survival
Calais (1999) found that the disease-free survival rate at 3 years was 42% (95%CI: 30 to 57) among patients treated with standard fractionated combined with carboplatin and 5-FU, and 20% among those treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.04). In the same study population, Denis (2004) found that the disease-free survival rate at 5 years was 26.6% among patients treated with standard fractionated combined with carboplatin and 5-FU, and 14.6% among those treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.01).

Olmi (2003) found that the disease-free survival rate at 2 years was 42% among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and 23% among patients treated with standard fractionated radiotherapy alone (p-value for log-rank test = 0.022).

Progression-free survival
Bourhis (2012) found that the progression-free survival rate at 3 years was 37.6% (95%CI: 32.1 to 43.4) among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU (arm A), 34.1% (95%CI: 28.7 to 39.8) among patients treated with accelerated radiotherapy combined with carboplatin and 5-FU (arm B), and 32.2% (95%CI: 27.0 to 37.9) among patients treated with very accelerated radiotherapy alone (arm C) (arm A versus C: HR 0.82; 95%CI: 0.67 to 0.99; arm B versus C: HR 0.83; 95%CI: 0.69 to 1.01); arm B versus A: HR 1.02; 95%CI: 0.84 to 1.23).

Adverse events
Bourhis (2012) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis was lower among patients treated with standard fractionated or accelerated radiotherapy combined with carboplatin and 5-FU (arm A and arm B, respectively), compared with patients treated with very accelerated radiotherapy alone (arm C). According to criteria of the RTOG, grade ≥ 3 mucositis occurred in 69% of patients in treatment arm A, in 76% of patients in treatment arm B, and in 84% of patients in treatment arm C (p = 0.0001). According to the criteria of the WHO, grade ≥ 3 mucositis occurred in 78% of

patients in treatment arm A, in 84% of patients in treatment arm B, and in 89% of patients in treatment arm C (p = 0.0016). The prevalence of grade ≥ 3 skin toxicity and grade ≥ 3 hematological toxic effects, including anemia, leukopenia and thrombocytopenia, did not differ significantly between treatment groups. The rate of patients in need of a feeding tube differed significantly between treatment arm A and treatment arm C, both during treatment (60% versus 70%; p = 0.013) and during 5-year follow-up (36% versus 43% at 1 year, 16% versus 23% at 2 years, 11% versus 18% at 3 years, 8% versus 14% at 4 years, and 13% versus 25% at 5 years; p = 0.027), but not between other treatment groups. The prevalence of late toxic effects, including xerostomia, neck fibrosis, mucositis, laryngeal toxicity and bone toxicity, 1 to 5 years after randomization did not differ significantly between treatment groups, but the severity (i.e. grade) of these late toxic effects is not reported.

Calais (1999) found that skin toxicity was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis (71% versus 39%; p = 0.005) and grade ≥ 3 skin toxicity (67% versus 59%; p = 0.02) was higher among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with standard fractionated radiotherapy alone. The prevalence of grade ≥ 3 hematological toxic effects, including neutropenia (4% versus 0%; p = 0.04), thrombocytopenia (6% versus 1%; p = 0.04) and anemia (3% versus 0%; p = 0.05), was also higher in the intervention group, but for anemia the result was not statistically significant. The rate of patients in need of a feeding tube during treatment differed significantly between treatment groups (36% versus 15%; p = 0.02). In the same study population, Denis (2004) found that the prevalence of late toxic effects during 5-year follow-up, including xerostomia, mucositis, skin toxicity and subcutaneous tissue fibrosis, neurological toxicity, mandibular bone necrosis, and taste-, hearing- and teeth-related toxicity, did not differ significantly between treatment groups.

Chitapanarux (2013) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis was lower among patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with hybrid accelerated radiotherapy alone (42% versus 68%; p = 0.01). The prevalence of grade ≥ 3 skin toxicity, grade ≥ 3 renal toxicity and grade ≥ 3 hematological toxic effects, including anemia, leukopenia and thrombocytopenia, did not differ significantly between treatment groups. The prevalence of grade ≥ 3 late toxic effects related to radiotherapy, including xerostomia, subcutaneous tissue fibrosis, mucositis and skin toxicity, did not differ significantly between treatment groups.

Olmi (2003) found that the prevalence of grade ≥ 3 acute toxic effects related to radiotherapy did not differ significantly between patients treated with standard fractionated radiotherapy combined with carboplatin and 5-FU, and patients treated with standard fractionated radiotherapy alone, except for mucositis (48% versus 15%; p = 0.0003) and skin toxicity (16% versus 4%; p = 0.0461). Grade ≥ 3 acute toxic effects related to chemotherapy included leukopenia (23% of patients), thrombocytopenia (5%), anemia (2%), anorexia (2%), and 1 fatal case of renal toxicity (1%). The prevalence of grade ≥ 3 late toxic effects related to radiotherapy during 2 year follow-up, including mucositis, skin toxicity, subcutaneous tissue fibrosis, xerostomia, spinal cord toxicity and laryngeal toxicity, did not differ significantly between treatment groups.

Staar (2001) found that mucositis was the main grade ≥ 3 acute toxic effect. The prevalence of grade ≥ 3 mucositis during treatment was higher among patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU, compared with patients treated with hyperfractionated

accelerated radiotherapy alone (68% versus 52%; p = 0.01). The prevalence of grade ≥ 3 skin toxicity (30% versus 28%) and grade ≥ 3 hematological toxic effects, including leukopenia (18% versus 0%) and thrombocytopenia (5% versus 0%), was also higher in the intervention group, but p-values are not reported and could not be calculated based on the data provided. Grade ≥ 3 anemia occurred less frequently in patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU (1% versus 0%), but it is unclear whether this result was statistically significant. Late toxic effects were reported for the total study population (Staar, 2001) or for all grades together (Semrau, 2006), except for swallowing problems and continuous use of a feeding tube, which occurred more frequently in patients treated with hyperfractionated accelerated radiotherapy combined with carboplatin and 5-FU (51% versus 25%; p = 0.02).

Quality of life
No data were reported for this outcome measure.

Level of evidence of the literature
The evidence was derived from 13 studies reporting on 9 different randomized trials. Therefore, the level of evidence for all reported outcome measures started at 'high quality'.

1. RT + cetuximab
The level of evidence regarding the outcome measure overall survival was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT and upper boundary of confidence interval exceeding the threshold of minimal clinically important difference). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure progression-free survival was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure quality of life was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). The level of evidence was not downgraded because of study limitations (i.e., active role of sponsor in collecting and analyzing the data), because no minimal clinically important difference in quality of life was observed between treatment groups. Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure adverse events was downgraded by 3 levels because of study limitations (-1; risk of bias due to active role of sponsor in collecting and analyzing the data); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measures <u>local recurrence</u> and <u>disease-free survival</u> could not be assessed, because the included studies did not report these outcome measures.

2. RT + carboplatin

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by 4 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Ruo Redda (2010), and premature termination of Jeremic (1997)); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by 4 levels because of risk of bias (-2; due to incomplete reporting and imbalanced study population); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients in a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by 5 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Ruo Redda (2010), and premature termination of Jeremic (1997)); inconsistency (-1; due to conflicting results); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Publication bias could not be assessed.

The level of evidence regarding the outcome measures <u>local recurrence</u>, <u>progression-free survival</u> and <u>quality of life</u> could not be assessed, because the included studies did not report these outcome measures.

3. RT + carboplatin and 5-FU

The level of evidence regarding the outcome measure <u>overall survival</u> was downgraded by 4 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Chitapanarux (2013), and premature termination of Chitapanarux (2013) and Olmi (2003)); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to low number of included patients in most studies). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>local recurrence</u> was downgraded by 3 levels because of study limitations (-1; risk of bias due to incomplete reporting); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients in a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>disease-free survival</u> was downgraded by 3 levels because of study limitations (-1; risk of bias due to incomplete reporting); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin); and imprecision (-1; due to low number of included patients per individual study). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>progression-free survival</u> was downgraded by 2 levels because of indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to reporting of results from a single RCT). Inconsistency and publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>adverse events</u> was downgraded by 5 levels because of study limitations (-2; risk of bias due to incomplete reporting, imbalanced study population in Chitapanarux (2013), and premature termination of Chitapanarux (2013) and Olmi (2003)); inconsistency (-1; due to conflicting results); indirectness (-1; due to study population not involving patients who are ineligible to receive cisplatin and use of different radiotherapy regimens); and imprecision (-1; due to low number of included patients in most studies). Publication bias could not be assessed.

The level of evidence regarding the outcome measure <u>quality of life</u> could not be assessed, because the included studies did not report this outcome measure .

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and fluorouracil (5-FU), compared with definitive radiotherapy alone, in patients with a locally advanced squamous cell carcinoma in the head and neck region who are ineligible to receive cisplatin?

P: Patients with a locally advanced squamous cell carcinoma in the head and neck region who are ineligible to receive cisplatin.
I: Definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and 5-FU.
C: Definitive radiotherapy alone.
O: Overall survival, local recurrence, disease-free survival, progression-free survival, quality of life, adverse events.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and local recurrence as critical outcome measures for decision making; and disease-free survival, progression-free survival, quality of life, and adverse events as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but, instead, used the definitions used in the studies.

The working group defined a minimal clinically important difference as follows:

- Overall survival: absolute difference > 5%, or absolute difference > 3% and hazard ratio (HR) < 0.7.
- Local recurrence: 0.8 or 1.25 as borders for risk or odds ratios.
- Disease-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.
- Progression-free survival: absolute difference > 5%, or absolute difference > 3% and HR < 0.7.

- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Adverse events: statistically significant difference in grade ≥ 3 adverse event rate.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms for systematic reviews published until November 12, 2020. The detailed search strategy is depicted under the tab Methods. Studies were selected if they fulfilled the following criteria: (a) patients with a locally advanced squamous cell carcinoma in the head and neck region; (b) comparison between definitive radiotherapy combined with cetuximab, carboplatin or carboplatin and 5-FU, and definitive radiotherapy alone. Studies were excluded if they only included patients with HPV-positive oropharyngeal cancer, because treatment options for this group of patients are described in a separate module. This search resulted in unique 296 hits. Based on title and abstract screening, 40 studies were initially selected. After reading the full text, all 40 studies were excluded. A table with reasons for exclusion is presented under the tab Methods. One of the excluded reviews (Iocca (2018)) compared several interventions based on a network meta-analysis of 57 RCTs, of which 7 RCTs were relevant for the current clinical question. Similarly, another 5 RCTs were identified via other excluded reviews.

To update the search performed by Iocca (2018) up to 1 September 2017, we searched for relevant RCTs published from 2017 until 18 October 2021. This search resulted in 452 hits. Based on title and abstract screening, 40 studies were initially selected. After reading the full text, all 40 studies were excluded (see table with reasons for exclusion).

<u>Results</u>

Via an excluded systematic review and network meta-analysis (Locca, 2018), 7 relevant studies (Bourhis, 2012; Bonner, 2010; Chitapanarux, 2013; Denis, 2004; Fountzilas, 2004; Ruo Redda, 2010 and Semrau, 2006) were included in the analysis of the literature. In addition, 6 relevant studies (Bonner, 2006; Curran, 2007; Calais, 1999; Jeremic, 1997; Olmi, 2003 and Staar, 2001) were identified via other excluded systematic reviews. Together, these 13 studies report the results of 9 different randomized trials. Studies that focused on the effects of definitive radiotherapy combined with either cetuximab (Bonner, 2006; Bonner, 2010 and Curran, 2007), carboplatin (Fountzilas, 2004; Jeremic, 1997 and Ruo Redda, 2010) or carboplatin and 5-FU (Bourhis, 2012; Calais, 1999; Chitapanarux, 2013; Denis, 2004; Olmi, 2003; Semrau, 2006 and Staar, 2001), compared with definitive radiotherapy alone, are analyzed separately. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Recidief T2-T4

Uitgangsvraag

Wanneer en hoe is re-irradiatie in een curatieve setting mogelijk in een recidief hoofd-halscarcinoom na chemo-radiotherapie, wanneer salvage chirurgie niet meer mogelijk is?

Aanbeveling

Bespreek met de patiënt de nadelen van re-irradiatie van een hoofd-halsplaveiselcelcarcinoom wat betreft toxiciteit. Voorspellende factoren voor toxiciteit die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: dosis eerdere radiotherapie, eerdere chirurgie, tumorlokalisatie, leeftijd, en orgaan(dys)functie.

Bespreek bij patiënten met een nasofarynxcarcinoom de kans op overleving na re-irradiatie. Factoren die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: leeftijd, tumorstadium en EBV-concentratie in het bloed.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De werkgroep heeft een literatuuronderzoek verricht naar de prestatie van (multivariabele) modellen welke (de kans op) toxiciteit en overleving tijdens of na re-irradiatie voorspellen. Er werden twee gevalideerde modellen gevonden die overleving en toxiciteit voorspellen. Vanwege een zeer lage bewijskracht kan geen uitspraak worden gedaan over de prestatie van deze modellen. De zeer lage bewijskracht wordt voornamelijk veroorzaakt door beperkingen in de studieopzet ten aanzien van de ontwikkeling van de modellen en het ontbreken van externe validatie van de modellen. De werkgroep concludeert dan ook dat er een kennislacune bestaat omtrent het bestaan van beslissingsmodellen welke op basis van risicofactoren overleving en toxiciteit tijdens of na re-irradiatie bij patiënten, bij wie opereren geen mogelijkheid meer is, kunnen voorspellen.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Toxiciteit is een belangrijke uitkomst voor patiënten, waarbij de balans tussen toxiciteit en overleving een belangrijke afweging is. Toxiciteit geeft veel bijwerkingen, zoals necrose, mucositis, zwelling, slikproblemen, en pijn. Daarom moet met de patiënt worden besproken wat de nadelen kunnen zijn van re-irradiatie, en wat de eventuele voordelen zijn wat betreft overleving.

Kosten (middelenbeslag)
Re-irradiatie heeft geen grote impact op de kosten. Alternatieven van re-irradiatie zijn palliatieve opties, wanneer resectie niet meer mogelijk is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Vanwege de zeer lage bewijskracht van de gevalideerde modellen, kan er geen sterke aanbeveling worden gedaan welke factoren van belang zijn bij de keuze voor re-irradiatie. Het is belangrijk de voor- en nadelen met de patiënt te bespreken.

Onderbouwing

Achtergrond

Het doel van deze module is om de beste behandeling van een recidief hoofd-halscarcinoom na (chemo)radiotherapie als primaire behandeling dan wel adjuvant na resectie in beeld te brengen. Daarbij is het vooral van belang uit te zoeken wanneer re-irradiatie mogelijk is, als chirurgie niet meer mogelijk is, bij een recidief hoofd-halscarcinoom of tweede primaire tumor in een gebied dat eerder (chemo)radiotherapie gehad heeft. Daarbij zouden schade aan normale weefsels, overleving, toxiciteit, complicaties en kwaliteit van leven mogelijke uitkomsten kunnen zijn, en de factoren die bepalen of re-irradiatie nog mogelijk is, zouden type tumor, locatie tumor, reeds aanwezige postradiatie-effecten, tijdsinterval tot eerdere radiotherapie en patiëntgeschiedenis.

Conclusies

Toxicity: The level of evidence regarding the outcome measure toxicity started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (one level, no external validation) and imprecision (only one study with relatively low numbers of patients and events).

Overall survival: The level of evidence regarding the outcome measure started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (two levels, no external validation and different population).

Toxicity

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Ward, 2019, where dose of radiotherapy during first course, tumor site, organ dysfunction, any surgery, age and recurrent or second primary are selected as factors that predict toxicity after re-irradiation for head and neck squamous cell carcinoma. *Sources: (Ward, 2019)*

Overall survival

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Sun, 2022, where patient age, rT stage, and EBV DNA level are selected as factors that predict overall survival after re-irradiation for nasopharyngeal carcinoma. *Sources: (Sun, 2022)*

Samenvatting literatuur

Description of studies
Ward, 2019: From 9 institutions, 505 patients were included with recurrent or second primary (RSP) squamous carcinoma originating in a field previously irradiated to ≥ 40 Gy and treated with IMRT-based re irradiation to ≥ 40 Gy. A multivariable competing-risk model was fit to the actuarial risk of late toxicity with progression or death as the competing risk, using a backwards stepdown procedure. The final bootstrap optimized model was converted into a nomogram.

Sun, 2022: A prognostic model was established and validated for locally recurrent nasopharyngeal carcinoma (lrNPC) patients. In total, 531 patients from one center with lrNPC were retrospectively reviewed, including 271 patients from 2006 to 2012 as the training cohort and 260 patients from 2013 to 2016 as the validation cohort. Overall survival (OS) was the primary endpoint. Multivariate analysis was performed to select the significant prognostic factors (P < 0.05). A prognostic model for OS was derived by recursive partitioning analysis (RPA) combining independent predictors using the algorithm of optimized binary partition.

Results

Toxicity:
Ward, 2019: The final model included six clinical factors:

- Dose of radiotherapy during first course (continuous, per Gy) (HR 1.075 (95%CI 1.031 to 1.122)).
- Tumor site (oropharynx, larynx or lypopharynx versus other) (HR 1.575 (95%CI 0.984 to 2.519)).
- Organ dysfunction (yes versus no) (HR 3.029 (95%CI 1.919 to 4.783)).
- Any surgery (yes versus no) (HR 1.232 (95%CI 0.781 to 1.943)).
- Age (continuous, per year) (HR 0.977 (95%CI 0.955 to 0.998)).
- RSP (second primary versus recurrence) (HR 1.061 {95% CI 0.656 to 1.713)).

The final model demonstrated an average bootstrapped C-index of 0.698.

Overall survival:
Sun, 2022: The final model included 3 factors:

- Patient age (> 60 versus 60: hazard ratio (HR): 1.757, 95% confidence interval (CI): 1.181 to 2.615, P = 0.005).
- rT stage (rT2 versus rT1: HR: 1.725, 95% CI: 0.919 to 3.241, P = 0.090; rT3 versus rT1: HR: 2.439, 95% CI: 1.453 to 4.096, P = 0.001; rT4 versus rT1: HR: 5.007, 95% CI: 2.989 to 8.388, P < 0.001).
- EBV DNA level (detectable versus undetectable: HR: 1.825, 95% CI: 1.355 to 2.459, P < 0.001).

The study reported that re-irradiation could benefit patients in the low (P < 0.001) and intermediate-risk subgroups (P = 0.017), while no association between re-RT and survival benefit was found in the high-risk subgroup (P = 0.328).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the prognostic factors of successful re-irradiation in patients in a curative setting with a locoregional recurrent head and neck carcinoma after primary or adjuvant (chemo)radiotherapy, where salvage surgery is no longer possible?

P: (Patients) = Patients with a head and neck carcinoma that is recurring after primary or adjuvant (chemo)-radiotherapy, where salvage surgery is no longer possible.
I: (Intervention)= A model that predicts for which patients re-irradiation is successful, defined by intervention success, tissue damage, overall survival, toxicity, complications and quality of life.

C: (Comparison)= A different model/care as usual.
O: (Outcomes)= Predictive value of the model.
T:(Timing)= When in recurring head/neck carcinoma a treatment plan is determined.
S: (Setting)= Specialized care.

Relevant outcome measures
The guideline development group considered overall survival and toxicity as critical outcomes.

The working group defined the performance of the included models in Area Under the ROC Curve (AUC) as follows:

- 0.7 ≤AUC< 0.8: acceptable.
- 0.8 ≤AUC< 0.9: excellent.
- AUC≥ 0.9: outstanding.

Prognostic research: Study design and hierarchy
When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, the effectiveness of a clinical decision model is evaluated in a randomized clinical trial. Unfortunately, these studies are very rare. If not available, studies in which prediction models are developed and validated in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to studies that are not externally validated. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prediction models internally (e.g. bootstrapping or cross validation) can be used to answer the research question, but downgrading the level of evidence is necessary due to risk of bias and/or indirectness as it is not clear whether models perform sufficiently in target populations. The confidence in the results of unvalidated prediction models is very low. Therefore, such models will not be graded. This is also applicable for association models.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 14th of February 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 133 hits. Studies were selected based on the following criteria:

- Being a systematic review, randomized controlled trial (RCT) or observational study (cohort study).
- Reporting multivariable longitudinal association model or prediction model with outcome (mortality or complications periprocedural or within 30 days) as dependent variable and independent variables (patient characteristics) determined before the treatment plan was made.
- Models do not take independent variables into account that were determined after the treatment plan was made.

Four studies were initially selected based on title and abstract screening. After reading the full text, two studies were excluded (see the table with reasons for exclusion under the tab Methods) and two studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Ward MC, Lee NY, Caudell JJ, Zajichek A, Awan MJ, Koyfman SA, Dunlap NE, Zakem SJ, Hassanzadeh C, Marcrom S, Boggs DH, Isrow D, Vargo JA, Heron DE, Siddiqui F, Bonner JA, Beitler JJ, Yao M, Trotti AM, Riaz N; Multi-Institution Re-Irradiation (MIRI) Collaborative. A competing risk nomogram to predict severe late toxicity after modern re-irradiation for squamous carcinoma of the head and neck. Oral Oncol. 2019 Mar;90:80-86. doi: 10.1016/j.oraloncology.2019.01.022. Epub 2019 Feb 8. PMID: 30846182.

Speekselkliercarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Het management van de klinisch negatieve hals tijdens de resectie van een carcinoom van de parotis of de glandula submandibularis

Uitgangsvraag

Wat is het management van de klinisch negatieve hals tijdens de resectie van een carcinoom van de parotis of de glandula submandibularis?

Aanbeveling

Carcinoom van de glandula parotis
Verricht bij een cN0 hals bij voorkeur een selectieve electieve halsklierdissectie (Level II en III) tijdens de chirurgische resectie van maligne glandula parotis tumoren.

Carcinoom van de glandula submandibularis
Verricht bij een cN0 hals bij voorkeur een selectieve electieve halsklierdissectie (Level Ib, II en III) tijdens de chirurgische resectie van maligne glandula submandibularis tumoren.

Overwegingen

Electieve selectieve behandeling hals bij een carcinoom van de glandula parotis
De literatuur levert slechts zeer zwak bewijs op voor dat een selectieve halsklierdissectie (Level II-III) tot minder lokale en regionale recidieven en tot hogere overleving na vijf jaar leidt ten opzichte van geen halsklierdissectie. Een systematische review laat echter zien dat er bij patiënten met een carcinoom van de glandula parotis een grote kans bestaat occulte metastasen in de ipsilaterale hals (gewogen gemiddelde 23%; range 20%-33%) (Valstar et al., 2010). Omdat het gewogen gemiddelde hoger is dan 20% is adviseert de werkgroep om de hals electief te behandelen bij patiënten met een tumor van de glandula parotis (Weiss et al., 1994).

Uit retrospectieve studies blijkt dat occulte metastasen in de hals met name voorkomen in Level II & III en dat die occulte metastasen met name voorkomen bij high- tot intermediate-grade tumoren (Ettl et al., 2012; Kawata et al., 2010; Klussmann et al., 2008; Armstrong et al., 1992; Stenner et al., 2012).

In de studie van Chrisholm zijn geen skipmetastasen gevonden naar Level I en V zonder dat Level II is aangedaan (Chrisholm et al., 2011). Daarom is het te overwegen om parotistumoren met een cN0 hals, zeker bij tumoren met een hoge maligniteitsgraad, de hals electief chirurgisch te behandelen middels een selectieve electieve halskiersdissectie van Level II & III.

Electieve selectieve behandeling hals bij een carcinoom van de glandula submandibularis
Bij glandula submandibularistumoren komt een N+ hals bij 40% van de patiënten voor (Pohar et al., 2011). De halskliermetastasen komen met name voor bij tumoren met een hoge malgniteitsgraad en dan voornamelijk in level I of II. Skip metastasen komen nauwelijks voor en occulte halskliermetastasen komen slechts in ongeveer 19,5% van de gevallen voor. (Han et al., 2012; Ettl et al., 2012). Omdat bij de resectie van de glandula submandibularis Level I & II al in het operatiegebied liggen is het aan te raden om deze Levels electief mee te nemen bij de tumorresectie, zonder dat dit extra morbiditeit veroorzaakt.

Electieve selectieve behandeling hals bij carcinoom van de glandula parotis en submandibularis
Uit de literatuur is niet te achterhalen of de electieve behandeling van de hals chirurgisch dan wel radiotherapeutisch verricht kan worden. Vanwege het feit dat bij de operatie van de glandula parotis of de glandula submandibularis de betrokken lymfeklieren in de hals in het directe operatiegebied ligt is het te overwegen om de hals meteen chirurgisch te behandelen. Voordeel is dan dat er zekerheid wordt verkregen over de histologie van de halsklieren, zodat de eventuele postoperatieve radiotherapie daarop kan worden afgestemd.

Indien postoperatief pas blijkt dat er sprake is van een maligniteit van de glandula parotis of submandibularis en er nog geen electieve halsklierdissectie is verricht, kan er op basis van het risicoprofiel een indicatie zijn voor electieve radiatie van de hals (Terhaard et al., 2005).

Onderbouwing

Achtergrond

Wanneer cytologie van een primaire speekselkliertumor van de parotis op maligniteit wijst, zal er, afhankelijk van de uitbreiding van de tumor, een oppervlakkige dan wel totale parotidectomie worden uitgevoerd. In het geval van een klinisch negatieve hals, is het de vraag of daarbij ook een electieve halsklierdissectie moet worden verricht. Vervolgens is het de vraag of er ook kan worden volstaan met een selectieve halsklierdissectie.

Conclusies

Zeer laag	*5-jaars lokale en regionale controle* Er zijn beperkte aanwijzingen dat een selectieve electieve halsklierdissectie de lokale en regionale controle verbetert bij patiënten met een parotis carcinoom en een klinisch negatieve hals. *Bronnen (Zbären et al., 2005)*

Zeer laag	*(Ziektevrije) overleving* Er zijn beperkte aanwijzingen dat de 5-jaars overleving hoger is na een electieve halsklierdissectie. Er zijn beperkte aanwijzingen dat de ziektevrije 5-jaars overleving gelijk is tussen de halsklierdissectie- en de controlegroep. *Bronnen (Zbären et al., 2005)*

> *Kwaliteit van leven, majeure postoperatieve complicaties, ernstige bijwerkingen radiotherapie*
>
> - Er is geen vergelijkende studie gevonden waarin onderzocht is of er een verschil is in kwaliteit van leven, het voorkomen van majeure postoperatieve complicaties of ernstige bijwerkingen radiotherapie tussen (super)selectieve halsklierdissectie en geen halsklierdissectie bij patiënten met een parotis carcinoom en een klinisch negatieve hals.

Ad 2) Electieve selectieve halsklierdissectie versus geen electieve selectieve halsklierdissectie bij patiënten met een carcinoom van de glandula submandibularis

De werkgroep heeft geen vergelijkende studies gevonden die deze vraagstelling hebben onderzocht.

> *Lokale en regionale controle, (ziektevrije) overleving, kwaliteit van leven, majeure postoperatieve complicaties, ernstige bijwerkingen radiotherapie*
>
> - Er is geen vergelijkende studie gevonden waarin onderzocht is of er een verschil is in lokale/regionale controle, (ziektevrije) overleving, kwaliteit van leven, het voorkomen van majeure postoperatieve complicaties of ernstige bijwerkingen radiotherapie tussen (super)selectieve halsklierdissectie en geen halsklierdissectie bij patiënten met een carcinoom van de glandula submandibularis en een klinisch negatieve hals.

Samenvatting literatuur

Ad 1) Electieve selectieve halsklierdissectie versus geen electieve selectieve halsklierdissectie bij patiënten met een carcinoom van de glandula parotis
In één retrospecief cohort (Zbären et al., 2005) ondergingen 83 patiënten met een primair carcinoom van de parotis en een klinisch negatieve hals een parotidectomie, eventueel gevolgd door postoperatieve radiatie. 41 patiënten hiervan ondergingen een electieve selectieve halsklierdissectie (niveau I-III) en 42 patiënten ondergingen geen electieve halsklierdissectie. De gemiddelde follow-up was 64 maanden in de groep halsklierdissectie en 76 maanden in de controlegroep.

5-jaars lokale en regionale controle
Zbären et al., (2005) rapporteerden een lokaal recidief bij vijf patiënten (12%) in de interventiegroep en 11 (26%) patiënten in de controlegroep (niet getoetst op significantie). Geen van de patiënten in de electieve halsklierdissectiegroep had een regionaal recidief, in de controlegroep hadden zeven patiënten (17%) een regionaal recidief (P=0,006).

(Ziektevrije) overleving
Aan het eind van de follow-up periode waren drie patiënten uit de interventiegroep en 4 uit de controlegroep overleden (doodsoorzaak: recidief). De overleving na 5 jaar was 86% in de halsdissectiegroep en 69% in de controlegroep (niet getoetst op significantie).

De uitkomstmaten 'kwaliteit van leven', 'majeure postoperatieve complicaties' en 'ernstige bijwerkingen radiotherapie' zijn niet onderzocht.

Zoeken en selecteren

Methode literatuuranalyse
Om de uitgangsvraag te kunnen beantwoorden is er een systematische literatuuranalyse verricht naar de volgende twee vraagstellingen:
1. Voor patiënten met een carcinoom van de glandula parotis:
Wat is het effect van superselectieve halsklierdissectie (level II-III) tijdens de parotidectomie vergeleken met geen halsklierdissectie (eventueel aangevuld met radiotherapie) of alleen halsklierdissectie na positieve uitslag van een level II halsklierbiopt op de hieronder genoemde uitkomstmaten?

2. Voor patiënten met een carcinoom van de glandula submandibularis:
Wat is het effect van (super)selectieve halsklierdissectie (level I-III) tijdens de resectie van de primaire tumor in de glandula submandibularis, vergeleken met geen halsklierdissectie (eventueel aangevuld met radiotherapie) of alleen halsklierdissectie na positieve uitslag van een biopt op de hieronder genoemde uitkomstmaten?

Relevante uitkomstmaten
De werkgroep achtte "lokaal en regionaal recidief" een voor de besluitvorming belangrijke uitkomst. Daarnaast achtte de werkgroep "metastase op afstand", "overleving", "overleving met zoveel mogelijk behoud van functie", "kwaliteit van leven", "majeure postoperatieve complicaties (zoals heroperatie of onbedoelde IC opname)" en "ernstige bijwerkingen radiotherapie (radionecrose van bot en kraakbeen, ototoxiciteit, xerostomie en slikproblemen) voor de besluitvorming belangrijke uitkomsten en "ernstige bijwerkingen systemische chemotherapie (ototoxiciteit, neurotoxiciteit, nierschade)" werden als minder belangrijk uitkomsten meegenomen.

Zoeken en selecteren van literatuur

In de databases Medline (OVID), Embase and Cochrane is gezocht naar carcinomen van de glandula parotis of glandula submandibularis en (super)selectieve halsklierdissectie. De zoekverantwoording is weergegeven onder het tabblad Verantwoording. De literatuurzoekactie leverde 224 treffers op.

Voor vraagstelling 1 werden studies geselecteerd op grond van de volgende criteria:

- vergelijkend onderzoek of systematische reviews van vergelijkend onderzoek;
- vergelijking van (super)selectieve halsklierdissectie met geen (super)selectieve halsklierdissectie of halsklierddissectie na positieve uitslag biopt;
- patiënten met een carcinoom van de glandula parotis;
- rapportage van minstens een van de hierboven genoemde uitkomstmaten.

Voor vraagstelling 2 werden studies geselecteerd op grond van de volgende criteria:

- vergelijkend onderzoek of systematische reviews van vergelijkend onderzoek;
- vergelijking van selectieve halsklierdissectie met geen selectieve halsklierdissectie;
- patiënten met een carcinoom van de glandula submandibularis;
- rapportage van minstens een van de hierboven genoemde uitkomstmaten.

In totaal werden 16 artikelen geselecteerd op basis van titel en abstract. Na het lezen van de volledige artikelen voldeed uiteindelijk één studie aan alle selectiecriteria voor wetenschappelijke vraagstelling 1 (Zbären et al., 2005). De evidencetabel hiervan kunt u in desbetreffende sectie in deze module vinden.

Bewijskracht van de literatuur

De bewijskracht voor de uitkomstmaten 'lokale controle', 'regionale controle' en '(ziektevrije) overleving' is verlaagd, omdat 1) het een systematische review van niet gerandomiseerde studies betreft 2) het onduidelijk is op basis van welke criteria patiënten aan de behandelgroepen zijn toegewezen en 3) in de analyse niet gecontroleerd is voor prognostische factoren (beperkingen in de onderzoeksopzet). Tevens is het aantal onderzochte patiënten laag (impresicie).

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Het beleid ten aanzien van de reconstructie van de nervus facialis bij patiënten met een parotiscarcinoom

Uitgangsvraag

Wat is het beleid ten aanzien van de reconstructie van de nervus facialis bij patiënten met een parotiscarcinoom?

Aanbeveling

Algemeen
Voer primaire reconstructie van de zenuw uit bij zenuwbeschadiging na parotischirurgie.

Voorkom uitdroging van het oog; denk hierbij aan druppels, horlogeglasverband en zalf. Bij onvoldoende resultaat kan gedacht worden aan bovenooglidverzwaring en onderooglid inkorting.

Zenuwreconstructie
Overbrug een zenuwdefect met een zenuwtransplantaat dat met microchirurgische technieken ingehecht wordt.

Statische correctie
Gebruik statische correcties zo nodig in aanvulling op reïnnerverende ingrepen.

Dynamische correctie
Gebruik locale, regionale of vrije spierlappen als reïnnerverende ingrepen niet mogelijk zijn.

Overwegingen

Gevolgen van beschadiging nervus facialis
Indien bij parotis chirurgie de oogtak beschadigd raakt kan een lagophthalmus ontstaan en dreigt uitdroging van de cornea. Dit kan meestal voorkomen worden door het gebruik van oogzalf en een horlogeglas verband. Sommige chirurgen stellen oogheelkundige consultatie hiervoor op prijs. Dit is aangewezen als het oog rood blijft ondanks locale therapie. Primaire perioculaire chirurgie (inbrengen goudgewichtje en onderooglid inkorting) verkleint de noodzaak voor het gebruik van deze middelen (Watts et al., 2007; Golio et al., 2007).

Indien bij de operatie de mondtak beschadigd raakt treedt er verlies van tonus op in de periorale spieren, die afhankelijk van de elasticiteit van het gelaat leidt tot scheefstand van de mond naar de gezonde zijde en problemen met praten, eten en drinken.
Schade aan de frontale tak leidt tot wenkbrauwptosis; schade aan de marginale tak tot onderlip dysfunctie.

Reconstructieve mogelijkheden: algemene opmerkingen
Voor reconstructie van facialis dysfunctie komen statische methoden (fascia lata plastieken en huidcorrecties), dynamische methoden (kauwspiertransposities en vrije gevasculariseerde en geïnnerveerde spiertransplantaties) en zenuwherstellende methoden in aanmerking (Werker et al., 2007). Bij de keuze hiertussen hoeft leeftijd geen rol te spelen en verdient primaire zenuwreconstructie van met name de oog- en

de mondtak - indien mogelijk - de voorkeur (Iseli et al., 2010). Secundaire reconstructie (nadat de bestraling is voltooid) heeft als potentieel nadeel dat er een grotere kans op het optreden van wondgenezingsstoornissen ontstaat.

Daarbij moet wel opgemerkt worden dat reconstructie met locale of regionale spierlappen of met fascia lata strips of met vrije spierlappen op zijn minst een theoretische kans geeft op tumor spil en bestraling van een groter veld noodzakelijk kan maken. De meningen over dit laatste zijn binnen de werkgroep richtlijn ontwikkeling overigens verdeeld en er ontbreekt literatuur hierover.

Reconstructieve mogelijkheden: zenuwreconstructie
Indien gekozen wordt voor zenuwreconstructie is het volgende van belang. Afhankelijk van de hoeveelheid transplantaat dat nodig is kan een veelheid aan zenuwen als graft gebruikt worden: de n. auricularis magnus, andere takken van de sensibele cervicale plexus, de n. suralis, de r. superficialis van de n. radialis, de n. cutaneus antebrachii medialis en lateralis en de n. peroneus superficialis.

De resultaten voor wat betreft reïnnervatie en functie van zenuwreconstructie van de mond- en de oogtak worden door de meeste auteurs als gunstig beschreven (tegenstanders: Stephanian et al., 1992; voorstanders: Volk et al., 2011; Iseliet al., 2010). Resultaten van reconstructie van de marginale tak met een zenuwtransplantaat zijn in functioneel opzicht teleurstellend (Kerrebijn et al., 1998). Volk (2011) rapporteert dat, indien proximaal slechts de hoofdstam van de nervus facialis resteert en distaal de verschillende facialis takken geïdentificeerd zijn, voor de periorbitale regio gebruik gemaakt kan worden van een transplantaat tussen de hoofdstam en oogtakken en voor de periorale regio van een transplantaat tussen de n. hypoglossus en de mondtakken.

Er zijn onvoldoende aanwijzingen dat aanvullende verbetering van de wondbodem met locale of regionale spierlappen nuttig is (Motomura et al., 2011). Er zijn geen aanwijzingen dat zenuw-uitgroei negatief wordt beïnvloed door bestraling (Guntinas et al., 2007; Gullane et al., 1987; Reddy et al.,1999). In experimentele setting is de zenuw regeneratie door gevasculariseerde zenuwtransplantaten beter dan door niet gevasculariseerde, vooral in een verlittekend wondbed (Shibata et al., 1988). Er zijn echter geen klinische studies die dit verschil bevestigen.

Reconstructieve mogelijkheden: statische correcties
Indien gekozen wordt voor statische correctie met fascia lata, is deze gericht op het voorkomen van het ontstaan van grove asymmetrie in rust. Strips worden aan de mediale zijde verankerd in boven en onderlip, aan de mondhoek en aan de nasolabiaalplooi. Lateraal worden fixatiepunten gezocht aan de arcus zygomaticus en aan de kaakhoek. Men dient te waken voor te strak aanspannen van de strips.

Reconstructieve mogelijkheden: dynamische correcties
Indien gekozen wordt voor dynamische correctie, kan de m. masseter caudaal gedeeltelijk losgemaakt worden van de kaakhoek en naar de mond gebracht worden. Ook kan de m. temporalis gebruikt worden ter reanimatie van zowel de lach als de oogsluiting. Tenslotte kan een vrij gevasculariseerd en geïnnerveerd spiertransplantaat (m. gracilis of m. pectoralis minor) aangewend worden. Dit kan gereïnnerveerd worden op

een facialis tak of gebruikmakend van de n. massetericus. In het eerste geval leidt dit veelal tot herstel van de spontane lach. In het tweede geval is het op elkaar zetten van de tanden nodig voor verplaatsing van de mondhoek.

Onderbouwing

Achtergrond

In een aantal gevallen is het noodzakelijk om in het proces van excisie van de tumor met marge (een deel van) de perifere n. facialis op te offeren. Hierdoor kan verstoring van de mimiek optreden. In deze module wordt samengevat wat de mogelijkheden voor reconstructie zijn.

Samenvatting literatuur

Niet van toepassing.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Wat indicaties voor postoperatieve radiotherapie voor patiënten met speekselkliertumoren zijn

Uitgangsvraag

Wat zijn indicaties voor postoperatieve radiotherapie voor patiënten met speekselkliertumoren?

Aanbeveling

Postoperatieve radiotherapie is geïndiceerd bij:

- krappe of irradicale resectie;
- T3, T4 tumoren;
- perineurale tumorgroei langs grote zenuwen (zenuwen met een naam);
- hooggradige tumoren;
- extranodale groei.

Overweeg postoperatieve radiotherapie bij:
twee of meer positieve klieren zonder kapseldoorbraak.

Overwegingen

In de literatuur worden geen gerandomiseerde studies gevonden naar postoperatieve radiotherapie voor maligne tumoren van de speekselklieren. Door de relatieve zeldzaamheid van speekselklier tumoren met ook wisselende locaties (vooral parotis, mondholte en submandibularis, maar ook veel kleine speekselklieren in de pharynx, lip) en wisselende histologie (24 subclassificaties, vaak onderverdeeld in laag en hoog maligne) valt ook niet te verwachten dat een gerandomiseerde studie mogelijk is. Vandaar dat de richtlijn gebaseerd is op de grote retrospectieve studies met een lange FU en een uitgebreide statistische analyse. De Nederlands NWHHT studie is hier een goed voorbeeld van. Bij analyse van deze studies komt enerzijds naar voren dat er geen indicatie voor postoperatieve radiotherapie is voor radicaal geopereerde, laaggradige, T1-T2 maligne tumoren van de speekselklier. Voor krappe en irradicaal geopereerde speekselklieren tumoren, T3-T4, perineurale groei en bij hoge graad wordt iha in de studies een positief effect op de lokale controle gezien van postoperatieve radiotherapie, de invloed op de algehele overleving levert wisselende resultaten op. In de Nederlandse studie leverde postoperatieve radiotherapie met betrekking tot de regionale controle winst op in geval van positieve klieren, ongeacht aantal en extranodale groei. Daar waar voor het plaveiselcelcarcinoom van de mucosa van hoofd-hals tumoren winst voor de regionale controle wordt gezien vanaf twee klieren zonder extranodale groei, dan wel vanaf één klier met extranodale groei, is dit bij maligne speekselkliertumoren niet uitgebreid bestudeerd. Vandaar de overweging om bij maligne speeksel kliertumoren vanaf twee of meer positieve klieren, onafhankelijk van extranodale groei, postoperatief regionaal te bestralen. Voor de veldkeuze en bestralingsdosis wordt verwezen naar de handboeken (Perez et al., Principles and practice of Radiation Oncology, 2013).

Onderbouwing

Achtergrond

Maligne tumoren van de speekselklieren werden vroeger als radioresistent beschouwd. Er bestaat echter veel literatuur dat, voor patiënten met een maligne speekseltumor met een verhoogd risico op recidief na chirurgie, postoperatieve radiotherapie de locoregionale controle verbetert. Er bestaan geen gerandomiseerde studies naar de waarde van postoperatieve radiotherapie. De bewijsvoering berust op retrospectieve studies, zoals in Nederland uitgevoerd door de NWHHT. Landelijke NWHHT-richtlijnen voor de indicaties van postoperatieve radiotherapie bij maligne speekselklier tumoren ontbreken.

Conclusies

1. Postoperatieve radiotherapie versus geen postoperatieve radiotherapie

Zeer laag GRADE	*10-jaars lokale controle* Er zijn aanwijzingen dat postoperatieve radiotherapie de 10-jaars lokale controle verbetert bij patiënten met T3-T4 tumoren, krappe resectie, irradicale resectie, botinvasie enperineurale invasie. *Bronnen (Terhaard et al., 2005)*

Zeer laag GRADE	*5-jaars lokale controle* Er lijkt een trend te zijn dat postoperatieve radiotherapie de 5-jaars lokale controle verbetert bij patiënten met T3-T4 tumoren en hooggradige tumoren. *Bronnen (Armstrong et al., 1990)*

Zeer laag GRADE	*5-jaars locoregionale controle* Er zijn aanwijzingen dat postoperatieve radiotherapie de 5-jaars locoregionale controle verbetert bij patiënten met kliermetastasen. *Bronnen (Armstrong et al., 1990)*

Zeer lage GRADE	*5-jaars regionale controle* Er zijn aanwijzingen dat postoperatieve radiotherapie de 5-jaars regionale controle verbetert bij patiënten met positieve halsklieren. *Bronnen (Terhaard et al., 2005)*

Zeer lage GRADE	*Ziektevrije overleving* Postoperatieve radiotherapie lijkt de vijf jaar-ziektevrije overleving te verhogen bij patiënten met T3-T4 tumoren. Er lijkt een trend te zijn dat postoperatieve radiotherapie de vijf jaar-ziektevrije overleving verbetert bij patiënten met kliermetastasen. Er lijkt een trend te zijn dat postoperatieve radiotherapie de vijf jaar-ziektevrije overleving verbetert bij patiënten met een hooggradige tumor. *Bronnen (Armstrong et al., 1990)*

-	*Kwaliteit van leven en overall overleving* Geen onderzoek heeft het effect van postoperatieve radiotherapie vergeleken met geen postoperatieve radiotherapie op kwaliteit van leven en overall overleving.

2. Onafhankelijke prognostische factoren

Zeer lage GRADE	*Lokaal recidief* Postoperatieve radiotherapie, hogere leeftijd, positieve klieren en nervus facialis parese lijken onafhankelijke prognostische voorspellers te zijn voor lokaal recidief. *Bronnen (Pohar et al., 2005; North et al., 1990)*

Zeer lage GRADE	*Locoregionaal recidief na tien jaar* T3-T4 speekselkliertumoren, hooggradige tumoren, positieve snijvlakken en lymfekliermetastasen lijken onafhankelijke prognostische factoren te zijn voor locoregionaal recidief na tien jaar. *Bronnen (Chen et al., 2006)*

Zeer lage GRADE	*Locoregionaal recidief na vijf jaar* Postoperatieve radiotherapie, toenemende TNM-stadiering, toenemende grootte van de tumor en hogere leeftijd lijken onafhankelijke prognostische factoren te zijn voor locoregionaal recidief na vijf jaar. *Bronnen (Renehen et al., 1999; Kirkbride et al., 2001; Shen et al., 2012; Armstrong et al., 1990)*

Samenvatting literatuur

1. Postoperatieve radiotherapie versus geen postoperatieve radiotherapie

Twee retrospectieve studies vergeleken de combinatie postoperatieve radiotherapie (N totaal=432) en chirurgie met alleen chirurgie(N totaal=158) bij patiënten met maligne speekselkliercarcinomen (submandibularis, parotis en mondholte)(Armstrong et al, 1990; Terhaard et al, 2005). In beide studies was de follow-up minstens 5 jaar. De bestraling schema's zijn te vinden in de evidencetabellen onder de desbetreffende kop.

Lokale controle
Postoperatieve radiotherapie verbeterde significant de 10-jaars lokale controle in vergelijking tot alleen chirurgie bij patiënten met a) T3-T4 tumoren (84% versus 18%; p<0.001), b) krappe resectie (95% versus 55%; p=0.003), c) irradicale resectie (82% versus 44%; p<0.001), d) botinvasie (86% versus 54%; p=0.04) en e) perineurale invasie (88%versus 60%; p=0.01) (Terhaard et al., 2005). Armstrong (1990) vond gunstigere resultaten voor de 5-jaars lokale controle in de groep postoperatieve radiotherapie bij patiënten met T3-T4 tumoren en/of patiënten met hooggradige tumor, statistisch niet significant.

5-jaars locoregionale controle
In de groep postoperatieve radiotherapie werd bij patiënten met kliermetastasen een locoregionale controle gevonden van 69% ten opzicht van 40% in de controlegroep (p=0.05) (Armstrong et al., 1990).

5-jaars regionale controle
Terhaard (2005) laat zien dat 86% van de patiënten met positieve halsklieren, die na de ingreep bestraald werden, vijf jaar na de ingreep tumorvrij zijn in vergelijking tot 62% in de controlegroep (p=0.03).

Ziektevrije overleving
Armstrong (1990) vond voor patiënten met een T1-T2 stadiëring een 5-jaars overleving van 82% wanneer deze werden bestraald ten opzichte van 96% wanneer deze niet werden bestraald (statistisch niet significant (NS)), voor patiënten met T3-T4 was de ziektevrije overleving 52% respectievelijk 10% (p=0.015), voor de klier metastases was deze 49% ten opzichte van 19% (p=NS) en voor een hooggradige tumor 57% ten opzichte van 28% (p=NS).

Kwaliteit van leven en overall overleving
Geen van de geïncludeerde studies had deze uitkomstmaten onderzocht.

2. Onafhankelijke prognostische factoren
Zeven retrospectieve studies onderzochten onafhankelijke prognostische factoren bij patiënten met speekselkliercarcinomen(submandibularis, parotis en mondholte) (Renehen et al., 1999; Kirkbride et al., 2001; Shen et al., 2012; Armstrong et al., 1990; Pohar et al., 2005; North et al., 1990; Chen et al., 2006). De follow-up periode varieerde van vier jaar (Pohar et al, 2011) tot een mediaan van 7,4 jaar (Kirkbride et al., 2001).

Lokaal recidief
Twee studies onderzochten voorspellers voor lokaal recidief na 5 jaar (Pohar et al., 2005; North et al., 1990). Postoperatieve radiotherapie (Pohar et al., 2005; North et al., 1990), toenemende leeftijd op het moment van diagnose (Pohar et al., 2005), aanwezigheid van positieve klieren (Pohar et al., 2005) en nervus facialis parese (North et al., 1990) werden als onafhankelijke prognostische factoren geïdentificeerd.

Locoregionaal recidief

Vier studies onderzochten voorspellers voor de uitkomstmaat locoregionaal recidief na 5 jaar (Renehen et al,1999; Kirkbride et al, 2001; Shen et al, 2012; Armstrong et al, 1990). Postoperatieve radiotherapie (Renehen et al,1999; Shen et al, 2012), toenemende grootte van de tumor (Renehen et al, 1999), toenemende T-stadiëring (Kirkbride et al, 2001; Shen et al, 2012; Armstrong et al, 1990), hogere leeftijd (Kirkbride et al, 2001) en NM-stadiëring (Armstrong et al, 1990) werden als onafhankelijke prognostische factoren gevonden. Chen et al (2007) heeft voorspellers geïdentificeerd voor de uitkomstmaat locoregionaal recidief na 10 jaar en vond T3-T4 tumoren, hooggradige tumoren, lymfekliermetastases en positieve snijvlakken als prognostisch onafhankelijke factoren.

Zoeken en selecteren

Methode literatuuranalyse

Om de uitgangsvraag te kunnen beantwoorden zijn is er twee systematische literatuuranalyse verricht naar de volgende vraagstellingen:

1.	Wat is het effect van postoperatieve radiotherapie op 1. lokale controle, 2.(loco)-regionale-controle, 3. (ziektevrije) overlevingen 4. kwaliteit van leven in vergelijking tot geen postoperatieve radiotherapie na een chirurgische ingreep van maligne speekselkliertumoren (parotis, submandibularis en mondholte)?

2.	Wat zijn onafhankelijke prognostische factoren voor lokale controle en (loco)-regionale-controle bij patiënten met maligne speekselkliertumoren (parotis, submandibularis en mondholte)?

In de databases Medline (OVID) en Embase is gezocht naar postoperatieve radiotherapie bij patiënten met speekselkliercarcinomen. De zoekverantwoording is weergegeven onder het tabblad Verantwoording. De literatuurzoekactie leverde 301 treffers op.

Studies voor vraagstelling 1 werden geselecteerd op grond van de volgende selectiecriteria:

- (systematische review van)vergelijkend onderzoek;
- vergelijking van postoperatieve radiotherapie versus geen postoperatieve radiotherapie;
- presentatie van het effect van postoperatieve radiotherapie per effect-modificator (T-stadiëring; histologie; resectievlakken; en zenuwinvasie)
- minimaal één van de volgende uitkomstmaten: lokale controle, (loco)-regionale controle, (ziektevrije) overleving of kwaliteit van leven.

Studies voor vraagstelling 2 werden geselecteerd op grond van de volgende selectiecriteria:

- (systematische review van) prognostisch onderzoek;
- identificatie van onafhankelijke prognostische factoren;
- presentatie van de hazard ratio met p-waarde of 95% BI van de co-variabelen verkregen uit multivariate analyse;
- en lokaal recidief of (loco-) regionaal recidief als uitkomstmaten.

Op basis van titel en abstract zijn 31 studies geselecteerd. Na raadpleging van de volledige tekst bleken acht studies te voldoen aan de selectiecriteria (Armstrong et al., 1990; Kirkbride et al., 2001; North et al., 1990; Pohar et al., 2005; Renehen et al., 1999; Chen, 2006; Shen et al., 2012; Terhaard et al., 2005).

Bewijskracht van de literatuur

1. Postoperatieve radiotherapie versus geen postoperatieve radiotherapie

De bewijskracht voor de uitkomstmaten de 10-jaars lokale controle, 5-jaars locoregionale controle, 5-jaars regionale controle, ziektevrije overleving is zeer laag omdat het geen gerandomiseerde onderzoeken betreft (beperkingen in onderzoeksopzet) en de studies van beperkte omvang zijn (imprecisie).

De bewijskracht voor de uitkomstmaten de 5-jaars lokale controle is zeer laag omdat het geen gerandomiseerde onderzoeken betreft (beperkingen in onderzoeksopzet), de studies van beperkte omvang zijn en de resultaten statistisch niet significant zijn (imprecisie).

2. Onafhankelijke prognostische factoren

De bewijskracht voor de uitkomstmaten lokaalrecidief en locoregionaal recidief na vijf jaar respectievelijk tien jaar is zeer laag. De vraag die de werkgroep feitelijk wenst te beantwoorden is wat de effectiviteit en complicaties zijn van postoperatieve radiotherapie. Dit is een interventievraag, waarbij gerandomiseerd onderzoek of observationeel vergelijkend onderzoek wenselijk is. Echter wordt nu een interventievraag beantwoord door middel van onderzoek op het domein van prognose (beperkingen in onderzoeksopzet). Tevens zijn de studies van beperkte omvang (imprecisie).

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Neus en neusbijholte tumoren

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Endoscopische chirurgie maligne neus(bij)holtetumoren

Uitgangsvraag

Wat is de rol van endoscopische chirurgie bij patiënten met maligne tumoren van neus of neus(bij)holte?

Aanbeveling

Overweeg bij de chirurgische behandeling van maligne neus(bij)holtetumoren zowel een uitwendige open benadering als een endoscopische benadering.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De geïncludeerde studies vergeleken een endoscopische resectie met een open resectie bij patiënten met een neusholte of neusbijholtecarcinoom. De systematische literatuuranalyse laat zien dat het onduidelijk is of behandeling met een endoscopische resectie positieve effecten heeft op algemene overleving, ziektevrije overleving en complicaties. Geen van de geïncludeerde studies rapporteerde over de uitkomstmaat kwaliteit van leven. Hierdoor is het niet mogelijk een uitspraak te doen over het effect van een endoscopische behandeling op kwaliteit van leven in vergelijking met een open resectie. De gerapporteerde duur van de opname is korter met endoscopische resecties. De overall bewijskracht van de literatuur werd gegradeerd als zeer laag. Dit heeft te maken met imprecisie van de bevindingen door het kleine aantal patiënten in de studiearmen, en beperkingen in de onderzoeksopzet. Het was daarnaast niet mogelijk een meta-analyse uit te voeren, vanwege de statistische heterogeniteit in de uitkomstmaten tussen de studies en wegens heterogeniteit in de patiëntpopulaties tussen de studies.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Er is geen objectief bewijs dat de patiënten voorkeur hebben voor endoscopisch of open resecties. In het algemeen worden endoscopische resecties geaccepteerd als patiëntvriendelijker en leiden zij tot een kortere opnameduur. Verwacht mag worden dat indien oncologisch gelijkwaardig patiënten de endoscopische procedure prefereren gezien het minder invasieve karakter en het ontbreken van de noodzaak tot een litteken in het gelaat.

Kosten (middelenbeslag)
Er is geen bewijs voor een betere kosten(effectiviteit) van endoscopische resecties. In Nederland zijn er geen groepen die nadeel zou hebben van de kosten geassocieerd aan de behandelmethoden.

Aanvaardbaarheid, haalbaarheid en implementatie
Er is geen gestructureerd onderzoek gedaan in de vorm van procesevaluatie naar de haalbaarheid van endoscopische resecties en externe benaderingen, maar beide worden in Nederland reeds breed toegepast. Er is zeer laag bewijs dat endoscopische resectie dezelfde effectiviteit heeft als open resecties (externe benadering). Endoscopische of open resecties zijn beide complexe ingrepen die uitgevoerd moeten worden door daarvoor opgeleide chirurgen. Er is geen subgroep in Nederland die geen toegang kan krijgen naar de aanbevolen behandeling. De behandeling van neus(bij)holtetumoren worden uitgevoerd in een aantal gespecialiseerde ziekenhuizen in Nederland. In al deze ziekenhuizen worden de ingrepen uitgevoerd door

daarvoor opgeleide chirurgen. De haalbaarheidscriteria van endoscopisch of open chirurgie van de neusbijholten zijn vergelijkbaar. Specifiek expertise is vereist, maar deze is in centra voorhanden. Dit type chirurgie kan zonodig, afhankelijk van de lokale situatie, in samenwerking tussen hoofd-halschirurg en KNO-arts gespecialiseerd in neusbijholtechirurgie uitgevoerd worden.

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>
Er is geen overtuigend bewijs dat endoscopische resectie van neus(bij)holtetumoren voordeliger of nadeliger is dan open resectie (via externe benadering) wat betreft de algemene overleving, ziekte specifieke overleving of kwaliteit van leven. De bestaande publicaties van retrospectieve data tonen vergelijkbare uitkomsten met endoscopische en open resecties. De opname duur is korter met endoscopische resecties. Endoscopische technieken zijn nieuwer en in de afwezigheid van nadelen in de geaccumuleerde data kunnen deze worden uitgevoerd door daarvoor opgeleide chirurgen. Deze aanbeveling is niet sterk onderbouwd. Open resecties blijven een geldige optie.

Onderbouwing

Achtergrond

Tot eind jaren 90 was de standaard behandeling van maligne neusbijholtetumoren een externe benadering middels sublabiale incisie, laterale rhinotomie, midfacial degloving of vergelijkbare technieken. Vervolgens werd een deel van maxilla (en eventueel andere benige structuren van de neusbijholten) verwijderd. In de laatste twee decennia met de vooruitgang van de endoscopische technieken wordt vaker een tumorresectie uitgevoerd op een 'piecemeal' manier. Deze techniek is patiëntvriendelijker. De vraag is of de endoscopische 'piecemeal' resectie van maligne neusbijholtetumoren dezelfde oncologische resultaten geeft als een externe chirurgische benadering.

Conclusies

<u>Overall survival</u>

Very low GRADE	It is uncertain whether treatment with endoscopic resection results in higher overall survival compared with treatment with open resection in patients with SNM/SNSCC. *Sources: (Cao, 2017; Ledderose, 2015; Lund, 2012; Meng, 2014; Miglani, 2017; Swegal, 2014; Won, 2015; Hagemann, 2019; Huang, 2018; Farquhar, 2016; Saedi, 2014; Kılıç, 2018)*

<u>Disease-free survival</u>

Very low GRADE	It is uncertain whether treatment with endoscopic resection results in higher disease-free survival compared with treatment with open resection in patients with SNM/SNSCC. *Sources: (Cao, 2017; Ledderose, 2015; Lee, 2015; Miglani, 2017; Swegal, 2014)*

<u>Complications/adverse events</u>

Very low GRADE	It is uncertain whether treatment with endoscopic resection results in less complications compared with treatment with open resection in patients with SNM/SNSCC. *Sources: (Hagemann, 2019; Huang, 2018; Fu, 2017; Farquhar, 2016; Mortuaire, 2016)*

<u>Quality of life</u>

- GRADE	None of the included studies reported quality of life.

Samenvatting literatuur

<u>Description of studies</u>
Systematic reviews
Hur (2019) performed a systematic review and meta-analysis comparing endoscopic resections with open resection in patients with sinonasal mucosal melanoma (SNM). They searched scientific literature up to May 2018. Inclusion criteria were: (1) participants: patients diagnosed with SNM; (2) intervention: endoscopic resection (ER) of SNM; (3) comparison: open resection (OR) or combined resection (endoscopic and open) of SNM; (4) outcomes: overall survival (OS) or disease-free survival (DFS). Exclusion criteria were: studies which did not report survival rates or no comparison was performed between endoscopic and open approaches. In total, 9 studies were included. Nine studies were included in the qualitative synthesis, and 7 studies were included in quantitative synthesis (meta-analysis). Eight studies were retrospective cohort studies, and one study was a prospective cohort study. The studies included a total of 485 participants. Two hundred thirty-two participants received endoscopic resection and 253 participants received open resection. Follow-up ranged from a median of 0.6 years to a mean of 40.9 months across studies. The following relevant outcome measures were reported: overall survival and disease-free survival.

Lu (2019) performed a systematic review and meta-analysis comparing endoscopic resections with open resections in patients with uncommon sinonasal malignancies (SNM). They searched scientific literature up to April 2019. Inclusion criteria were: (1) histopathological primary malignancies involving the sinonasal cavity; (2) in comparative cohorts managed by both endoscopic resection and open resection approaches; (3) with reported at least one surgical outcome; and (4) in patients aged 18 years or older. Exclusion criteria were: (1) mucosal melanoma histology as that represents a distinctly different tumor type; (2) tumors that are not deemed malignant, for example, angiofibroma and papilloma; (3) recurrent pathologies; (4) hybrid cranioendoscopic approaches to resection; and (5) case series/reports with no comparative cohort. In total, 10 studies were included in the quantitative synthesis (meta-analysis). All 10 studies were retrospective observational cohort studies. The studies included a total of 900 participants. Three hundred ninety-nine participants received endoscopic resection and 501 participants received open resection. Follow-up ranged from a median of 21.0 months to a median of 79.2 months across studies. The following relevant outcome measure was reported: overall survival.

Observational studies
Kiliç (2018) performed a propensity score-matched analysis comparing endoscopic resections with open resection in cases with sinonasal squamous cell carcinoma (SNSCC) without cervical or distant metastases.

Cases of SNSCC diagnosed between January 1, 2010 and December 31, 2014 were used. The selection was further limited to cases that received definitive primary site surgery, with a known surgical approach. Exclusion criteria were: (1) preoperative chemotherapy and/or radiotherapy > 180 days after surgery; (2) any N stage other than N0 (which would necessitate neck dissection); (3) M1/stage IVC; (4) unknown vital status or follow-up time. A total of 1483 cases were included in the study. Three hundred fifty-three cases underwent endoscopic resection and 1130 patients underwent open resection. Propensity score-matched analyses were performed with 652 patients: 326 with endoscopic resection and 326 matching patients with open resections. The mean length of follow-up was not reported. The following relevant outcome measures were reported: 5-year overall survival.

Results

Overall survival
Overall survival was reported in three studies (Hur, 2019; Lu, 2019; Kiliç, 2018).

In the systematic review of Hur (2019), seven studies (Cao, 2017; Ledderose, 2015; Lund, 2012; Meng, 2014; Miglani, 2017; Swegal, 2014; Won, 2015) reported the hazard-ratio (HR) for five-year overall survival. Intervention group = endoscopic resection, control group: open resection.

- Cao (2017): HR = 1.43 (95% CI= 0.09 to 23.64), in favour of open resection.
- Ledderose (2015): HR = 0.96 (95% CI= 0.09 to 10.71), in favour of endoscopic resection.
- Lund (2012): HR = 0.52 (95% CI= 0.30 to 0.92), in favour of the intervention group.
- Meng (2014): HR = 1.21 (95% CI= 0.61 to 2.40), in favour of open resection.
- Miglani (2017): HR = 0.06 (95% CI= 0.00 to 31.88), in favour of endoscopic resection.
- Swegal (2014): HR = 1.01 (95% CI= 0.15 to 6.76), in favour of endoscopic resection. Won (2015): HR = 0.58 (95% CI= 0.34 to 0.99), in favour of endoscopic resection.

In the systematic review of Lu (2019), four studies (Hagemann, 2019; Huang, 2018; Farquhar, 2016; Saedi, 2014) reported overall survival outcomes. The studies reported different statistical outcome measures and follow-up lengths. Hagemann (2019) reported the five-year overall survival rate (%). Huang, 2018) reported the mean overall survival in months. Farquhar (2016) reported the three-year overall survival rate (%). Saedi (2014) reported the median overall survival in months.

- Hagemann (2019): The five-year overall survival rate was 76% in the endoscopic resection group and 59% in the open resection group.
- Huang (2018): The mean overall survival was 80 months in the endoscopic resection group and 65 months in the open resection group.
- Farquhar (2016): The three-year overall survival rate was 91% in the endoscopic resection group and 76% in the open resection group.
- Saedi (2014): The median overall survival was 24 months in the endoscopic resection group and 28 months in the open resection group.

The study of Kiliç (2018) reported the five-year overall survival rate.

- The five-year overall survival rate after propensity matching was 50.8% (95% CI= 37.7% to 63.5%) in the intervention group and 56.53% (95% CI= 46.5% to 66.5%) in the control group (p=0.850).

Disease-free survival
Disease-free survival was reported in one systematic review (Hur, 2019).

In the systematic review of Hur (2019), five studies (Cao, 2017; Ledderose, 2015; Lee, 2015; Miglani, 2017; Swegal, 2014) reported the hazard-ratio (HR) for five-year disease-free survival. The definition of disease-free survival was not explicitly reported in the study. Since the study reported five-year overall survival, it is assumed that the study also used five-year disease-free survival a study outcome.

- Cao (2017): HR = 1.36 (95% CI= 0.35 to 5.38), in favour of open resection.
- Ledderose (2015): HR = 0.38 (95% CI= 0.03 to 5.34), in favour of endoscopic resection.
- Lee (2015): HR = 0.35 (95% CI= 0.10 to 1.20), in favour of endoscopic resection.
- Miglani (2017): HR = 0.49 (95% CI= 0.06 to 3.74), in favour of endoscopic resection.
- Swegal (2014): HR = 0.60 (95% CI= 0.06 to 5.72), in favour of endoscopic resection.

Complications
Complications were reported in one systematic review (Lu, 2019).

In the systematic review of Lu (2019), five studies (Hagemann, 2019; Huang, 2018; Fu, 2017; Farquhar, 2016; Mortuaire, 2016) reported the risk-ratio (RR) for complications.

- Hagemann (2019): RR= -4.75 (95% CI= -5.27 to -4.23), in favour of endoscopic resection.
- Huang (2018): RR= -3.50 (95% CI= -5.57 to 1.43), in favour of endoscopic resection.
- Fu (2017): RR= -0.70 (95% CI= -1.30 to -0.11), in favour of endoscopic resection.
- Farquher (2016): RR= -2.90 (95% CI= -3.95 to -1.85), in favour of endoscopic resection.
- Mortuaire (2016): RR= -2.60 (95% CI= -3.45 to -1.75), in favour of endoscopic resection.

Quality of life
None of the included studies reported quality of life as an outcome measure.

<u>Level of evidence of the literature</u>
Overall survival
The certainty of the evidence regarding **overall survival** started low, as the evidence originated from observational studies, and was downgraded by one level because of the small number of patients in the studies (imprecision). The level of evidence was graded as *very low*.

Disease-free survival

The certainty of the evidence regarding **disease-free survival** started low, as the evidence originated from observational studies, and was downgraded by one level because of the small number of patients in the studies (imprecision). The level of evidence was graded as very low.

Complications
The certainty of the evidence regarding **complications** started low, as the evidence originated from observational studies, and was downgraded by one level because of the small number of patients in the studies (imprecision). The level of evidence was graded as very low.

Quality of life
The level of evidence was not graded because no studies reported **quality of life**.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

P: Patients with nasal cavity and paranasal sinus carcinoma;
I: Endoscopic surgery;
C: External surgery;
O: Overall survival, disease-free survival, complications/adverse events, quality of life.

<u>Relevant outcome measures</u>
The guideline development group considered overall survival and disease-free survival as a critical outcome measure for decision making; and complications/adverse events, quality of life as an important outcome measure for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Time from randomisation to death from any cause, with a minimum follow-up of 5 years
Disease-free survival	Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence, with a minimum follow-up of 5 years
Complications/adverse events	All negative effects related to the treatment (lethal, acute/serious, chronic)
Quality of life (QoL)	Overall QoL or regarding a specific domain, measured with a validated and reliable instrument, such as the SF-36 or EORTC QLQ-C30 or EORTC QLQ-HN35/43.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 6th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 241 hits.

Studies were selected based on the following criteria: included with nasal cavity and paranasal sinus carcinoma, compared endoscopic surgery with external surgery, reported at least one of the outcomes of interest, the study design was a systematic review (SR), randomized controlled trial (RCT) or observational study, and were written in English language.

Fifty-six studies were initially selected based on title and abstract screening. After reading the full text, 51 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 3 studies were included.

Data-synthesis
Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis) separately. A priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:

- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results
Three studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Chemotherapie toegevoegd aan radiotherapie

Uitgangsvraag

Wat is de rol van chemotherapie toegevoegd aan radiotherapie als primaire behandeling bij patiënten met neus(bij)holtecarcinoom?

Aanbeveling

De werkgroep kan geen aanbeveling geven over de rol van chemotherapie toegevoegd aan radiotherapie als primaire behandeling, omdat onderzoek hiernaar ontbreekt.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ter onderbouwing van een aanbeveling.

Een narrative review van **Bossi (2015)** beschreef de rol van systemische therapie als onderdeel van een multidisciplinaire aanpak van (locally advanced) neus en neusbijholtecarcinomen. Zij rapporteerden dat, omdat het een zeldzame ziekte is, er alleen beperkte ervaringen zijn met kleine aantallen patiënten, en dat er tot nu toe geen prospectieve, gerandomiseerd trials zijn uitgevoerd (Bossi, 2015). Zij concludeerden dat, net zoals bij andere types hoofd-halstumoren, een multidisciplinaire aanpak voor diagnose en behandeling nodig is voor neus- en neusbijholtecarcinomen. Ondanks dat er geen gerandomiseerde trials zijn, suggereren data van meerdere observationele studies dat systemische therapie mogelijk een bijdrage kan leveren in het verbeteren van overleving, met een mogelijke rol in orgaan-/structuurbehoud. Echter er is meer onderzoek nodig om de exacte rol van chemotherapie en de optimale volgorde ten opzichte van lokale behandelingen vast te stellen.

Er bestaan echter wel kleine series die voor bijvoorbeeld esthesioneuroblastoom een mogelijk voordeel laten zien van de toevoeging van chemotherapie, bijvoorbeeld in geval van inductie bij inoperabele tumoren (Fiani, 2019). In overleg binnen het team en met de patiënt kan besloten worden tot chemotherapie.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Een recidief na behandeling van neus- of neusbijholtecarcinoom na chirurgie, meestal gevolgd door radiotherapie, heeft een negatieve impact op de overleving en de kwaliteit van leven van de patiënt. De toevoeging van chemotherapie aan de behandeling zou van grote waarde kunnen zijn als dit de locoregionale controle zou verhogen. Gezien de mogelijke toxiciteit van de chemotherapie moet bij voorkeur de meerwaarde zijn aangetoond.

Er zijn echter geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de

wetenschappelijke literatuur ten aanzien van de belangrijkste doelen van de interventie voor de patiënt en eventueel verzorger(s) en er is niet bekend welke voor- en nadelen van de interventies de patiënt ziet en welke waarde de patiënt aan deze voor- en nadelen (prioritering van de uitkomstmaten) hecht. De eventuele belasting voor, en de belastbaarheid van de patiënt is onbekend. En er zijn dan ook geen subgroepen waarbij de waarden en voorkeuren van patiënten (en eventueel hun verzorgers) anders zijn.

Kosten (middelenbeslag)
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ten aanzien van kosten (middelenbeslag), echter de ervaring bij andere hoofd-halscarcinomen is dat toevoeging van cisplatin geen grote impact heeft op de totale kosten van de behandeling.

Aanvaardbaarheid, haalbaarheid en implementatie
Er zijn geen gerandomiseerde studies of kwalitatief goede vergelijkende observationele studies gevonden die de effecten van chemotherapie toegevoegd aan radiotherapie hebben onderzocht bij neus- en neusbijholtecarcinomen. Er kunnen daarom geen conclusies worden getrokken op basis van de wetenschappelijke literatuur ten aanzien van de aanvaardbaarheid en haalbaarheid van de interventies (bijvoorbeeld procesevaluatie). Echter de ervaring bij andere hoofd-halscarcinomen leert dat chemoradiatie een toxische behandeling is en als zodanig door patiënten wordt ervaren. Echter gezien het ontbreken van evidence is implementatie van chemotherapie als standaardbehandeling in de curatieve setting bij neus- en neusbijholtecarcinomen niet aan de orde.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
In kleine studies lijkt er een mogelijk voordeel te zijn van inductiechemotherapie bij een inoperabel proces of voor functiebehoud, met name bij SNUC (ongedifferentieerd carcinoom) en esthesioneuroblastoma. Ondanks gebrek aan evidence kan dit na overleg in het team met patiënt als optie besproken worden.

Onderbouwing

Achtergrond

Het is niet duidelijk wat de beste manier is om chemotherapie in te zetten voor de behandeling van neusholte- en neusbijholtecarcinoom. Chemotherapie kan op verschillende manieren worden toegepast: vóór de operatie, na de operatie of als primaire behandeling. Chemotherapie wordt vaak gebruikt in combinatie met radiotherapie.

Conclusies

Crucial outcome measures
Overall survival

- **GRADE**	No studies were found that could answer the question on the effects of chemotherapy added to radiotherapy on overall survival.

Disease-free survival

- GRADE	No studies were found that could answer the question on the effects of chemotherapy added to radiotherapy on disease-free survival.

Important outcome measures
Distant metastasis-free survival, complications/adverse events and quality of life

- GRADE	No studies were found that could answer the question on the effects of chemotherapy added to radiotherapy, on important outcome measures.

Samenvatting literatuur

Description of studies
Not applicable.

Results
No studies were found that reported on the crucial and important outcome measures.

Certainty of the evidence
No studies were selected that reported on the crucial and important outcome measures, and therefore, GRADE could not be applied, and no conclusions could be drawn on the effect of chemotherapy added to radiotherapy, on overall survival.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of chemotherapy added to radiotherapy, compared to radiotherapy alone in patients with nasal cavity and paranasal sinus carcinomas?

P: patients with nasal cavity and paranasal sinus carcinoma;
I: chemotherapy added to radiotherapy;
C: radiotherapy;
O: overall survival, disease-free survival, distant metastasis-free survival, complications/adverse events, quality of life.

Relevant outcome measures
The guideline development group considered overall survival and disease-free survival as a crucial outcome measure for decision making; and distant metastasis-free survival, complications/adverse events and quality of life as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Time from randomisation to death from any cause, with a minimum follow-up of 5 years
Disease-free survival	Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence, with a minimum follow-up of 5 years
Distant metastasis-free survival	Time to appearance of a distant metastasis, with a minimum follow-up of 5 years
Complications/adverse events	All negative effects related to the treatment (lethal, acute/serious, chronic)
Quality of life (QoL)	Overall QoL or regarding a specific domain, measured with a validated and reliable instrument, such as the SF-36 or EORTC QLQ-C30 or EORTC QLQ-HN35/43.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR <0.7.
- Relapse-free survival: HR< 0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until Jun 17th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 298 hits.

Studies were selected based on the following criteria: included patients with nasal cavity and paranasal sinus carcinoma, compared chemotherapy added to radiotherapy with radiotherapy alone, reported at least one of the outcomes of interest, the study design was a systematic review (SR) or randomized controlled trial (RCT), and were written in English language.

Nineteen studies were initially selected based on title and abstract screening. After reading the full text and thorough assessment of the studies, 19 studies were excluded (see the table with reasons for exclusion under the tab Methods) and no studies were included.

Data-synthesis
Results from RCTs and observational studies were described and synthesized (preferably by meta-analysis)

separately. A priori, the guideline development group decided that observational studies should be of sufficient quality to allow a useful GRADE assessment and to allow conclusions that can guide the recommendations. The guideline development group used the following criteria for eligible observational studies of sufficient quality:

- Compared at least two interventions.
- Included at least 50 patients.
- Corrected for at least one plausible confounder, for example by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

Results
No studies were included in the analysis of the literature.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Bossi, P., Saba, N. F., Vermorken, J. B., Strojan, P., Pala, L., De Bree, R.,... & Takes, R. P. (2015). The role of systemic therapy in the management of sinonasal cancer: a critical review. Cancer treatment reviews, 41(10), 836-843.
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Nasofarynxcarcinoom

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Behandeling nasofarynxcarcinoom - inductie chemotherapie

Uitgangsvraag

Wat is de plaats van inductie chemotherapie bij de behandeling van het nasofarynxcarcinoom?

Aanbeveling

Voor patiënten < 70 jaar, met een WHO conditie 0 tot 1 met een ongedifferentieerd nasofarynxcarcinoom voor stadium IV en een selectie stadium III wordt inductiechemotherapie gevolgd door concomitante chemoradiotherapie aanbevolen.

Voor stadium T3N0 wordt inductie chemotherapie niet aanbevolen. Voor T3N1 en T4N0 kan inductie chemotherapie worden overwogen.

Voor het plaveiselcelcarcinoom stadium III/IV wordt inductie chemotherapie gevolgd door chemoradiatie niet aanbevolen. Een winst van inductie chemotherapie is niet aangetoond en er is risico op toegenomen toxiciteit.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De combinatie van inductie chemotherapie met concomitante chemoradiatie therapie lijkt de algehele overleving, ziektevrije overleving en afstandsmetastase vrije overleving van patiënten met stadium III/IV, nasofarynxcarcinoom te verbeteren ten opzichte van concomitante chemoradiatie therapie alleen, maar het leidt mogelijk ook tot meer complicaties en bijwerkingen. De overall bewijskracht van de cruciale uitkomstmaten is laag.

Echter we dienen te beseffen dat het overgrote aantal patiënten komt uit studies uitgevoerd in Aziatische landen waarbij nasofarynxcarcinoom ten dele een andere etiologie heeft en het doorgaans een ongedifferentieerd niet-verhoornend carcinoom betreft. Zo worden in het Westen meer tumoren gezien die niet ongedifferentieerd zijn; het betreft vaker een plaveiselcelcarcinomen, die waarschijnlijk een correlatie met roken hebben.

Bij analyse van de individuele studies blijkt dat bij alle positieve studies (Cao, 2017; Hong, 2018; Li, 2019; Sun, 2016; Yang, 2019) alleen WHO subtype 2/3 patiënten zijn geselecteerd. Er is dus geen evidence dat inductie chemotherapie bij WHO subtype 1 leidt tot betere overleving, het type dat in het Westen bij 1 op 3 patiënten wordt gezien. Voor de patiënten met een WHO subtype 2/3 werden niet alle stadium III/IV patiënten geselecteerd in de positieve studies. De studie van Hong (2018) betrof alleen stadium IV. Stadium T3N0-N1 werden uitgesloten in de studies van Sun (2016), Cao (2017) en Yang (2019); Stadium T3-T4 N0 in de studie van Li (2019). Op basis van deze analyse luidt de conclusie dat voor stadium IV WHO subtype 2/3 er evidence is dat inductie chemotherapie leidt tot betere algehele overleving, ziektevrije overleving en afstandsmetastase vrije overleving. Hiervoor is voor stadium III T3N0 geen evidence. Patiënten met stadium III T3N1 (Cao, 2017; Yang, 2019) en stadium IVa T4N0 (Li, 2019; Sun, 2016) werden in enkele studies

uitgesloten. De conclusie voor deze stadia luidt dat inductie chemotherapie <u>mogelijk</u> tot een betere overleving leidt, en voor deze stadia kan worden overwogen om inductie chemotherapie toe te voegen aan concomitante chemoradiatie therapie.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
Het belangrijkste doel van de interventie voor de patiënt is betere overleving en deze lijkt, met inductie chemotherapie iets beter dan zonder. Dit moet wel worden afgewogen tegen de toegenomen toxiciteit. Derhalve is van belang om te zien welke patiëntencategorie het meeste voordeel heeft bij toevoeging van inductie chemotherapie. Op basis van de boven vermelde analyse betreft dit de groep patiënten met een ongedifferentieerde tumor, omdat deze patiëntengroep de grootste kans op afstandsmetastasen heeft. Tevens dienen patiënten, gezien de toxiciteit van de behandeling en de nog volgende chemoradiatie, in principe < 70 jaar te zijn en een WHO 0-1 te hebben om in aanmerking te komen voor inductie chemotherapie. Het risico bestaat anders dat patiënten niet aan hun concomitante chemotherapie toekomen, welke waarschijnlijk belangrijker voor de overleving is dan inductie chemotherapie. Voor plaveiselcelcarcinoom van de nasofarynx is superioriteit van inductiechemotherapie niet aangetoond en heeft ook gezien de verhoogde toxiciteit concomitante chemoradiotherapie zonder inductiechemotherapie de voorkeur.

<u>Kosten (middelenbeslag)</u>
Inductie chemotherapie gevolgd door concomitante chemoradiotherapie leidt tot een aanzienlijke verlenging van de behandelduur voor de patiënt, en hogere kosten als gevolg van de toegevoegde inductiechemotherapie. Daarnaast kan verhoogde toxiciteit ook tot een toename in kosten leiden. Dit moet gewogen worden tegen een besparing door minder noodzaak tot eventuele salvage therapie (waarvan mogelijkheden voor de primaire tumor beperkt zijn) en een (beperkt) verlies in levensjaren. Voor de Nederlandse situatie zijn geen studies naar kosteneffectiviteit voor de behandeling van nasofarynxcarcinomen uitgevoerd.

Voor de subgroep met een goede algehele conditie < 70 jaar en een ongedifferentieerd stadium III (exclusief T3N0 en mogelijk T3N1) en met name stadium IV zijn de baten mogelijk hoger dan de kosten.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
Inductie chemotherapie gevolgd door concomitante chemoradiotherapie wordt vaker toegepast bij zeer uitgebreide hoofd-halstumoren en wordt in het algemeen redelijk verdragen, maar er is wel een risico dat (bij een klein percentage, te halen uit de gerandomiseerde studies) dat door de toxiciteit van het inductie deel het concomitante deel (samen met de radiotherapie) niet of niet volledig kan worden gegeven. Chemotherapie is een haalbare interventie, maar de patiënt moet wel jonger dan 70 jaar zijn en in een WHO conditie 0 tot 1, een goede nierfunctie en geen aanmerkelijk gehoorverlies hebben.

Als bezwaar geldt een toegenomen belasting voor de patiënt tegenover een relatief kleine winst. In Nederland heeft iedereen voldoende toegang tot een hoofd-halsoncologisch centrum zodat implementatie van inductie chemotherapie goed haalbaar is. Deze zorg wordt alleen geleverd in een hoofd-halsoncologisch centrum, waarvan er 8 in Nederland zijn en 6 een preferred partner hebben. Daar is voldoende expertise aanwezig. Wanneer in plaats van fotonen, op basis van geschatte lagere kans op toxiciteit, protonen een deel

van de behandeling vormen, dan kan de reisafstand een belemmering vormen, niet in financiële maar in praktische zin. Het kan betekenen dat de chemotherapie en radiotherapie in twee centra plaatsvinden of dat naast de radiotherapie ook de chemotherapie in het protonencentrum zal worden gegeven. Er is een goede afstemming nodig tussen het hoofd-halsoncologisch centrum en het protoneninstituut.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Op basis van een meta-analyse van gerandomiseerde studies uitgevoerd in voornamelijk Aziatische landen naar het voordeel van inductie chemotherapie gevolgd door concomitante chemoradiotherapie voor stadium IV en geselecteerde patiënten met stadium III nasofarynx carcinomen kan worden geconcludeerd dat hiermee de ziektevrije overleving wordt verbeterd, met name de afstandsmetastase vrije overleving en in mindere mate de algehele overleving, ten koste van een verhoogde acute toxiciteit. Dit geldt echter niet voor patiënten met stadium T3N0. Voor stadium T3N1 en stadium T4N0 geldt dat ze in diverse studies zijn uitgesloten. Voor patiënten met deze stadia kan inductie chemotherapie gevolgd door chemoradiatie worden overwogen.

In de Aziatische landen zijn de nasofarynxcarcinomen voornamelijk ongedifferentieerde tumoren. In Nederland is 1/3 van de tumoren een plaveiselcelcarcinoom met een associatie met roken, een hoger risico op locoregionaal recidief en minder kans op afstandsmetastasen.

Voor het plaveiselcelcarcinoom is er geen bewijs om in stadium III/IV inductie chemotherapie gevolgd door concomitante chemoradiotherapie aan te bevelen. De beperkte winst moet afgewogen worden tegen de toegenomen toxiciteit en dit moet met de patiënt besproken worden.

Onderbouwing

Achtergrond

De toevoeging van chemotherapie als inductie of adjuvant regime aan chemoradiatie therapie is in verschillende studies onderzocht, met wisselende resultaten. De toxiciteit van systemische therapie na chemoradiatie blijft een actueel onderwerp.

Conclusies

Crucial outcome measures
Overall survival (5 year)

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may result in a slight increase of overall survival in WHO subtype 2/3, stage III/ IV, excluding T3N0 nasopharyngeal cancer patients at 5-year follow-up, when compared to concurrent chemoradiation therapy alone. *Sources: (Hong, 2018; Li, 2019; Yang, 2019)*

Disease-free survival (5 year)

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may result in an increase of disease-free survival in WHO subtype 2/3, stage III/ IV, excluding T3N0 nasopharyngeal cancer patients at 5-year follow-up, when compared to concurrent chemoradiation therapy alone. *Sources: (Hong, 2018; Li, 2019; Yang, 2019)*

Important outcome measures

Distant metastasis-free survival (5 year)

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may result in an increase of distant metastasis-free survival in WHO subtype 2/3, stage III/ IV, excluding T3N0 nasopharyngeal cancer patients at 5-year follow-up, when compared to concurrent chemoradiation therapy alone. *Sources: (Hong, 2018; Li, 2019; Yang, 2019)*

Complications/adverse events

Low GRADE	Induction chemotherapy combined with concurrent chemoradiation therapy may increase grade ≥ 3 adverse events in advanced nasopharyngeal cancer patients when compared to concurrent chemoradiation therapy alone. *Sources: (Cao, 2017; Sun, 2016; Tan, 2015; Zhang, 2019)*

Quality of life

Very low GRADE	We are unsure about the effect of induction chemotherapy combined with concurrent chemoradiation therapy on quality of life in advanced nasopharyngeal cancer patients when compared to chemoradiation therapy alone. *Sources: (Tan, 2015)*

Samenvatting literatuur

Description of studies

We included the SR of **Wang (2020)** in the analyses. They searched the scientific literature up to September 2019. Inclusion criteria of this systematic review were: prospective studies in previously untreated patients with nasopharynx carcinoma (NPC); studies were registered clinical trials and registration numbers were provided; study design was randomized controlled clinical studies; the experimental group was treated with induction chemotherapy (IC) combined with concurrent chemoradiation therapy (CCRT), and the control group was treated with CCRT alone; and studies were published in English language. Neoadjuvant chemotherapy described in the articles was deemed as induction chemotherapy. Exclusion criteria were: IC or CCRT was combined with target therapy, or conference abstracts.

In total, nine papers, describing the results of seven RCTs were included, with 2311 patients, of whom 1160

patients were randomised to IC+CCRT and 1151 patients were randomised to CCRT alone. Type and dosage of IC, chemotherapy (CT) and radiotherapy (RT) are described in the evidence table.

Four studies reported results after three-year follow-up (Fountzilas, 2012; Frikha, 2018; Tan, 2015; Zhang, 2019), two studies reported results on both three- and five-years follow-up, in two separate articles (Cao, 2017 & Yang, 2019; Sun, 2016 & Li, 2019), and one study reported results after five-year follow-up (Hong, 2018). Three studies were done in China (Cao, 2017 & Yang, 2019; Sun, 2016 & Li, 2019; Zhang, 2019), and the rest in Taiwan (Hong, 2018), Singapore (Tan, 2015), France/Tunisia (Frikha, 2018), and Europe (country not specified) (Fountzilas, 2012). Study characteristics and distributions of important patient characteristics (WHO types and clinical stage) is reported per study in Table 1.

Wang (2020) performed a meta-analysis using a fixed-effect model. All enrolled trials were identified as high quality (a score of ≥3), using the Jadad scoring scale. This SR was considered to have high quality, according to the AMSTAR criteria.

Table 1 Overview of study characteristics included in the SR of Wang (2020)

Author (year)	Country	Patient population	Scheme	Pathology	WHO	Intervention	Control	Clinical stage	Interv
Fountzilas (2011)	Europe	Biopsy-proven, previously untreated WHO type I, II or III NPC; stage IIB–IVB (AJCC 2002)	Cis/VP16/Taxol		I	7 (10%)	5 (7%)	IIB	14 (19
					II	15 (21%)	15 (22%)	III	27 (38
					III	50 (69%)	49 (71%)	IVA	19 (26
								IVB	12 (17
Tan (2015)	Singapore	Newly diagnosed with World Health Organization type 2 or 3 NPC, Union for International Cancer Control (1997) stage T3-4NxM0 or TxN2-3M0	Taxane versus non-Taxane		II	6 (7%)	6 (7%)	III	50 (58
					III	80 (93%)	80 (93%)	IVA	16 (19
								IVB	20 (23

Sun/Li (2016/2019)	China	Patients with previously untreated, non-distant metastatic, newly histologically confirmed non-keratinising stage III–IVB nasopharyngeal carcinoma (except T3–4N0; 7th UICC and AJCC)). Age <59 years.	TPF	non-keratinising	Not reported			III	129 (54
								IVA	73 (30
								IVB	39 (16
Cao/Yang (2017/2019)	China	Previously untreated, biopsy-proven WHO types II-III NPC; Stage III-IVB disease, excluding T3N0-1 (UICC/AJCC 6th edition). Age <60 years	Cis/5-FU		Not reported			II	1 (<1%
								III	117 (4
								IV	120 (5
Frikha (2018)	France/ Tunisia	Histological WHO type 2 or 3, stage T2b, T3, T4 and/or N1-N3, M0	TPF	WHO II-III	II	4 (10%)	7 (17%)	Not reported	
					III	36 (90%)	34 (83%)		
Hong (2018)	Taiwan	Histologically proved stage IVA or IVB NPC (fifth edition of the AJCC/UICC staging system, 1997). Ages <70 years.	MEPFL		I	1 (<1%)	0 (0%)	IVA-T4N0–2	111 (4
					IIa	65 (27%)	71 (30%)	IVB-N3a	57 (24
					IIb	173 (72%)	169 (70%)	IVB-N3b	71 (30

Zhang (2019)	China	Histologic confirmation of nonkeratinizing nasopharyngeal carcinoma; no previous treatment for cancer; nondistant metastatic, newly diagnosed stage III to IVB (AJCC–UICC 7th edition). Age <65 years.	Cis/Gem	non-keratinising	Not reported	III	111 (4…
						IVA	104 (4…
						IVB	27 (11…

Results

Crucial outcome measures

Overall survival

Three studies addressed this outcome at **five-year** follow-up (Hong, 2018; Li, 2019; Yang, 2019). In total, 1435 patients were analysed, with 718 patients in the IC+CCRT arm and 717 in the CCRT arm. In the IC+CCRT arm 588/718 (82%) patients were alive at 5 years follow-up, and in the CCRT arm 532/717 (74%). The hazard ratio was 0.76 (95% CI 0.61 to 0.95) in favour of IC+CCRT, using a random-effect model (Figure 1). The risk difference was 8% (95% CI: 4 to 12), which is clinically relevant.

Figure 1 Forest plot for 5-year overall survival of IC+CCRT versus CCRT alone

Six studies addressed this outcome at **three-year follow-up** (Cao, 2017; Fountzilas, 2012; Frikha, 2018; Sun, 2016; Tan, 2015; Zhang, 2019). In total, 1832 patients were analysed, with 921 patients in the IC+CCRT arm and 911 patients in the CCRT arm. The hazard ratio was 0.69 (95% CI 0.51 to 0.94) in favour of IC+CCRT (Figure 2).

Figure 2 Forest plot for 3-year overall survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year	Hazard Ratio IV, Random, 95% CI
Fountzilas 2012	-0.0513	0.3483	72	69	14.5%	0.95 [0.48, 1.88]	2012	
Tan 2015	0.0488	0.3751	86	86	13.0%	1.05 [0.50, 2.19]	2015	
Sun 2016	-0.5276	0.2521	241	239	22.0%	0.59 [0.36, 0.97]	2016	
Cao 2017	-0.1076	0.231	238	238	24.2%	0.90 [0.57, 1.41]	2017	
Frikha 2018	-0.9163	0.5004	42	41	8.2%	0.40 [0.15, 1.07]	2018	
Zhang 2019	-0.844	0.2975	242	238	18.0%	0.43 [0.24, 0.77]	2019	
Total (95% CI)			921	911	100.0%	0.69 [0.51, 0.94]		

Heterogeneity: Tau² = 0.05; Chi² = 7.49, df = 5 (P = 0.19); I² = 33%
Test for overall effect: Z = 2.36 (P = 0.02)

0.2   0.5   1   2   5
Favours IC+CCRT   Favours CCRT

Disease-free survival

Three studies addressed this outcome at **five-year follow-up** (Hong, 2018; Li, 2019; Yang, 2019). In total, 1435 patients were analysed, with 718 patients in the IC+CCRT arm and 717 in the CCRT arm. In the IC+CCRT arm 507/718 (71%) patients were disease-free at 5 years follow-up, and in the CCRT arm 429/717 (60%). The hazard ratio was 0.70 (95% CI 0.51 to 0.94) (Figure 3). The risk difference was 11% (95% CI: 6 to 16), which is clinically relevant.

Figure 3 Forest plot for 5-year disease-free survival of IC+CCRT versusCCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year	Hazard Ratio IV, Random, 95% CI
Hong 2018	-0.3025	0.137	239	240	42.4%	0.74 [0.56, 0.97]	2018	
Yang 2019	-0.4155	0.1625	238	238	30.1%	0.66 [0.48, 0.91]	2019	
Li 2019	-0.4005	0.1702	241	239	27.5%	0.67 [0.48, 0.94]	2019	
Total (95% CI)			718	717	100.0%	0.70 [0.58, 0.83]		

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 4.07 (P < 0.0001)

0.2   0.5   1   2   5
Favours IC+CCRT   Favours CCRT

Six studies addressed this outcome at **three-year** follow-up (Cao, 2017; Fountzilas, 2012; Frikha, 2018; Sun, 2016; Tan, 2015; Zhang, 2019). In total, 1832 patients were analysed, with 921 patients in the IC+CCRT arm and 911 patients in the CCRT arm. The hazard ratio was 0.67 (95% CI 0.53 to 0.86) (Figure 4).

Figure 4 Forest plot for 3-year disease-free survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year	Hazard Ratio IV, Random, 95% CI
Fountzilas 2012	0.3365	0.3464	72	69	10.0%	1.40 [0.71, 2.76]	2012	
Tan 2015	-0.2614	0.2855	86	86	13.4%	0.77 [0.44, 1.35]	2015	
Sun 2016	-0.3857	0.1777	241	239	24.4%	0.68 [0.48, 0.96]	2016	
Cao 2017	-0.4005	0.1809	238	238	23.9%	0.67 [0.47, 0.96]	2017	
Frikha 2018	-0.821	0.4023	42	41	7.8%	0.44 [0.20, 0.97]	2018	
Zhang 2019	-0.6733	0.2069	242	238	20.6%	0.51 [0.34, 0.77]	2019	
Total (95% CI)			921	911	100.0%	0.67 [0.53, 0.86]		

Heterogeneity: Tau² = 0.03; Chi² = 7.60, df = 5 (P = 0.18); I² = 34%
Test for overall effect: Z = 3.23 (P = 0.001)

0.2   0.5   1   2   5
Favours IC+CCRT   Favours CCRT

<u>*Important outcome measures*</u>
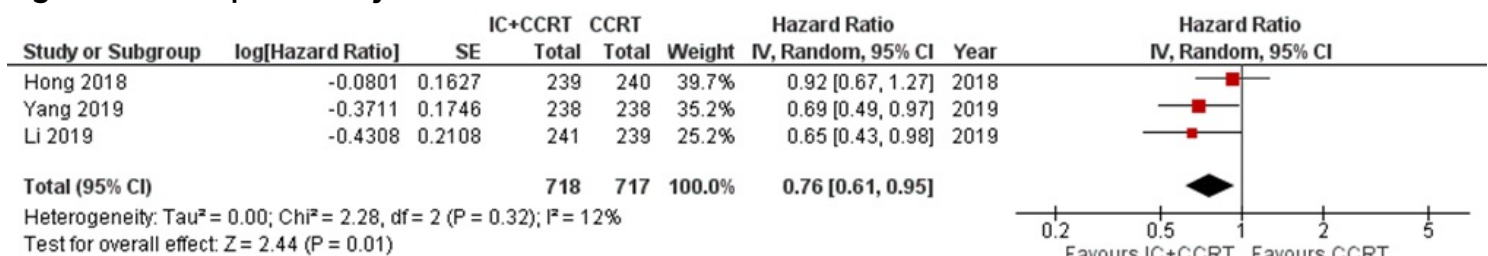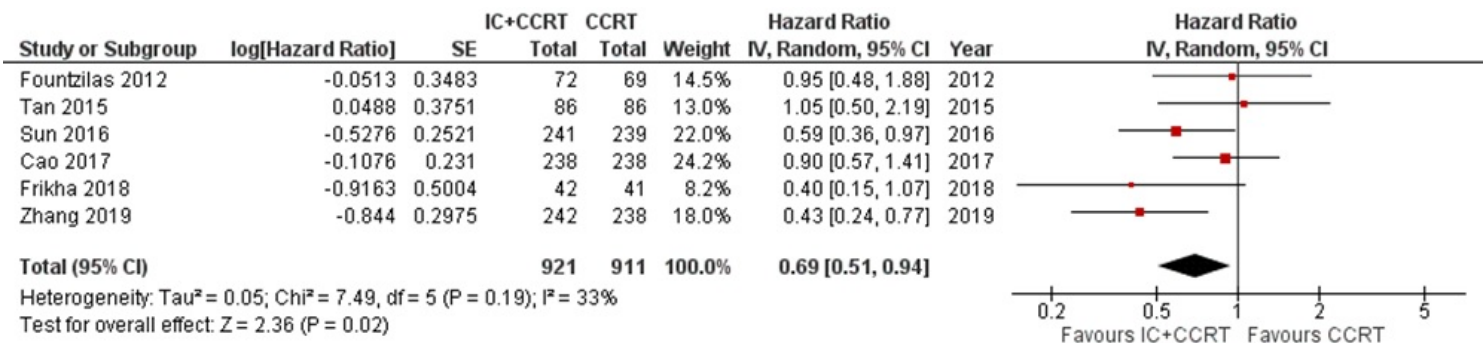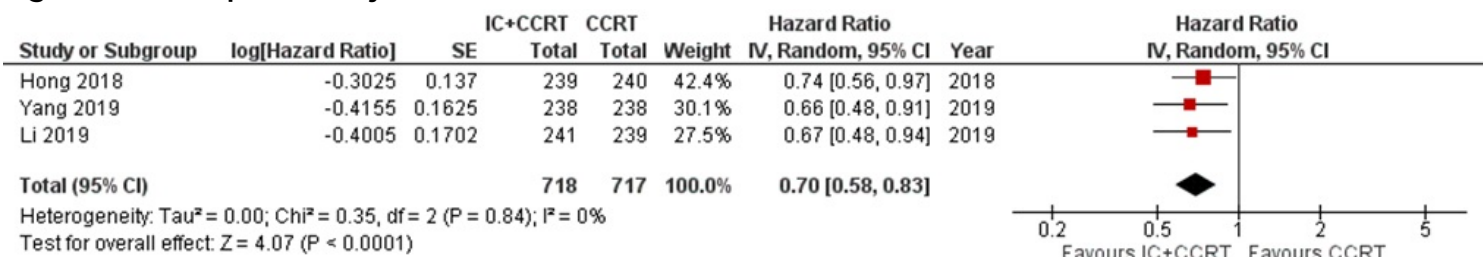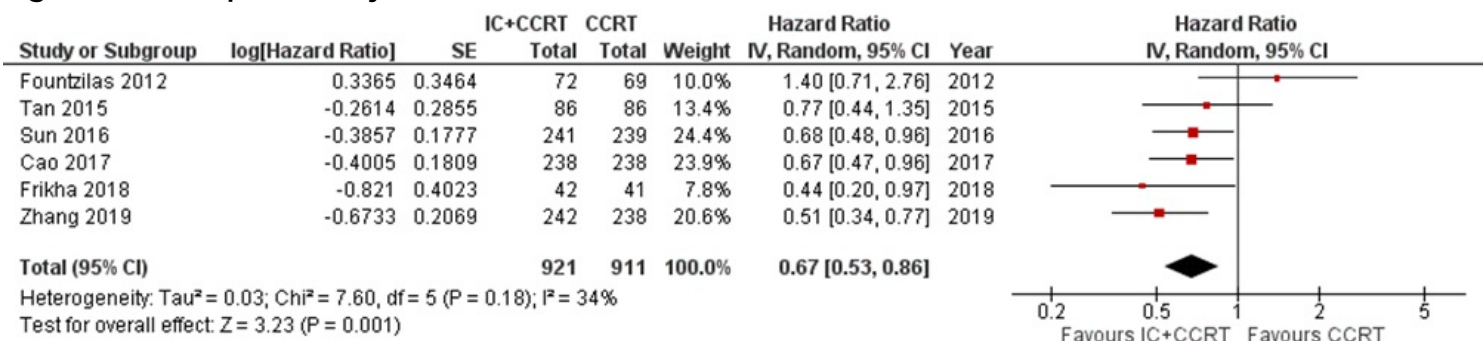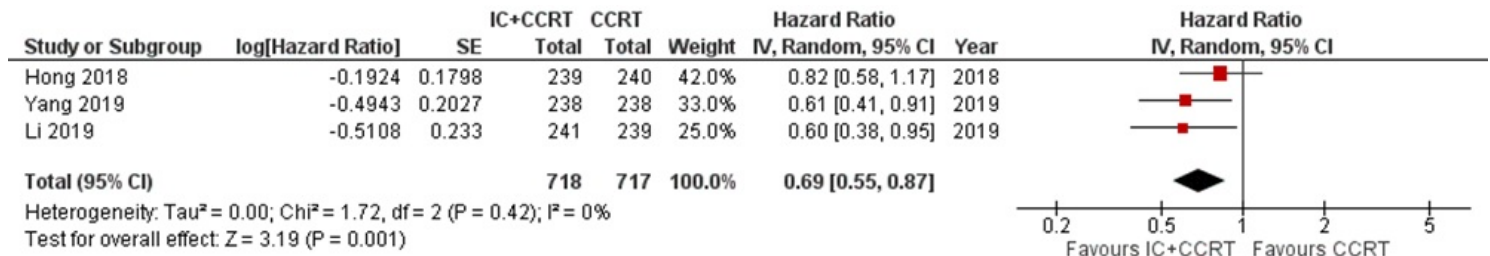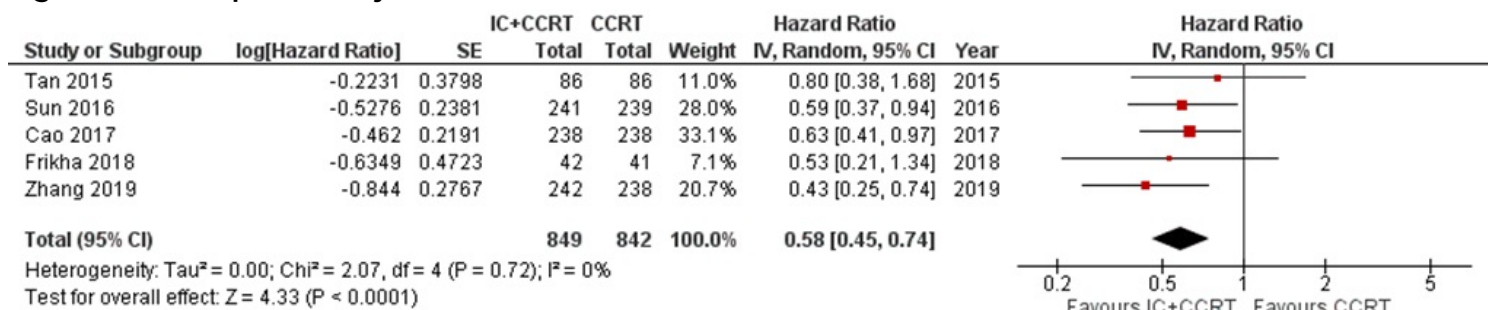*Distant metastasis-free survival*

Three studies addressed this outcome at **five-year** follow-up (Hong, 2018; Li, 2019; Yang, 2019). In total, 1435 patients were analysed, with 718 patients in the IC+CCRT arm and 717 in the CCRT arm. The hazard ratio was 0.69 (95% CI 0.55 to 0.87) (Figure 5).

Figure 5 Forest plot for 5-year distant metastasis-free survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hong 2018	-0.1924	0.1798	239	240	42.0%	0.82 [0.58, 1.17]	2018
Yang 2019	-0.4943	0.2027	238	238	33.0%	0.61 [0.41, 0.91]	2019
Li 2019	-0.5108	0.233	241	239	25.0%	0.60 [0.38, 0.95]	2019
Total (95% CI)			718	717	100.0%	0.69 [0.55, 0.87]	

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)

Favours IC+CCRT   Favours CCRT

Five studies addressed this outcome at **three-year** follow-up (Cao, 2017; Frikha, 2018; Sun, 2016; Tan, 2015; Zhang, 2019). In total, 1691 patients were analysed, with 849 patients in the IC+CCRT arm and 842 patients in the CCRT arm. The hazard ratio was 0.58 (95% CI 0.45 to 0.74) (Figure 6).

Figure 6 Forest plot for 3-year distant metastasis-free survival of IC+CCRT versus CCRT alone

Study or Subgroup	log[Hazard Ratio]	SE	IC+CCRT Total	CCRT Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Tan 2015	-0.2231	0.3798	86	86	11.0%	0.80 [0.38, 1.68]	2015
Sun 2016	-0.5276	0.2381	241	239	28.0%	0.59 [0.37, 0.94]	2016
Cao 2017	-0.462	0.2191	238	238	33.1%	0.63 [0.41, 0.97]	2017
Frikha 2018	-0.6349	0.4723	42	41	7.1%	0.53 [0.21, 1.34]	2018
Zhang 2019	-0.844	0.2767	242	238	20.7%	0.43 [0.25, 0.74]	2019
Total (95% CI)			849	842	100.0%	0.58 [0.45, 0.74]	

Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)
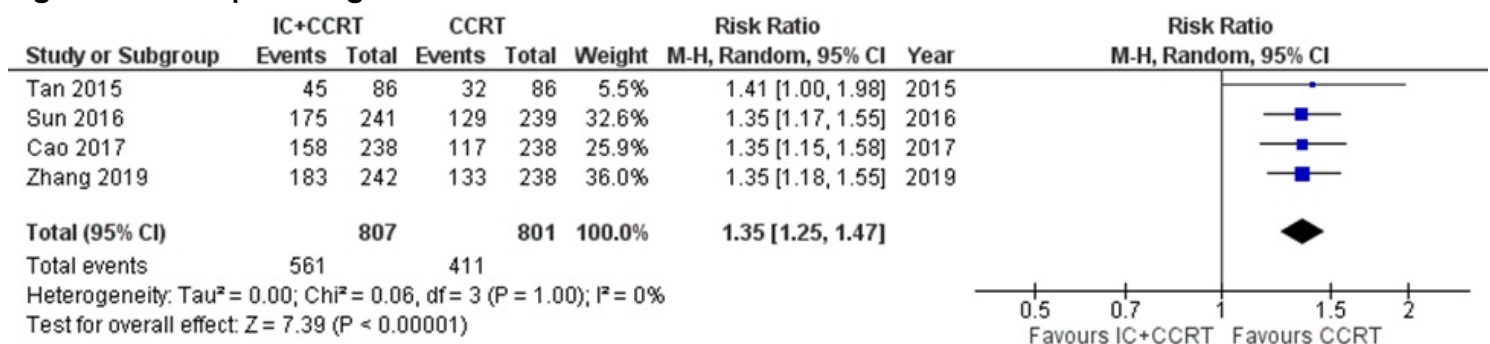
Favours IC+CCRT   Favours CCRT

Complications/adverse events
Four studies addressed this outcome (Cao, 2017; Syn, 2016; Tan, 2015; Zhang, 2019). In total, 1608 patients were analysed, with 807 patients in the IC+CCRT arm and 801 in the CCRT arm.

In the IC+CCRT arm 561/807 (70%) reported grade ≥ 3 adverse events, compared to 411/801 (51%) in the CCRT arm (risk ratio (RR): 1.35; 95% CI 1.25 to 1.47), in favour of CCRT (Figure 7).

Figure 7 Forest plot for grade ≥ 3 adverse events of IC+CCRT versus CCRT alone

Study or Subgroup	IC+CCRT Events	IC+CCRT Total	CCRT Events	CCRT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tan 2015	45	86	32	86	5.5%	1.41 [1.00, 1.98]	2015
Sun 2016	175	241	129	239	32.6%	1.35 [1.17, 1.55]	2016
Cao 2017	158	238	117	238	25.9%	1.35 [1.15, 1.58]	2017
Zhang 2019	183	242	133	238	36.0%	1.35 [1.18, 1.55]	2019
Total (95% CI)		807		801	100.0%	1.35 [1.25, 1.47]	
Total events	561		411				

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 7.39 (P < 0.00001)

Favours IC+CCRT   Favours CCRT

During overall treatment: In hematological toxicities, there were no significant differences in leukopenia (risk ratio (RR): 1.77, 95% CI: 0.98 to 3.19, p = 0.06) and anemia (RR: 2.97, 95% CI: 0.20 to 44.40, p = 0.43) between IC + CCRT group and CCRT group. However, the IC + CCRT group showed significantly higher risks of neutropenia (RR: 3.93, 95% CI: 1.78 to 8.68, p = 0.0007) and thrombocytopenia (RR: 6.55, 95% CI: 2.58 to 16.63, p < 0.0001) than the CCRT group.

In non-hematological toxicities, patients treated with IC + CCRT showed significantly higher risks of nausea (RR: 1.43, 95% CI: 1.09 to 1.87, p = 0.01), vomiting (RR: 1.40, 95% CI: 1.08 to 1.82, p = 0.01) and hepatotoxicity (RR: 5.37, 95% CI: 1.40 to 20.58, p = 0.01) rather than mucositis (RR: 1.04, 95% CI: 0.87 to 1.24, p = 0.68) and dermatitis (RR: 0.73, 95% CI: 0.37 to 1.44, p = 0.37) in comparison with patients treated with CCRT.

Quality of life (QoL)
One study addressed this outcome (Tan, 2015), with 86 patients in the IC+CCRT arm and 86 in the CCRT arm. They reported that the mean global QOL scores of the EORTC QLQ-30 module were balanced between the 2 arms. The IC+CCRT arm had significantly poorer symptom scores for dyspnea (24.3 versus 15.3; P=0.014) and diarrhea (15.2 versus 9.3; P=0.018) during CCRT compared with the CCRT alone arm. However, these differences were no longer significant during follow-up. There were no statistically significant differences in any of the functional scales between the two arms. For the EORTC H&N35 module, the control arm had significantly poorer scores for pain, swallowing, and use of pain killers during CCRT, and for social contact at the third month of follow-up, compared with the GCP arm.

Certainty of the evidence
Crucial outcome measures
Overall survival (5 year)
The certainty of the evidence regarding overall survival started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for imprecision (the pooled estimate crossed the line of clinically relevant difference), and indirectness (study population may not be comparable to Dutch population of nasopharynx carcinoma patients). We did not downgrade for risk of bias (lack of blinding), because overall survival was considered as a 'hard' outcome measure. Level of evidence was graded as low.

Disease-free survival (5 year)
The certainty of the evidence regarding disease-free survival started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for imprecision (the pooled estimate crossed the line of clinically relevant difference), and indirectness (study population may not be comparable to Dutch population of nasopharynx carcinoma patients). We did not downgrade for risk of bias (lack of blinding), because disease-free survival was considered as a 'hard' outcome measure. Level of evidence was graded as low.

Important outcome measures
Distant metastasis-free survival (5 year)
The certainty of the evidence regarding distant metastasis-free survival started high, as the evidence

originated from an RCT. The level of evidence was downgraded by one level for imprecision (the pooled estimate exceeded clinically relevant difference), and indirectness (study population may not be comparable to Dutch population of nasopharynx carcinoma patients). We did not downgrade for risk of bias (lack of blinding), because distant metastasis-free survival was considered as a 'hard' outcome measure. Level of evidence was graded as low.

Complications/adverse events
The certainty of the evidence regarding complications/adverse events started high, as the evidence originated from an RCT. The level of evidence was downgraded by one level for risk of bias (participants, care providers and outcome assessors were not blinded) and one level for imprecision (small number of included patients). Level of evidence was graded as low.

Quality of life
The certainty of the evidence regarding quality of life started high, as the evidence originated from an RCT, and was downgraded by three levels because of risk of bias (one level for study limitations: participants, care providers and outcome assessors were not blinded); very serious imprecision (two levels because data originated from only one study with a very small number of included patients); publication bias. Level of evidence was graded as very low.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the effects of induction chemotherapy or induction chemotherapy + concurrent chemoradiation therapy compared with concurrent chemoradiation therapy alone in patients with T3/T4 nasopharynx carcinomas?

P: patients with nasopharynx carcinoma (T-stage 3-4);
I: induction chemotherapy or induction therapy + concurrent chemoradiotherapy;
C: concurrent chemoradiotherapy;
O: overall survival, disease-free survival, distant metastasis-free survival, complications/adverse events, quality of life.

Relevant outcome measures
The guideline development group considered overall survival, disease-free survival and toxicity as a critical outcome measure for decision making; and distant metastasis-free survival, complications/adverse events and quality of life as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival	Time from randomisation to death from any cause, with a minimum follow-up of 5 years
Disease-free survival	Time during and after cancer treatment that the patient survives without any signs or symptoms of cancer recurrence, with a minimum follow-up of 5 years
Distant metastasis-free survival	Time to appearance of a distant metastasis, with a minimum follow-up of 5 years
Complications/adverse events/toxicity	All negative effects related to the treatment (lethal, acute/serious, chronic)
Quality of life (QoL)	Overall QoL or regarding a specific domain, measured with a validated and reliable instrument, such as the SF-36 or EORTC QLQ-C30.

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of a median follow-up period of three years) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:

- Overall survival: > 5% difference, or > 3% and HR< 0.7.
- Relapse-free/disease-free survival: HR <0.7.

And, in case of absence of a clinically relevant difference in overall survival or relapse-free survival:

- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Complications/adverse events: Statistically significant less complications/adverse events.

Data-analysis
A meta-analysis was performed to pool the results of the included studies. We used a random-effect model.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until June 17th, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 189 hits. Studies were selected based on the following criteria:

- included patients with nasopharynx carcinoma;
- compared induction chemotherapy or induction therapy + concurrent chemoradiotherapy with concurrent chemoradiotherapy alone;
- reported at least one of the outcomes of interest;
- the study design is a systematic review (SR) (preferably of randomized controlled trials; RCTs), or RCT;
- written in English language.

Based on title and abstract screening, 44 studies were initially selected. After reading the full text and

thorough assessment of the studies, 43 studies were excluded (see table with reasons for exclusion under the tab Methods), and one study was included.

Results

One SR was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Yang, Q., Cao, S. M., Guo, L., Hua, Y. J., Huang, P. Y., Zhang, X. L.,... & Xie, Y. L. (2019). Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial. European Journal of Cancer, 119, 87-96.

Zhang, Y., Chen, L., Hu, G. Q., Zhang, N., Zhu, X. D., Yang, K. Y.,... & Cheng, Z. B. (2019). Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. New England Journal of Medicine, 381(12), 1124-1135.

Recidief T2-T4

Uitgangsvraag

Wanneer en hoe is re-irradiatie in een curatieve setting mogelijk in een recidief hoofd-halscarcinoom na chemo-radiotherapie, wanneer salvage chirurgie niet meer mogelijk is?

Aanbeveling

Bespreek met de patiënt de nadelen van re-irradiatie van een hoofd-halsplaveiselcelcarcinoom wat betreft toxiciteit. Voorspellende factoren voor toxiciteit die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: dosis eerdere radiotherapie, eerdere chirurgie, tumorlokalisatie, leeftijd, en orgaan(dys)functie.

Bespreek bij patiënten met een nasofarynxcarcinoom de kans op overleving na re-irradiatie. Factoren die van belang kunnen zijn voor de keuze voor re-irradiatie, zijn: leeftijd, tumorstadium en EBV-concentratie in het bloed.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De werkgroep heeft een literatuuronderzoek verricht naar de prestatie van (multivariabele) modellen welke (de kans op) toxiciteit en overleving tijdens of na re-irradiatie voorspellen. Er werden twee gevalideerde modellen gevonden die overleving en toxiciteit voorspellen. Vanwege een zeer lage bewijskracht kan geen uitspraak worden gedaan over de prestatie van deze modellen. De zeer lage bewijskracht wordt voornamelijk veroorzaakt door beperkingen in de studieopzet ten aanzien van de ontwikkeling van de modellen en het ontbreken van externe validatie van de modellen. De werkgroep concludeert dan ook dat er een kennislacune bestaat omtrent het bestaan van beslissingsmodellen welke op basis van risicofactoren overleving en toxiciteit tijdens of na re-irradiatie bij patiënten, bij wie opereren geen mogelijkheid meer is, kunnen voorspellen.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)
Toxiciteit is een belangrijke uitkomst voor patiënten, waarbij de balans tussen toxiciteit en overleving een belangrijke afweging is. Toxiciteit geeft veel bijwerkingen, zoals necrose, mucositis, zwelling, slikproblemen, en pijn. Daarom moet met de patiënt worden besproken wat de nadelen kunnen zijn van re-irradiatie, en wat de eventuele voordelen zijn wat betreft overleving.

Kosten (middelenbeslag)
Re-irradiatie heeft geen grote impact op de kosten. Alternatieven van re-irradiatie zijn palliatieve opties, wanneer resectie niet meer mogelijk is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Vanwege de zeer lage bewijskracht van de gevalideerde modellen, kan er geen sterke aanbeveling worden gedaan welke factoren van belang zijn bij de keuze voor re-irradiatie. Het is belangrijk de voor- en nadelen met de patiënt te bespreken.

Onderbouwing

Achtergrond

Het doel van deze module is om de beste behandeling van een recidief hoofd-halscarcinoom na (chemo)radiotherapie als primaire behandeling dan wel adjuvant na resectie in beeld te brengen. Daarbij is het vooral van belang uit te zoeken wanneer re-irradiatie mogelijk is, als chirurgie niet meer mogelijk is, bij een recidief hoofd-halscarcinoom of tweede primaire tumor in een gebied dat eerder (chemo)radiotherapie gehad heeft. Daarbij zouden schade aan normale weefsels, overleving, toxiciteit, complicaties en kwaliteit van leven mogelijke uitkomsten kunnen zijn, en de factoren die bepalen of re-irradiatie nog mogelijk is, zouden type tumor, locatie tumor, reeds aanwezige postradiatie-effecten, tijdsinterval tot eerdere radiotherapie en patiëntgeschiedenis.

Conclusies

Toxicity: The level of evidence regarding the outcome measure toxicity started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (one level, no external validation) and imprecision (only one study with relatively low numbers of patients and events).

Overall survival: The level of evidence regarding the outcome measure started at high and was downgraded to very low because of risk of bias (one level, see evidence table), indirectness (two levels, no external validation and different population).

Toxicity

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Ward, 2019, where dose of radiotherapy during first course, tumor site, organ dysfunction, any surgery, age and recurrent or second primary are selected as factors that predict toxicity after re-irradiation for head and neck squamous cell carcinoma. *Sources: (Ward, 2019)*

Overall survival

Very low GRADE	The evidence is very uncertain about the performance of the model proposed by Sun, 2022, where patient age, rT stage, and EBV DNA level are selected as factors that predict overall survival after re-irradiation for nasopharyngeal carcinoma. *Sources: (Sun, 2022)*

Samenvatting literatuur

Description of studies

Ward, 2019: From 9 institutions, 505 patients were included with recurrent or second primary (RSP) squamous carcinoma originating in a field previously irradiated to ≥ 40 Gy and treated with IMRT-based re irradiation to ≥ 40 Gy. A multivariable competing-risk model was fit to the actuarial risk of late toxicity with progression or death as the competing risk, using a backwards stepdown procedure. The final bootstrap optimized model was converted into a nomogram.

Sun, 2022: A prognostic model was established and validated for locally recurrent nasopharyngeal carcinoma (lrNPC) patients. In total, 531 patients from one center with lrNPC were retrospectively reviewed, including 271 patients from 2006 to 2012 as the training cohort and 260 patients from 2013 to 2016 as the validation cohort. Overall survival (OS) was the primary endpoint. Multivariate analysis was performed to select the significant prognostic factors (P < 0.05). A prognostic model for OS was derived by recursive partitioning analysis (RPA) combining independent predictors using the algorithm of optimized binary partition.

<u>Results</u>

Toxicity:
Ward, 2019: The final model included six clinical factors:

- Dose of radiotherapy during first course (continuous, per Gy) (HR 1.075 (95%CI 1.031 to 1.122)).
- Tumor site (oropharynx, larynx or lypopharynx versus other) (HR 1.575 (95%CI 0.984 to 2.519)).
- Organ dysfunction (yes versus no) (HR 3.029 (95%CI 1.919 to 4.783)).
- Any surgery (yes versus no) (HR 1.232 (95%CI 0.781 to 1.943)).
- Age (continuous, per year) (HR 0.977 (95%CI 0.955 to 0.998)).
- RSP (second primary versus recurrence) (HR 1.061 {95% CI 0.656 to 1.713)).

The final model demonstrated an average bootstrapped C-index of 0.698.

Overall survival:
Sun, 2022: The final model included 3 factors:

- Patient age (> 60 versus 60: hazard ratio (HR): 1.757, 95% confidence interval (CI): 1.181 to 2.615, P = 0.005).
- rT stage (rT2 versus rT1: HR: 1.725, 95% CI: 0.919 to 3.241, P = 0.090; rT3 versus rT1: HR: 2.439, 95% CI: 1.453 to 4.096, P = 0.001; rT4 versus rT1: HR: 5.007, 95% CI: 2.989 to 8.388, P < 0.001).
- EBV DNA level (detectable versus undetectable: HR: 1.825, 95% CI: 1.355 to 2.459, P < 0.001).

The study reported that re-irradiation could benefit patients in the low (P < 0.001) and intermediate-risk subgroups (P = 0.017), while no association between re-RT and survival benefit was found in the high-risk subgroup (P = 0.328).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the prognostic factors of successful re-irradiation in patients in a curative setting with a locoregional recurrent head and neck carcinoma after primary or adjuvant (chemo)radiotherapy, where salvage surgery is no longer possible?

P: (Patients) = Patients with a head and neck carcinoma that is recurring after primary or adjuvant (chemo)-radiotherapy, where salvage surgery is no longer possible.
I: (Intervention)= A model that predicts for which patients re-irradiation is successful, defined by intervention success, tissue damage, overall survival, toxicity, complications and quality of life.

C: (Comparison)= A different model/care as usual.
O: (Outcomes)= Predictive value of the model.
T:(Timing)= When in recurring head/neck carcinoma a treatment plan is determined.
S: (Setting)= Specialized care.

Relevant outcome measures
The guideline development group considered overall survival and toxicity as critical outcomes.

The working group defined the performance of the included models in Area Under the ROC Curve (AUC) as follows:

- 0.7 ≤AUC< 0.8: acceptable.
- 0.8 ≤AUC< 0.9: excellent.
- AUC≥ 0.9: outstanding.

Prognostic research: Study design and hierarchy
When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, the effectiveness of a clinical decision model is evaluated in a randomized clinical trial. Unfortunately, these studies are very rare. If not available, studies in which prediction models are developed and validated in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to studies that are not externally validated. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prediction models internally (e.g. bootstrapping or cross validation) can be used to answer the research question, but downgrading the level of evidence is necessary due to risk of bias and/or indirectness as it is not clear whether models perform sufficiently in target populations. The confidence in the results of unvalidated prediction models is very low. Therefore, such models will not be graded. This is also applicable for association models.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until the 14th of February 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 133 hits. Studies were selected based on the following criteria:

- Being a systematic review, randomized controlled trial (RCT) or observational study (cohort study).
- Reporting multivariable longitudinal association model or prediction model with outcome (mortality or complications periprocedural or within 30 days) as dependent variable and independent variables (patient characteristics) determined before the treatment plan was made.
- Models do not take independent variables into account that were determined after the treatment plan was made.

Four studies were initially selected based on title and abstract screening. After reading the full text, two studies were excluded (see the table with reasons for exclusion under the tab Methods) and two studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld   : 20-09-2023
Laatst geautoriseerd : 20-09-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Sun XS, Zhu MY, Wen DX, Luo DH, Sun R, Chen QY, Mai HQ. Establishment and validation of a recursive partitioning analysis based prognostic model for guiding re-radiotherapy in locally recurrent nasopharyngeal carcinoma patients. Radiother Oncol. 2022 Jan 29;168:61-68. doi: 10.1016/j.radonc.2022.01.026. Epub ahead of print. PMID: 35101468.
Ward MC, Lee NY, Caudell JJ, Zajichek A, Awan MJ, Koyfman SA, Dunlap NE, Zakem SJ, Hassanzadeh C, Marcrom S, Boggs DH, Isrow D, Vargo JA, Heron DE, Siddiqui F, Bonner JA, Beitler JJ, Yao M, Trotti AM, Riaz N; Multi-Institution Re-Irradiation (MIRI) Collaborative. A competing risk nomogram to predict severe late toxicity after modern re-irradiation for squamous carcinoma of the head and neck. Oral Oncol. 2019 Mar;90:80-86. doi: 10.1016/j.oraloncology.2019.01.022. Epub 2019 Feb 8. PMID: 30846182.

Hoofd-halstumoren generiek

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Radiotherapie

De werkgroep verwijst voor aanbevelingen over radiotherapie bij HHT naar:LPRHHT

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Indicatie van postoperatieve radiotherapie dan wel chemoradiatie bij plaveiselcelcarcinoom van het hoofd-halsgebied

Uitgangsvraag

Bij welke patiënten met een plaveiselcelcarcinoom van het hoofd-halsgebied is postoperatieve radiotherapie dan wel postoperatieve chemoradiatie geïndiceerd?

Aanbeveling

In geval van positieve of krappe sneevlakken, multipele lymfkliermetastasen en lymfkliermetastase(n) met kapseldoorbraak, T3-T4-tumoren, perineurale groei is een adjuvante behandeling na chirurgie geïndiceerd.

Het interval tussen chirurgie en radiotherapie of chemoradiatie is bij voorkeur maximaal zes weken.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Fotodynamische therapie

Uitgangsvraag

Wat is de plaats van fotodynamische therapie bij patiënten met hoofd-halskanker?

Aanbeveling

Behandel een patiënt met een lokaal recidief hoofd-halscarcinoom bij wie een conventionele in opzet curatieve therapie met chirurgie, radiotherapie en/of systemische therapie niet mogelijk of onvoldoende effectief is, en er een indicatie voor palliatieve behandeling is, bij voorkeur met chemotherapie of immunotherapie.

In situaties waar chemotherapie en immunotherapie gecontra-indiceerd zijn of door de patiënt niet wenselijk worden geacht, of in specifieke situaties waar de behandelend arts inschat dat PDT voordeel kan hebben ten opzichte van chemotherapie en immunotherapie, kan temoporfine-PDT overwogen worden.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs
Er zijn geen RCTs of vergelijkende observationele studies gevonden die de effectiviteit van temoporfine-gemedieerde fotodynamische therapie (PDT) hebben vergeleken met chemotherapie of immunotherapie bij patiënten met een lokaal recidief van hoofd-halskanker. Er zijn daarom geen studies geïncludeerd in de samenvatting van de literatuur als ook geen conclusies geformuleerd. Om deze reden zal de keuze voor de ene dan wel de andere behandeling dus afhangen van andere factoren.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Hoofd-halskankerpatienten ontwikkelen helaas vaak een recidief, welke lokaal, regionaal en/of op afstand kan zijn, of een nieuwe tumor in een al eerder behandeld gebied. De behandelopties kunnen dan beperkt zijn. Helaas moet dan vaak gekozen worden voor een palliatief beleid. De klachten die dan gepallieerd moeten worden, worden meestal door het lokale recidief veroorzaakt.

De voorkeur zal dan in eerste instantie vaak uitgaan naar een lokale behandeling, bijvoorbeeld chirurgie, radiotherapie of PDT. Het voordeel van een systemische behandeling, bijvoorbeeld chemotherapie of immunotherapie, is dat recidief tumor niet alleen lokaal, maar in het hele lichaam behandeld wordt. Vaak zijn bij een lokaal recidief tumor radiotherapie en chirurgie niet meer mogelijk en kan gekozen worden tussen systemische therapie en PDT of een andere (lokale) experimentele behandeling. PDT is een complexe behandeling met daarnaast rondom de behandeling leefregels voor de patiënt ten aanzien van het vermijden van daglicht of intensief kunstlicht. Bij blootstelling aan te veel licht kunnen ernstige bijwerkingen optreden, zoals het ontstaan van blaren in de huid, met name rondom de inspuitplaats van de lichtgevoelige stof. De in de literatuur gemelde bijwerkingen worden beschreven als tijdelijke effecten die weer genezen, doch wel met littekens en pigmentafwijkingen. Een enkele keer is lipo-atrofie gemeld (onbedoeld verlies van vet volume) bij het gebruik van temoporfine. Afhankelijk van de anatomische locatie en het diepte effect in de weefsels kan na de behandeling ook pijn ontstaan waarvoor morfine noodzakelijk kan zijn. Indien in de voedingsweg wordt behandeld, kan het noodzakelijk zijn om sondevoeding te starten. PDT is doorgaans een eenmalige

behandeling, terwijl een systemische behandeling meestal herhaaldelijk met een interval van enkele weken plaatsvindt. De bijwerkingen van PDT zullen met name lokaal zijn, terwijl die van systemische therapie ook andere organen kan betreffen. De keuze tussen PDT en systemische therapie zal individueel bepaald moeten worden, waarbij de mogelijkheid van het toepassen van de behandeling (o.a. comorbiditeit en toegankelijkheid van de tumor), de mogelijke bijwerkingen en de wens van de patiënt moeten worden meegenomen.

Kosten (middelenbeslag)
In 2013 is er een kosteneffectiviteitsstudie uitgevoerd in Nederland welke temoporfine-PDT heeft vergeleken met chemotherapie. Deze analyse is aangevraagd door het Zorginstituut Nederland en werd gefinancierd door een beurs van ZonMw. De studie omvatte 35 patiënten met recidiverend plaveiselcarcinoom van het hoofd-halsgebied die werden behandeld met PDT. De controlegroep omvatte een retrospectief cohort van 30 patiënten die werden behandeld met palliatieve chemotherapie. In de PDT groep, de gemiddelde kosten per één gespaarde *quality adjusted life year* (QALY) was € 57,675 (CI95% 38,652 - 82,097), vergeleken met € 118,073 per QALY in de chemotherapie groep (CI95% 80,201 - 167,738). Deze resultaten werden teruggekoppeld aan het Zorginstituut en ZonMw, en staat als verslag op de website van het Zorginstituut. Daaropvolgend gaf het CVZ het volgende advies:
"Het College voor zorgverzekeringen (CVZ) adviseert u op basis van deze herbeoordeling om temoporfine (Foscan®) op te nemen in de beleidsregel dure geneesmiddelen voor patiënten met gevorderd plaveiselcelcarcinoom in het hoofd-halsgebied die niet meer zijn te behandelen met chirurgie, radiotherapie en/of chemotherapie."

Hopper (2003) heeft een kosteneffectiviteitsstudie uitgevoerd die de kosteneffectiviteit van temoporfine gemedieerde fotodynamische therapie (temoporfine-PDT) heeft vergeleken met palliatieve chemotherapie bij patiënten met gevorderde hoofd-hals kanker in het Verenigd Koninkrijk. Temoporfine-PDT bleek te resulteren in 48 dagen extra overleving vergeleken met vier cycli van palliatieve chemotherapie. Daarnaast bleken de kosten van temoporfine-PDT (£5741) lager te liggen dan die van vier cycli van palliatieve chemotherapie (£9924). De kosten voor temoporfine-PDT bleven lager dan die van palliatieve chemotherapie totdat het aantal cycli werd verminderd tot twee of minder. Een kanttekening daarbij is dat de gezondheidsvoordelen ook verminderen bij minder cycli van palliatieve chemotherapie.

Samengevat lijkt temoporfine-PDT kosteneffectiever te zijn dan palliatieve chemotherapie bij patiënten met gevorderde hoofd-halskanker in Nederland en het Verenigd Koninkrijk.

Aanvaardbaarheid, haalbaarheid en implementatie
Er zijn prospectieve en retrospectieve studies uitgevoerd op het gebied van fotodynamische therapie, maar goede vergelijkende studies ontbreken.

In 2007 is het gebruik van temoporfine-gemedieerde PDT door de European Medicines Agency (EMA) goedgekeurd voor de indicatie van palliatieve behandeling van patiënten met een vergevorderd plaveiselcelcarcinoom van het hoofd-halsgebied (head and neck squamous cell carcinoma; HNSCC) bij falen van eerdere therapieën en ongeschiktheid voor radiotherapie, chirurgie of systemische chemotherapie. Deze beslissing was gebaseerd op een multicenter fase II trial bij patiënten met (ver)gevorderd, ongeneeslijke

HNSCC (D'Cruz, 2004). Van de 128 patiënten die werden geïncludeerd in de studie, werd bij 38% van de patiënten een overall (partiele of complete) tumorrespons gezien, en 16% vertoonde een complete tumorrespons. Subgroepanalyses toonden twee patiëntgroepen aan waarin significant betere responses werden gezien: 1) patiënten met tumoren met een dikte van 10 mm of kleiner, en 2) patiënten met een volledig te belichten laesie. Bij patiënten die aan beide categorieën voldeden, was de algehele tumorrespons 54%, was de complete tumorrespons 30%, en vertoonde 61% een significant voordeel op klinische kwaliteit van leven.

Op verzoek van de EMA werd een *confirmatory, multicentre, multinational, single-group, open-label, single-dose* studie uitgevoerd (Tan, 2010). Het primaire doel van deze studie was om de algehele tumorrespons te beoordelen bij patiënten met gevorderd plaveiselcelcarcinoom van het hoofd-halsgebied bij wie eerdere therapieën hebben gefaald en die niet geschikt zijn voor curatieve therapie met radiotherapie, chirurgie of systemische therapie. De secundaire doelstellingen van de studie waren het beoordelen van de complete tumorrespons, de duur van tumorrespons, de tijd tot ziekteprogressie, kwaliteit van leven, overleving, prestatiestatus en gewicht van de Eastern Cooperative Oncology Group (ECOG), globale beoordeling door de patiënt van het behandelingsvoordeel en de toxiciteit, verdraagbaarheid en veiligheid van temoporfine-PDT. In totaal werden 39 patiënten behandeld en geanalyseerd, waarvan 19 patiënten een complete respons (CR) en twee patiënten een partiële respons (PR) lieten zien, resulterend in een algeheel responspercentage van 54% (95% BI 37% tot 70%). De mediane progressie-vrije overleving was 131 weken voor patiënten die een respons lieten zien, terwijl dit 31 weken was voor alle patiënten samengenomen. Het geschatte overlevingspercentage op 40 weken voor patiënten die een respons vertoonden was 91%, versus 39% voor patiënten die geen respons vertoonden en 67% voor de hele studiepopulatie. Daarnaast behielden 20 patiënten (51%) dezelfde prestatiestatus gedurende de studie, lieten 15 patiënten (39%) een verbetering zien (ECOG 1 naar 0), en drie patiënten (8%) lieten een achteruitgang zien (ECOG 0 naar 1). Deze resultaten hebben geleid tot de registratie van temoporfine-gemedieerde PDT voor de behandeling van vergevorderde en recidiverende HNSCC door de EMA.

De afwezigheid van RCT's die temoporfine-PDT vergelijken met chemotherapie of immunotherapie maakt het vergelijken van deze modaliteiten onmogelijk. PDT kan echter worden beschouwd als een goedgekeurde behandeling voor palliatieve behandeling van patiënten met gevorderd plaveiselcelcarcinoom van het hoofd-halsgebied bij wie eerdere therapieën niet (gaan) werken en die niet geschikt zijn voor radiotherapie, chirurgie of systemische chemotherapie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies:
Er zijn geen RCT's die temoporfine-PDT met chemotherapie of immunotherapie hebben vergeleken. Temoporfine-PDT is echter een geregistreerde en goedgekeurde behandeling voor de indicatie voor palliatieve behandeling van patiënten met gevorderd plaveiselcelcarcinoom van het hoofd-halsgebied bij wie eerdere therapieën niet werken en die niet geschikt zijn voor radiotherapie, chirurgie of systemische chemotherapie. In situaties waar chemotherapie en immunotherapie gecontra-indiceerd zijn of door de patiënt niet wenselijk worden geacht, kan temoporfine-PDT overwogen worden.

Onderbouwing

Achtergrond

Patiënten met een lokaal recidief hoofd-halscarcinoom bij wie conventionele in opzet curatieve behandelingen niet lijken te (gaan) werken, komen in aanmerking voor palliatieve therapie. Deze kan bestaan uit palliatieve chirurgie, radiotherapie, systemische therapie (chemo-/immunotherapie) of fotodynamische therapie. Het is echter niet duidelijk welke patiënten in aanmerking komen voor fotodynamische therapie.

Conclusies

No GRADE	No evidence was found regarding the effect of photodynamic therapy on disease free survival, overall survival, local recurrence, tumor activity, complications/adverse events and quality of life when compared with chemotherapy/immunotherapy in patients with a local recurrence of head and neck cancer.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the advantages and disadvantages of photodynamic therapy versus chemotherapy and immunotherapy in patients with a local recurrence of head and neck cancer?

P = Patients with a local recurrence of head and neck cancer.
I = Photodynamic therapy.
C = Chemotherapy/immunotherapy.
O = Disease free survival, overall survival, local recurrence, tumor activity, complications/adverse events, quality of life.

Relevant outcome measures
The guideline development group considered disease free survival and quality of life as critical outcome measures for decision making; and overall survival, local recurrence, tumor activity and complications/adverse events as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a minimal clinically relevant difference as:

- 0.8 or 1.25 as borders for clinical decision-making for risk or odds ratios of neck recurrence and tumor activity.
- 5% difference or more (absolute) and HR< 0.7 in disease-specific survival.
- 5% difference or more (absolute) and HR< 0.7 in overall survival.
- A difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Statistically significant less complications/adverse events.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until May 23th, 2022. The detailed search strategy is depicted under the tab Methods. The systematic

literature search resulted in 377 hits. Studies were selected based on the following criteria: studies comparing photodynamic therapy versus chemotherapy or immunotherapy in patients with a local recurrence of head and neck cancer. Two studies were initially selected based on title and abstract screening. After reading the full text, two studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results

No studies were included in the analysis of the literature, as there were no studies found that studied the advantages and disadvantages of photodynamic therapy versus chemotherapy or immunotherapy in patients with a local recurrence of head and neck cancer.

Verantwoording

Laatst beoordeeld   : 01-10-2023
Laatst geautoriseerd : 01-10-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Follow-up/Nazorg

Verantwoording

Laatst beoordeeld   :
Laatst geautoriseerd :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

De follow-up bij de behandeling van hoofd-halstumoren

Definitie: het routinematig controleren van een patiënt die in opzet curatief is behandeld voor een maligne tumor in het hoofd-halsgebied. Het doel van de follow-up is het vroegtijdig opsporen van een lokaal en/of regionaal recidief, morbiditeit en tweede primaire tumoren.

Daarnaast kunnen als doelen kunnen worden genoemd:

- psychosociale begeleiding;
- begeleiding en revalidatie na behandeling;
- mogelijkheid van evaluatie van het eigen therapeutisch handelen.

Deze module betreft niet de directe therapie evaluatie.
Voor de diagnostiek en behandeling van recidieven en secundaire tumoren wordt verwezen naar de betreffende behandelhoofdstukken.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Hoe frequent en hoe lang de follow-up dient te zijn bij patiënten die in opzet curatief zijn behandeld

Uitgangsvraag

Hoe frequent en hoe lang dient de follow-up te zijn bij patiënten die in opzet curatief zijn behandeld?

Aanbeveling

Individualiseer de follow-up. Daarbij kan onderstaand controleschema voor plaveiselcelcarcinomen van het hoofd-hals gebied worden aangehouden:

	Eerste jaar	Tweede jaar	Derde jaar	Vierde jaar	Vijfde jaar
Interval controles (mnd)	2-3	3	4-6	6	6

Volg patiënten met verhoogde risico's op tumorgroei en/of late morbiditeit, zoals bepaalde typen speekselkliertumoren, langer dan vijf jaar.

Overwegingen

De waarde van follow-up voor de vroegtijdige behandeling van een lokaal en/of regionaal recidief of een tweede primaire tumor hangt af van de volgende parameters:

- bestaan van een curatieve of levensverlengende behandeling;
- recidief of tweede primaire tumor moet een betere prognose hebben bij vroegere ontdekking;
- frequentie van recidief of tweede primaire tumor moet niet te laag zijn;
- patiënt moet in staat zijn de behandeling voor het recidief of tweede primaire tumor te ondergaan;
- beschikbaarheid van een diagnostische test met idealiter de volgende kenmerken: een hoge sensitiviteit en specificiteit, weinig belastend voor de patiënt, betaalbaar en in staat een asymptomatisch recidief te herkennen.

Loco-regionale recidieven
Het optreden van een loco-regionaal recidief doet zich bij plaveiselcelcarcinomen voornamelijk voor in de eerste drie tot vijf jaar (IKNL, 2013). Het risico op recidieven is in de eerste jaren na de primaire behandeling het hoogst. De frequentie van de follow-up dient daarom in de eerste jaren hoger te zijn en kan daarna tot vijf jaar na de primaire behandeling geleidelijk afgebouwd worden. Er zijn patiënten die na 5 jaar nog verhoogde risico's op tumorgroei en/of late morbiditeit hebben, zoals bepaalde typen speekselkliertumoren. Dit kan een reden zijn om sommige patiënten gedurende een langere periode te volgen.

Tweede primaire tumoren
Het risico op tweede primaire tumoren na de behandeling van een plaveiselcelcarcinoom van de bovenste adem- en voedingsweg is na vijf jaar nog steeds verhoogd (het totale risico is ongeveer 20%) (Haring et al., 2009). Bij patiënten met een grote kans op tweede primaire tumoren kan daarom een follow-up van langer dan vijf jaar geïndiceerd zijn.

Hypothyreoïdie

Bij de behandeling van hoofd-hals tumoren treedt regelmatig hypothyreoïdie op bij patiënten bij wie de schildklier geheel of gedeeltelijk in het bestralingsveld heeft gelegen. Het is aan te bevelen om bij deze patiënten regelmatig (bijvoorbeeld elke zes maanden) de schildklierfunctie gedurende de gehele follow-up periode te controleren.

Onderbouwing

Samenvatting literatuur

Niet van toepassing.

Verantwoording

Laatst beoordeeld　　: 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Hoe de follow-up dient te zijn bij patiënten die in opzet curatief zijn behandeld

Uitgangsvraag

Hoe dient de follow-up te zijn bij patiënten die in opzet curatief zijn behandeld?

Aanbeveling

Voer in het kader van follow-up de volgende onderzoeken uit gericht op klachten passend bij recidief, morbiditeit en tweede primaire tumor:
Altijd: anamnese, lichamelijk onderzoek
Bij verdachte symptomen dient gericht onderzoek plaats te vinden.

Zorg voor duidelijke afspraken over wie verantwoordelijk is voor welke delen van de follow-up.

Overwegingen

In het kader van de follow-up bestaan er geen vergelijkende studies waarin de toegevoegde waarde van een diagnostische interventie wordt vergeleken met standaard zorg. Frequentie en uitvoering van follow-up is daarom vooral gebaseerd op expertise (geconcentreerde zorg).

Vanwege de multidisciplinaire behandeling van hoofd-halstumoren zullen alle disciplines die bij de behandeling betrokken zijn geweest in principe een rol spelen bij de follow-up. Er moet duidelijkheid zijn over welke discipline verantwoordelijk is voor welk deel van de follow-up.

Onderbouwing

Samenvatting literatuur

Niet van toepassing.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

De plaats van een PET-CT voor respons evaluatie en voor het detecteren van een recidief bij patiënten met een resectabel plaveiselcelcarcinoom in het hoofd-halsgebied, die behandeld zijn met chemoradiatie of bioradiatie

Uitgangsvraag

Wat is de plaats van een PET-CT voor respons evaluatie en voor het detecteren van een recidief bij patiënten met een resectabel plaveiselcelcarcinoom in het hoofd-halsgebied, die behandeld zijn met chemoradiatie of bioradiatie?

Aanbeveling

Evalueer de respons niet eerder dan drie maanden na de laatste bestraling wanneer er gekozen wordt voor een FDG PET-CT scan.

Verricht een FDG PET-CT-scan bij verdenking op een locaal recidief hoofd-hals carcinoom en overweeg invasieve diagnostiek achterwege te laten wanneer de FDG PET-CT scan geen lokaal recidief opspoort .

Overwegingen

Wanneer de FDG PET-CT scan geen locaal recidief hoofd-halscarcinoom opspoort, kan invasieve diagnostiek aanvankelijk achterwege gelaten worden, ondanks de klinische verdenking op een lokaal recidief. Een FDG PET-CT scan is potentieel minder belastend voor een patiënt dan een scopie onder narcose. Complicaties (ontstekingen, slechte wondgenezing en oedeemvorming) van een scopie onder narcose met nemen van biopten van eerder bestraald weefsel kunnen worden voorkomen wanneer een FDG PET-CT scan volstaat. Een FDG PET-CT scan is kosteneffectief, wanneer een scopie onder narcose in (dag)opname wordt beperkt tot met een FDG PET-CT scan voorgeselecteerde patiënten waarbij de scopie met nemen van biopten wordt gebruikt om de bevindingen van de FDG PET-CT scan te bevestigen (Uyl et al 2010).

Onderbouwing

Achtergrond

Bij verdenking op een residu/recidief hoofd-halscarcinoom wordt standaard een endoscopisch onderzoek onder narcose verricht met nemen van biopten. De diagnostiek van een recidief tumor in een vroeg stadium verhoogt de kans op curatie. Radiotherapie veroorzaakt oedeem, fibrose en necrose, waardoor differentiatie tussen recidief tumor en post-therapeutische veranderingen bemoeilijkt wordt. Het nemen van biopten in bestraald weefsel kan leiden tot ontstekingen, slechte wondgenezing en oedeemvorming. Een FDG PET-CT scan is, in tegenstelling tot een scopie , een niet-invasief onderzoek. Bij voldoende hoge sensitiviteit en specificiteit kan de niet-invasieve FDG PET-CT scan bijdragen aan de selectie van patiënten voor het invasieve endoscopische onderzoek en onnodige scopiën onder narcose voorkomen. In deze module wordt de waarde en de kosteneffectiviteit van de FDG PET-CT scan voor het diagnosticeren van een recidief hoofd-halscarcinoom vergeleken met de huidige standaard: endoscopisch onderzoek.

Conclusies

Zwak bewijs	Een FDG PET-CT scan heeft een sensitiviteit van 71 tot 100% en een negatief voorspellende waarde van 89% tot 100% voor het diagnosticeren van een recidief hoofd-halscarcinoom. Een FDG PET-CT kan worden gebruikt als triagetest, waarbij het te rechtvaardigen is om patiënten met een niet-afwijkende FDG PET-CT scan klinisch te vervolgen. Patiënten met een positieve FDG PET-CT scan kan een scopie onder narcose met biopten niet worden onthouden. *Bronnen (Kim et al., 2013; Zundel et al., 2011; Ong et al., 2008; Fakhry et al., 2007; Brouwer et al., 2008)*

Samenvatting literatuur

Er werden vier retrospectieve cohort onderzoeken geïncludeerd (Kim et al. 2013, Zundel et al. 2011, Ong et al. 2008 en Fakhry et al. 2007 en een systematisch review van Brouwer et al 2008 betreffende het larynxca.)

Alle studies onderzochten patiënten, die behandeld zijn voor een primair hoofd-halscarcinoom. Alle studies hebben een hoog risico op verificatie bias omdat de gouden standaard: biopsie, afhankelijk van de resultaten van de indextest werd toegepast. Hierdoor zijn de resultaten mogelijk overschat.

Sensitiviteit en negatief voorspellende waarde
De sensitiviteit wordt uitgedrukt als het percentage terecht positieve testuitslagen onder alle patiënten die de ziekte hebben. Hoe hoger de sensitiviteit van een test, hoe groter de kans dat iemand die daadwerkelijk de ziekte heeft, een positieve testuitslag krijgt (weinig vals negatieve uitslagen). De studies rapporteerden een sensitiviteit van 71%, 93%, 94%, 96% en 100%. De sensitiviteit van 71% gerapporteerd door Ong et al. is een uitbijter die mogelijk verklaard kan worden door de relatief korte periode tussen het einde van de therapie en de FDG PET-CT scan (bij 35 van de 65 patiënten had het onderzoek binnen acht tot twaalf weken na de therapie plaats met een hoog risico op vals positieve bevindingen ten gevolge van een persisterend verhoogd metabolisme door de recente behandeling). Daarnaast rapporteerde Ong et al. op laesie niveau, terwijl de overige studies op patiëntniveau rapporteerden.

De negatief voorspellende waarde (NVW) geeft het percentage patiënten weer met een negatieve testuitslag, die de ziekte daadwerkelijk niet hebben. De studies rapporteerden NVWen van 89%, 97%, 98%, 99% en 100%.

De bewijskracht voor het inzetten van de FDG PET-CT scan als triagetest voor de diagnostiek van een recidief hoofd-halscarcinoom is zwak. De methodologie van de geïncludeerde studies had ernstige tekortkomingen, die mogelijk hebben geleid tot vertekening van de resultaten. De studies waren veelal klein en hadden over het algemeen een laag percentage pathologie.

Zoeken en selecteren

Methode literatuuranalyse
Om de uitgangsvraag te kunnen beantwoorden is er een systematische literatuuranalyse verricht naar de volgende vraagstelling:

Wat is de betrouwbaarheid van de FDG PET-CT scan ten opzichte van endoscopisch onderzoek voor het diagnosticeren van een lokaal recidief bij patiënten die behandeld zijn met (chemo)radiatie of bioradiatie therapie voor een hoofd-halscarcinoom?

Relevante uitkomstmaten
De werkgroep achtte de sensitiviteit en negatief voorspellende waarde voor de besluitvorming kritieke uitkomstmaten.

Zoeken en selecteren van literatuur
In de Medline (OVID), Embase and Cochrane databases is zowel voor uitgangsvraag 1 als voor uitgangsvraag 2 breed gezocht naar systematische reviews over FDG PET-CT in de diagnostiek bij patiënten met een hoofd-halstumor en naar origineel onderzoek waarin het kostenperspectief voor FDG PET-CT in de diagnostiek bij patiënten met een (recidief) hoofd-halstumor werd meegenomen. Dit leverde 192 treffers op. Op basis van titel en abstract werden 33 artikelen geselecteerd, waarvan uiteindelijk geen systematische review geschikt bleek voor de beantwoording van de vraagstelling.

Aanvullend op systematische reviews werd er voor de vraagstelling gezocht naar origineel onderzoek van recentere data (vanaf januari 2006). Dit leverde 65 treffers op. Op basis van titel en abstract werden negen artikelen geselecteerd, waar na het lezen van de volledige teksten vier artikelen konden worden geïncludeerd. Redenen voor exclusie waren een ongeschikte patiëntpopulatie (patiënten hadden geen of deels geen radiotherapie ondergaan: Rangaswamy et al. 2013; Bransetter et al. 2005 en Zimmer et al. 2005), diagnosestelling te kort na het einde van de radiotherapie (binnen vier weken: Shintani et al. 2008) geen origineel onderzoek (narratieve review: Becker et al. 2009).

Studies werden geselecteerd op grond van de volgende selectiecriteria:
origineel onderzoek; patiënten met verdenking op een recidief tumor in het hoofd-halsgebied, die eerder behandeld zijn met chemoradiatie of bioradiatie therapie; diagnose met FDG PET-CT tenminste acht weken na de initiële radiotherapie; referentietest: biopsie of follow-up; de studie heeft als uitkomst de sensitiviteit en/of negatief voorspellende waarde voor het diagnosticeren van een recidief carcinoom

De zoekverantwoording en de evidence tabel van de geselecteerde studies zijn te vinden onder het tabblad Verantwoording. Alleen de data die relevant zijn voor het beantwoorden van de vraagstelling zijn in de evidence tabellen opgenomen.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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primary cancer in patients with head and neck squamous cell carcinoma. Br J Cancer 2013;109(12):2973-9.

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De wijze waarop radiatieschade na radiotherapie behandeld kan worden

Uitgangsvraag

Op welke wijze kan radiatieschade na radiotherapie behandeld te worden?

Aanbeveling

Radiatieschade en vooral late schade moet zorgvuldig en zo compleet mogelijk worden gegradeerd en geregistreerd.

Ter preventie van late radiatieschade is het bij toepassen van geaccelereerde bestraling essentieel dat het interfractie-interval lang genoeg is: tenminste zes uur en bij voorkeur acht uur.

Ter preventie van osteoradionecrose dienen tandheelkundige ingrepen voor aanvang van radiotherapie te zijn uitgevoerd.

Hyperbare zuurstof therapie kan overwogen worden bij de behandeling van ernstige laryngeale chondronecrose en osteoradionecrose van de mandibula.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Het beleid ten aanzien van routinematige profylactische PEG-sonde plaatsing bij patiënten met een hoofd-halstumor die chemoradiatie ondergaan

Uitgangsvraag

Deze module is in herziening (2023-2024)

Wat is het beleid ten aanzien van routinematige profylactische PEG-sonde plaatsing bij patiënten met een hoofd-halstumor die chemoradiatie ondergaan?

Aanbeveling

Bij patiënten met een hoofd-halscarcinoom met een indicatie voor chemoradiatie:
Plaats niet routinematig een PEG sonde, maar alleen op indicatie.

Overwegingen

Door het beperkte wetenschappelijk bewijs is het niet mogelijk om harde uitspraken te doen omtrent het profylactisch dan wel op indicatie plaatsen van een PEG-sonde bij patiënten met een hoofd-halstumor die behandeld worden met chemoradiatie.

Uit bovenstaande literatuur lijkt er geen verschil te zijn in gewichtsverlies tussen een profylactische PEG-sonde en een PEG-sonde op indicatie. Vergelijkbare resultaten worden ook gevonden in een retrospectieve studie van Strom et al. (2013). In deze studie werd geen significant verschil in gewichtsverlies gevonden tussen het profylactisch plaatsen van de PEG-sonde of een PEG-sonde op indicatie (N=300) één maand en drie maanden na chemoradiatie. Voor het plaatsen van een PEG-sonde op indicatie werden de volgende risicofactoren gevonden: geaccelereerde fractionering van de radiotherapie (OR 4.3), tumor stadium III of IV, cumulatieve cisplatinum dosering ≥200 mg/m^2 (OR 6,2) en BMI<25 (OR 5.8). Hierbij dient te worden opgemerkt dat het plaatsen van een PEG-sonde in deze studie relatief laat wordt gedaan en de indicatie mogelijk eerder een late complicatie betreft dan acute toxiciteit. Bij de meeste patiënten ontstaat de indicatie voor een PEG-sonde al gedurende de behandeling.

Het besluit tot plaatsing van een PEG-sonde zal tijdens multidisciplinaire bespreking aan de orde dienen te komen, waarbij parameters uit het onderzoek van Strom et al. (2013) een handvat kunnen bieden voor het moment van PEG –plaatsing. Gezien het relatief lage percentage van PEG-plaatsing op indicatie (11,7%) in de studie van Strom et al. (2013), lijkt plaatsing van een PEG-sonde op indicatie bij patiënten met een hoofd-halstumor die worden behandeld met chemoradiatie een verantwoorde keuze. Hierbij spelen de mogelijke complicatierisico's van een PEG-sonde ook een rol.

Onderbouwing

Achtergrond

Veel patiënten met hoofd-halstumoren hebben moeite met orale intake door de tumor en/of door de behandeling. Voor patiënten jonger dan 70 jaar met een stadium III-IV hoofd-halstumor geldt dat de locoregionale controle en overleving verbetert door het toevoegen van chemotherapie aan de standaard

behandeling met radiotherapie. Dit veroorzaakt echter wel een hogere morbiditeit, waaronder mucositis, odynophagie en dysphagie. Deze morbiditeit zorgt ervoor dat de meeste patiënten tijdens de behandeling op enig moment sondevoeding nodig hebben. Sondevoeding kan toegediend worden via een neusmaagsonde (NMS), een percutane endoscopische gastrostomie (PEG) of percutane radiologische gastrostomie (PRG). In deze module zal de term PEG gebruikt worden voor zowel het gebruik van een PRG, als een PEG.

Conclusies

Laag	*Voedingsstatus* Zowel direct als na zes maanden na behandeling met chemoradiate lijkt er geen verschil te zijn in de afname in BMI tussen patiënten met een profylactische PEG-sonde en een PEG-sonde op indicatie. *Bronnen (Salas et al., 2009)*

Laag	*Kwaliteit van leven* De profylactische PEG-sonde lijkt ten opzichte van de PEG-sonde op indicatie direct na behandeling met chemoradiatie een gunstig effect te hebben op de kwaliteit van leven op mentaal domein. Voor de kwaliteit van leven op fysiek domein lijkt er geen verschil te zijn. Op de lange termijn (zes maanden na behandeling met chemoradiatie) lijkt er geen verschil te zijn in het effect op de kwaliteit van leven. *Bronnen (Salas et al., 2009)*

-	*Dysfagie op korte en lange termijn, duur sondevoeding, complicaties en kosten* Er is geen vergelijkend onderzoek waarin bij patiënten met een hoofd-halstumor is onderzocht of er een verschil is tussen de profylactische PEG-sonde en de PEG-sonde op indicatie in het effect op dysfagie op korte en lange termijn, duur van de sondevoeding en complicaties.

Samenvatting literatuur

Beschrijving studies
Salas et al., (2009) vergelijkt patiënten met chemoradiatie die profylactisch een PEG-sonde krijgen (N=21) met patiënten die de PEG-sonde niet profylactisch, maar alleen op indicatie krijgen (N=18). Van deze laatste groep hebben 13 patiënten een PEG-sonde gekregen. De follow-up duur is 6 maanden. Mediane duur van de sondevoeding was 1,5 maand na eind van de behandeling (range één tot twee maanden).

Voedingsstatus

Salas et al., (2009) vonden zes maanden na behandeling met chemoradiatie een BMI-afname van 2,5(±1,9) in de groep met een profylactische PEG-sonde ten opzichte van een afname van 1,8(±1,4) in de groep met een PEG-sonde op indicatie. Dit verschil was niet significant (p=0.36).

Kwaliteit van leven
Salas et al., (2009) hebben de kwaliteit van leven gemeten met de vragenlijsten SF-36 en EORTC QLQ-C30. Met de SF-36 vragenlijst werden zowel op de korte termijn (direct na de behandeling) als op de langere termijn (zes maanden na de behandeling) geen verschillen gevonden voor de fysieke component. Voor de mentale component was er op de korte termijn een significant verschil in het voordeel van de profylactische PEG-sonde. Op de lange termijn werd geen significant verschil meer gevonden. Met de EORTC QLQ-C30 vragenlijst werden zowel op de korte als op de lange termijn geen verschillen gevonden in kwaliteit van leven.

Dysfagie op korte en lange termijn
Deze uitkomstmaat is niet onderzocht.

Duur sondevoeding
Deze uitkomstmaat is niet onderzocht.

Complicaties
Deze uitkomstmaat is niet onderzocht.

Zoeken en selecteren

Methode literatuuranalyse
Om de uitgangsvraag te kunnen beantwoorden is er een systematische literatuuranalyse verricht naar de volgende vraagstellingen: "Wat is het effect van het plaatsen van een profylactische PEG-sonde in vergelijking met een PEG-sonde op indicatie bij patiënten met een hoofd-halstumor die chemoradiatie ondergaan?"

De volgende belangrijke uitkomstmaten werden gedefinieerd: voedingsstatus, kwaliteit van leven, dysfagie op korte en lange termijn, duur sondevoeding en complicaties.

In de databases Medline (OVID) en Embase is gezocht naar PEG-sonde bij patiënten met een hoofd-halstumor die chemoradiatie ondergaan. De zoekverantwoording is weergegeven onder desbetreffende kop in deze module. De literatuurzoekactie leverde 81 treffers op.

Studies werden geselecteerd op grond van de volgende selectiecriteria:

- Gerandomiseerd onderzoek;
- Systematische review van gerandomiseerd onderzoek;
- Vergelijking van PEG sonde met reguliere intake;
- Literatuur van 2000 tot en met heden;
- Nederlandse en Engelse literatuur.

Op basis van titel en abstract zijn 24 studies geselecteerd. Na raadpleging van de volledige tekst voldeed één gerandomiseerd onderzoek (Salas et al, 2009) aan de selectiecriteria. De reden voor exclusie van de andere studies is te vinden in de *'Zoekverantwoording'*. De zoekverantwoordingen en de evidencetabellen van de geselecteerde studies zijn tevens te vinden onder het tabblad Verantwoording. Alleen de data die relevant zijn voor het beantwoorden van de vraagstelling zijn in de evidence tabellen opgenomen.

Bewijskracht van de literatuur

De bewijskracht voor voedingsstatus en kwaliteit van leven is met twee niveaus verlaagd omdat het de enige studie is, van beperkte omvang, die deze uitkomstmaat heeft onderzocht (imprecisie).

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

Corry J, Poon W, McPhee N, et al. Randomized study of percutaneous endoscopic gastrostomy versus nasogastric tubes for enteral feeding in head and neck cancer patients treated with (chemo)radiation. Journal of Medical Imaging & Radiation Oncology 2008;52(5):503-10.
Salas S, Baumstarck-Barrau K, Alfonsi M, et al. The prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: Prospective randomized trial. Radiother Oncol. 2009;93(3):503-9.
Strom T, Trotti AM, Kish J, Rao NG, McCaffrey J, Padhya TA, Lin HY, Fulp W, Caudell JJ.Risk factors for percutaneous endoscopic gastrostomy tube placement during chemoradiotherapy for oropharyngeal cancer. JAMA Otolaryngol Head Neck Surgery 2013;139(11):1242-46.

Hoe een gedragsverandering wat betreft roken en alcohol kan worden bereikt

Uitgangsvraag

Deze module is in herziening (2023-2024)

Hoe kan een gedragsverandering wat betreft roken en alcohol worden bereikt?

Aanbeveling

Het is van belang een actief anti-rookbeleid en alcoholontwenningsbeleid te voeren.

Elke patiënt met een hoofd-halscarcinoom die rookt, dient adviezen te krijgen om te stoppen met roken. Hulp bij stoppen kan worden gegeven door gesprekken, nicotinesubstitutie, medicamenteuze ondersteuning en folders.

Om te voorkomen dat patiënten ontwenningsverschijnselen krijgen door alcoholonthouding, is het aan te bevelen om een protocol te hanteren, waarin interventies beschreven worden, zoals het geven van medicatie, folders en verwijzingen naar de huisarts en hulpverleningsinstanties.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Aan welke eisen de voorlichting aan patiënten met kanker in het hoofd-halsgebied moet voldoen

Uitgangsvraag

Deze module is in herziening (2023-2024)

Aan welke eisen moet de voorlichting aan patiënten met kanker in het hoofd-halsgebied voldoen?

Aanbeveling

Aan de patiënt met kanker in het hoofd-halsgebied en aan diens naasten moet structureel gestandaardiseerde voorlichting worden aangeboden.

De voorlichting aan patiënten met kanker in het hoofd-halsgebied moet niet alleen betrekking hebben op medisch biologische aspecten van diagnose en behandeling, maar ook op de gang van zaken rond de behandeling, de prognose en vooruitzichten en de te verwachten gevolgen voor het dagelijkse leven op kortere en langere termijn.

Aanbevolen wordt om de verpleegkundige een belangrijke rol te laten spelen in de voorlichting over de behandeling en over het omgaan met de beperkingen als gevolg van ziekte en behandeling. Daarnaast is ook een rol weggelegd voor andere professionals met wie de patiënt te maken krijgt.

Naast mondelinge informatie moet ook schriftelijke informatie gegeven worden. Het gebruik van moderne ict-technologie kan bijdragen aan verbetering van de informatievoorziening. Deze vormen van aanvullende informatie dienen te worden gegeven ter ondersteuning van de mondelinge voorlichting door de hulpverlener en mag niet als vervanging daarvan dienen.

De voorlichting is het meest effectief wanneer deze aansluit bij de behoeften van de patiënt. Het gebruik van een gestandaardiseerde kwaliteit van leven lijst voor de screening van aanwezige (somatische en psychosociale) problematiek is behulpzaam voor het opsporen van problemen en wordt aanbevolen.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld : 02-01-2014

Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Op welke wijze dient revalidatie van de slik- en stemfunctie plaats te vinden bij patiënten met een hoofd-halstumor

Uitgangsvraag

Deze module is in herziening (2023-2024)

Op welke wijze dient revalidatie van de slik- en stemfunctie plaats te vinden?

Aanbeveling

De werkgroep is van mening dat:
De logopedist deel dient uit te maken van het begeleidings- of revalidatieteam van patiënten met een hoofd-halscarcinoom.

De logopedist voorafgaand aan de behandeling reeds ingeschakeld kan worden bij te verwachten ernstige slikproblemen en/of stemproblemen ten gevolge van (chemo)radiatie om de patiënt voor te lichten en te adviseren.

Er in de follow-up goede signaleringsmomenten ingebouwd dienen te worden met aandacht voor slik- en stemproblematiek.

De stem- en slikrevalidatie na oncologische behandeling wordt gestart vanuit een op dit gebied deskundige logopedische setting bij voorkeur verbonden aan het centrum waar de primaire behandeling heeft plaatsgevonden.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Bij welke patiënten met een hoofd-halstumor fysiotherapie wordt geïndiceerd

Uitgangsvraag

Deze module is in herziening (2023-2024)

Bij welke patiënten met een hoofd-halstumor is fysiotherapie geïndiceerd?

Aanbeveling

Het verdient aanbeveling om bij patiënten die een halsklierdissectie hebben ondergaan de functie van de m. trapezius descendens te evalueren. Bij uitval van de m. trapezius descendens wordt fysiotherapie geadviseerd.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Op welke wijze een trismus behandeld dient te worden bij patiënten met een hoofd-halstumor

Uitgangsvraag

Deze module is in herziening (2023-2024)

Op welke wijze dient een trismus behandeld te worden bij patiënten met een hoofd-halstumor?

Aanbeveling

De werkgroep is van mening dat het regelmatig meten van de mondopening (interincisale afstand) bij patiënten met een mondholte- of orofarynxcarcinoom zinvol is.

Het verdient aanbeveling patiënten, bij wie de mondopening afneemt tijdens de behandeling, te oefenen.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

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Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

De vereiste mondzorg voor patiënten met hoofd-halstumoren

Uitgangsvraag

Deze module is in herziening (2023-2024)

Welke mondzorg is vereist voor patiënten met hoofd-halstumoren?

Aanbeveling

Patiënten met een hoofd-halscarcinoom dienen voorafgaande aan de oncologische behandeling, voor focusonderzoek en behandeling van foci, te worden gezien door een tandheelkundig team.

Dentale patiënten, die in het hoofd-halsgebied worden bestraald, dienen ter preventie van bestralingscariës, naast het zorgen voor een goede mondhygiëne, om de dag 1% neutrale NaF gel op het gebit aan te brengen, bijvoorkeur met fluoridekappen.

Overwegingen

Bij deze module zijn geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

De voedingsbehoefte van patiënten met een hoofd-halstumor die behandeld worden met (chemo)radiotherapie

Uitgangsvraag

Deze module is in herziening (2023-2024)

Wat is de voedingsbehoefte van patiënten met een hoofd-halstumor die behandeld worden met (chemo)radiotherapie?

Aanbeveling

Tijdens radiotherapie en chemoradiatie dient 130% tot 150% van het basaalmetabolisme aan energie en 1,0 - 1,5 gram eiwit per kg lichaamsgewicht per dag te worden toegediend (BMI 18,5 - 27).

Screening op ondervoeding is verplicht.

Overwegingen

Bij deze module werden geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

De vereiste psychosociale zorg voor patiënten met hoofd-halstumoren

Uitgangsvraag

Deze module is in herziening (2023-2024)

Welke psychosociale zorg is vereist voor patiënten met hoofd-halstumoren?

Aanbeveling

De patiënt met een hoofd-halscarcinoom wordt, naast de medisch specialist, bij voorkeur gezien door een oncologieverpleegkundige of een maatschappelijk werker, welke gespecialiseerd zijn ten aanzien van psychosociale oncologische problematiek bij de patiënt met tumoren in het hoofd-halsgebied.

Bij psychosociale problematiek dient er een verwijzing plaats te vinden naar een psycholoog, psychiatrisch verpleegkundige of psychiater.

Overwegingen

Bij deze module werden geen overwegingen geformuleerd.

Onderbouwing

Achtergrond

Vanwege de gedateerdheid van deze module is alle onderbouwende tekst komen te vervallen. De richtlijncommissie hoofd-halstumoren adviseert deze module op korte termijn te reviseren. Alleen de aanbevelingen die de richtlijncommissie als actueel heeft beoordeeld, worden hier gepresenteerd.

Verantwoording

Laatst beoordeeld   : 02-01-2014
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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Transmurale overdracht bij hoofd-halstumoren

Deze module is in herziening (2023-2024)

Waar in deze modules over transmurale overdracht huisarts staat geschreven, kan ook een andere eerstelijns zorgverlener, zoals de specialist ouderengeneeskunde, de tandarts of de AVG-arts, worden gelezen.

De huisarts blijkt in de praktijk vaak onvoldoende betrokken te worden in diverse fasen van het ziekte- en behandeltraject, vooral bij het opstellen en uitvoeren van het behandelplan, van een patiënt met een hoofd-halstumor. Het betreft laag-volume hoog complexe zorg bij patiënten met veel comorbiditeit. Continuïteit van informatie naar en van de huisarts en diens betrokkenheid is tijdens alle fasen van het zorgproces van belang, vooral bij kwetsbare (oudere) patiënten en patiënten met complexe somatische comorbiditeit en/of psychosociale problematiek. Het doel van deze module is om in het belang van de patiënt de overdracht en samenwerking tussen de specialist en huisarts optimaal te organiseren zowel tijdens de behandelfase als gedurende de follow-up.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Bij wie de patiënt terecht kan met vragen of problemen waarbij het in eerste instantie niet duidelijk is wie de patiënt kan helpen

Uitgangsvraag

Bij wie kan de patiënt terecht met vragen of problemen waarbij het in eerste instantie niet duidelijk is wie de patiënt kan helpen?

Aanbeveling

Geef de patiënt de contactgegevens van zijn of haar aanspreekpunt in het ziekenhuis.

Overwegingen

Tijdens de behandelfase zal de patiënt in het algemeen terug vallen op de specialist die op dat moment de hoofdbehandelaar is, vb. de hoofd-halschirurg, radiotherapeut of medisch oncoloog, dan wel een daartoe aangewezen contactpersoon (coördinerend verpleegkundige of case manager). Mensen vallen nu vooral na de behandelfase soms tussen wal en schip en weten niet goed wie zij dan aan moeten spreken, de mantelzorger, huisarts of specialist?

Onderbouwing

Samenvatting literatuur

Niet van toepassing.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Wat de specialist minimaal terugkoppelt aan de huisarts en eventueel andere eerstelijns zorgverlener voorafgaand aan de behandeling van patiënten met hoofd-halstumoren

Uitgangsvraag

Wat koppelt de specialist minimaal terug aan de huisarts en eventueel andere eerstelijns zorgverlener voorafgaand aan de behandeling?

Aanbeveling

Koppel voorafgaand aan de behandeling minimaal de volgende gegevens terug aan de huisarts en eventueel andere eerstelijns zorgverlener:

- de diagnose, overwegingen en het behandelplan;
- leefstijladviezen.

Overwegingen

In de periode voorafgaand aan de behandeling kan de patiënt contact opnemen met de huisarts/eerstelijns zorgverlener om aan de hand van de gegeven adviezen door de specialist de behandelopties te bespreken. Vandaar dat de huisarts door de specialist op de hoogte dient te worden gebracht van de diagnose en de overwegingen die hebben geleid tot een behandelvoorstel. In het behandelvoorstel dient ook de wijze van voedselinname benoemd te worden. Het belang van leefstijladviezen zoals stoppen met roken en overmatig alcoholgebruik vormt hiervan een onderdeel. Uitgebreide beschrijving over de prognose zal meestal niet kunnen worden gegeven omdat deze afhankelijk is van de resultaten (histologische bevindingen, respons op therapie) in de behandelfase.

Onderbouwing

Samenvatting literatuur

Niet van toepassing.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

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Wat de specialist minimaal terugkoppelt aan de huisarts en eventueel andere eerstelijns zorgverlener na de behandelfase van patiënten met hoofd-halstumoren

Uitgangsvraag

Wat koppelt de specialist minimaal aan de huisarts en eventueel andere eerstelijns zorgverlener terug na de behandelfase?

Aanbeveling

Koppel na de behandelfase minimaal de volgende gegevens terug aan de huisarts en eventueel andere eerstelijns zorgverlener:

- welke (para)medische specialismen betrokken zijn bij de patiënt;
- contactgegevens van het aanspreekpunt van de patiënt binnen het ziekenhuis;
- belangrijke gespreksonderwerpen, zoals leefstijladviezen;
- actuele problematiek;
- aanpassingen van medicatie voor comorbiditeit, zoals COPD of diabetes;
- medicatie, toedieningswijze en eventuele afbouwschema's;
- Te verwachten verloop van meest frequente bijwerkingen en advies daarbij;
- alert zijn op aanwezigheid van de volgende klachten of symptomen die langer dan drie weken bestaan:
  - zweren in de mond;
  - slikklachten;
  - heesheid;
  - zwellingen in de hals;
  - eenzijdige oorpijn;
  - eenzijdige bloedige afscheiding uit de neus;
  - veranderingen in klachtenpatroon.

Overwegingen

Aan het einde van de behandelfase kan de patiënt nog veel klachten hebben van bijwerkingen. De patiënt kan dan met nog veel vragen blijven zitten, zoals medicatie die moet worden aangepast of afgebouwd. De patiënt heeft te maken (gehad) met veel zorgverleners. De patiënt zal met vragen vaak contact zoeken met de huisarts/eerstelijns zorgverlener. De huisarts/eerstelijns zorgverlener dient dan ook op de hoogte te worden gebracht wie er betrokken zijn bij de behandeling van de patiënt en wie waarvoor de contactpersoon is. Het verwachte verloop van de bijwerkingen en, indien relevant, de wijze van nabehandeling kan in de brief na de behandelfase worden aangegeven.

Onderbouwing

Achtergrond

Niet van toepassing.

Verantwoording

Laatst beoordeeld   : 02-01-2014
Laatst geautoriseerd : 02-01-2014

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Wat de specialist minimaal terugkoppelt aan de huisarts en eventueel andere eerstelijns zorgverlener aan het einde van de follow-up periode van patiënten met hoofd-halstumoren

Uitgangsvraag

Wat koppelt de specialist minimaal aan de huisarts en eventueel andere eerstelijns zorgverlener terug aan het einde van de follow-up periode?

Aanbeveling

Koppel aan het einde van de follow-up periode minimaal de volgende gegevens terug aan de huisarts en eventueel andere eerstelijns zorgverlener:

- alert zijn op aanwezigheid van de volgende klachten of symptomen die langer dan drie weken bestaan:

    - zweren in de mond;
    - slikklachten;
    - heesheid;
    - zwellingen in de hals;
    - eenzijdige oorpijn;
    - eenzijdige bloedige afscheiding uit de neus;
    - veranderingen in klachtenpatroon.

- alert zijn op late gevolgen van de behandeling, zoals verdenking op osteoradionecrose;
- alert zijn op het risico op osteoradionecrose bij tandheelkundige ingrepen. In overleg met de radiotherapeut kan hiervoor een risicoschatting worden gemaakt afhankelijk van de lokaal gegeven dosis. Het gebruik van antibiotica profylaxe bij bloedige tandheelkundige ingrepen kan zijn aangewezen;
- alert zijn op verhoogd risico op schildklierdysfunctie (vooral hypothyreoïdie) en eventueel behandeling instellen;
- alert zijn op symptomen die duiden op een mogelijke secundaire tumor.

Overwegingen

Patiënten met een hoofd-hals tumor worden in het algemeen gedurende 5 jaar gecontroleerd door de specialist, primair gericht op recidief tumoractiviteit en (vroege) gevolgen van de behandeling. Na deze periode wordt de kans op een recidieftumor dusdanig laag geschat dat de controles worden gestaakt. De huisarts/eerstelijns zorgverlener dient in de ontslagbrief te worden geïnformeerd over mogelijk blijvende bijwerkingen van de behandeling en de mogelijkheid van late complicaties zoals hypothyreoïdie en radionecrose na (chemo)radiatie. Zo dient de huisarts/tandarts ook alert te zijn op het risico op osteoradionecrose bij tandheelkundige ingrepen. In overleg met de radiotherapeut kan hiervoor een risicoschatting worden gemaakt afhankelijk van de lokaal gegeven dosis. Het gebruik van antibiotica profylaxe bij bloedige tandheelkundige ingrepen kan zijn aangewezen.

Patiënten met een hoofd-hals tumor betreffen veelal oudere mensen met veel comorbiditeit en/of met een ongezonde levensstijl (roken en overmatig alcoholgebruik). Hierdoor is het risico op secundaire tumoren verhoogd, vooral in het hoofd-hals gebied. In een ontslagbericht dient op deze aspecten te worden gewezen, waarin afhankelijk van de toekomstverwachting kan worden verwezen naar de richtlijnen pijnbestrijding, palliatieve zorg, stoppen met roken en de zorgstandaard kanker.

Onderbouwing

Samenvatting literatuur

Niet van toepassing.

Verantwoording

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Laatst geautoriseerd : 02-01-2014

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