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Danish Head and Neck Cancer Group

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Content

Background

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Clinical Registries (RKKP). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high quality cancer care across the Danish healthcare system. The guideline content is approved by the disease specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The target users of this guideline are health care professionals working in the Danish healthcare system. The guideline consists of systematically prepared statements that can be used as a decision-making support tool by healthcare professionals and patients, when deciding on appropriate and correct care in a specific clinical situation.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome and sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The clinical practice guideline contains central recommendations (chapter 1) and a description of the scientific evidence (chapters 3+4). Recommendations marked A are the strongest, whereas recommendations marked D are the weakest. For further information on strength of evidence see the "Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. Please see the table of contents for page reference.
Information on the national integrated cancer pathways – descriptions of the patient journey through the healthcare system – can be accessed at the Danish Health Authority website: https://www.sst.dk/en/.

Development of this clinical practice guideline has been funded by The Danish Health Authority (National Cancer Plan IV) and the Danish Clinical Registries (RKKP).

1. Anbefalinger - DA (Quick Guide)

Tumor (target) indtegning (GTV)

1. *Alle dele af stråleplanlægningen skal kvalitetssikres; immobilisation, skanning, billedrekonstruktion, billedoverførelse og co-registreringer (D)*
2. *Alle skanninger, der bruges til tumorindtegning, skal være mindre end 3 uger gamle (D)*
3. *Den ansvarlige onkolog skal tage del i alle dele af targetindtegningen på komplekse tilfælde (D)*
4. *En planlægnings-CT-skanning i optimal kvalitet, med anvendelse af metal-artefakt-reduktion og en snit tykkelse på 2 mm, skal anvendes til targetindtegning (D).*
5. *MRI sekvenser skal være T1 med og uden kontrast + T2 med og uden fedtsupprimering (STIR/ Dixon) (D)*
6. *PET/CT procedure skal følge EANM guidelines fra 2015 (D)*
7. *PET-CT og MR skal anvendes til targetindtegning ved cancer i mundhule og svælg. (D)*
8. *PET-CT og MR skal anvendes til targetindtegning af larynxcancer (D)*
9. *Hvis larynx tumorer ikke er synlige på diagnostiske skanninger (f.eks. T1N0 glottisk larynx) er PET-CT og MR ikke indiceret (D)*
10. *Undersøgelse i general anæstesi med tegninger eller foto skal bruges til at indtegne superficielt spredende larynxcancere (D)*
11. *PET-CT og MR skal bruges til targetindtegning af tumorer i næse-bihuler og spytkirtler (D)*
12. *Indtegning af lymfeknudetarget følger anbefalingerne for primær tumor. I tilfælde af ukendt primær tumor følges enten retningslinjerne for postoperative strålebehandling (kun MRI) eller radikal strålebehandling (PET-CT og MR) (D)*
13. *Indikationen for postoperative strålebehandling besluttes på en multidisciplinær teamkonference (D)*
14. *Alle tilfælde med T3/T4, ekstranodulær vækst (ENE), høj-risiko histologi eller ikke-radikal kirurgi diskuteres på en multidisciplinær teamkonference (D.*
15. *Alle informationer skal anvendes til definition af target – også postoperativt. (D)*
16. *Navngivning og markering af operationspræparater skal være optimal for at kunne definere det præ-operative volumen og områder med ENE eller R1 resektion. (D)*
17. *Komplicerede targets skal defineres i samarbejde med den opererende kirurg (D)*
18. *MR skal anvendes til planlægning af postoperativ strålebehandling, undtagen de tilfælde hvor tumor ikke er synlig på diagnostiske scanninger (f.eks. T1N0 glottisk larynx), og der ikke er lavet rekonstruktion (D)*
19. *Der er ingen indikation for PET-CT til postoperativ strålebehandling, medmindre der er mistanke om makroskopisk efterladt tumorvæv eller halsen skal evalueres (D).*

Definition af volumina ud over GTV

20. *Nomenklaturen for volumina følger ICRU og definitionen på lymfeknudetarget følger internationale retningslinjer (D)*

Normalvæv

21. *Nomenklatur (D), dosis-volumen-begrænsninger (C), og definitionen af volumina (D) følger retningslinjerne i Appendix 1 og Tabel 1.*

Radioterapi dosisplanlægning

22. *Dosisplanlægning bør tilstræbe at følge toleranceniveauer for targetdækning og normalvævs-besparelse defineret i table 2(D).*

Recommendations - ENG (Quick Guide)

Target Delineation (GTV)

1. **All steps in immobilisation, scanning, image reconstruction, image transfer and co-registration should be quality assured (D)**
2. **All scans used for target delineation in radical radiotherapy should be less than 3 weeks old (D)**
3. **The responsible oncologist should take part in all parts of the target definition in complex cases (D)**
4. **A planning CT scan of optimal quality with the use of metal artefact reduction should be acquired with a maximal slice thickness of 2 mm (D)**
5. **MRI sequences for target delineation should be T1 with and without contrast + T2 with and without fat suppression (STIR/ Dixon) (D)**
6. **The procedures related to PET/CT should follow EANM guidelines from 2015 (D)**
7. **PET-CT and MRI should be used for target delineation of cancers in the oral cavity and pharynx (D)**
8. **PET-CT and MRI should be used for target delineation of cancers in the larynx (D)**
9. **In case of laryngeal tumours not visible on the diagnostic scans (e.g. T1N0 larynx cancer), PET and MRI are not indicated (D)**
10. **Examination in general anaesthesia, drawings or photos should be used for the delineation of superficially spreading laryngeal tumours (D)**

11. **PET-CT and MRI should be used for target delineation of sinonasal and salivary gland cancers (D)**

12. **The choice of imaging modality for nodal targets follows the primary tumour. In case of unknown primary it follows either the guidelines for post-operative radiotherapy (MRI only) or radical radiotherapy (PET-CT + MRI) (D)**

13. **The indication for postoperative radiotherapy is decided at a multidisciplinary team conference (D)**

14. **All cases of T3/T4, extranodal extension (ENE), high-risk histology and non-radical surgery, must be discussed at the multidisciplinary team conference (D)**

15. **Also for postoperative radiotherapy, all available information must be used for target delineation (D)**

16. **Optimal naming and marking of the surgical specimen is essential for optimal delineation of e.g. ENE or R1 resections (D)**

17. **Complicated targets should be defined with the operating surgeon (D)**

18. **MRI should be used for target delineation in post-operative radiotherapy, except when there was no visible pre-operative target and no reconstruction, e.g. T1 glottic larynx (D)**

19. **There is no indication for PET-CT in immediate post-operative radiotherapy, unless macroscopic tumour is suspected, or the neck needs evaluation (D)**

Definition of volumes beyond the GTV

20. **The nomenclature of volumes by the ICRU should be applied, and the definitions of nodal levels according to international consensus guidelines should be followed (D).**

Normal tissues

21. **The nomenclature (D), dose-volume constraints (C), and definition of volumes (D) should follow the guidelines of Appendix 1 and Table 1.**

Radiotherapy dose planning

22. Dose planning should attempt to comply with the tolerance levels for target-coverage and normal tissue sparring described in Table 2 (D).

2. Introduction

Head and neck cancer is a heterogeneous group of cancers located between the base of scull and the clavicles. The anatomical region is characterized by an abundance of critical normal structures, important for senses, appearance, breathing, communication, and eating. The population of patients with head and neck cancer varies with a large proportion of patients having a smoking-induced cancer, and thus, a high risk of co-morbidity and socio-economic problems. The number of patients with head and neck cancer is slightly increasing due to an increase in the number of HPV-induced oropharyngeal cancers. In 2018, 913 patients received radiotherapy for head and neck cancer (annual report 2018 of the Danish Head and Neck Cancer Group, DAHANCA). Most of the treatments were given as radical therapy with curative intent, and tumour control rates are high according to national reports by DAHANCA. Unfortunately, radiotherapy often leads to severe acute and late side effects. Both side effects and the chance of cure are very dependent on the quality of radiotherapy. DAHANCA has a long standing tradition for conducting clinical trials as well as establishing national guidelines for radiotherapy for head and neck cancer to improve outcome. DAHANCA guidelines and treatment recommendations have been applied worldwide.

The evidence for the recommendations are scarce, and based on indirect conclusions from retrospective studies modelling the risk of side effects and likelihood of loco-regional tumour control, as well as technical studies on the inaccuracies of radiation equipment and uncertainties in treatment setup. Nevertheless, the recommendations for adhering to the guidelines is strong as the possibility to evaluate the treatment quality on a national level depends on the consistency of the treatment. Overall, the guideline is a product of discussions within in the DAHANCA radiotherapy quality assurance group and endorsed by DAHANCA (Level 5 evidence). When nothing else is mentioned, this forms the evidence of the guidelines, and specific literature review is not included in the chapters which may be characterized as a “cookbook”.
Nevertheless, DAHANCA is very concerned about adherence to the guidelines and has evaluated the clinical consequences of any variation. DAHANCA has thoroughly analysed and reported on these issues[1][2][3].
As mentioned, several international groups have evaluated previous editions of the present guidelines, and thereby produced new recommendations [4][5]. These guidelines have, in turn, to some extent been incorporated into the present edition.

High quality radiotherapy is to a large extent driven by development in equipment and software technology, and is as such a very dynamic field. The need for research, quality assurance, and evaluation of new techniques is therefore a continuous process that continuously must be implemented via endorsed national clinical guidelines to ensure equal and high levels of treatment quality.

Objective

The overall objective of this guideline is to support high quality cancer care across the Danish healthcare system.

The specific objective of the present guidelines is to secure a high and consistent quality of radiotherapy for patients with head and neck cancer. To increase the quality of care, both within and outside of clinical protocols, we strive for a high degree of consistency and adherence to guidelines. This aspiration goes far beyond recommendations based on high quality evidence. The guidelines are therefore far from evidence based, but it has been recognized that DAHANCAs previous guidelines have inspired international groups to produce similar guidelines [4][5].

Target population

Radiotherapy for all patients with head and neck cancer can be planned according to the principles of the guidelines.

Target User

This guideline is developed to support clinical decision-making and quality improvement. Thus the target users are healthcare professionals working in Danish cancer care. The guidelines are applicable to all treatments in the head and neck area, and should serve as a guideline for radiotherapy at all Danish centers treating head and neck cancer patients. They are applicable for the whole process of radiotherapy from scanning, target delineation, dose planning, and evaluation and quality assurance and should therefore guide both physicians and physicists involved in radiotherapy for head and neck cancer.

3. Scientific evidence

Target delineation (GTV)

In order to cure a patient, it must be ensured that all clonogenic cells receive a tumoricidal dose, i.e., the target is covered by a relevant dose. Tumour deposits may occur far from the bulk of disease, i.e. in lymph nodes or via perineural spread. These deposits will not be covered by the clinical target volumes irrespectively of the GTV to CTV margin. Utmost care must therefore be put into the identification of tumour extension , and all available information must be used.
According to the ICRU 83, the GTV is the gross demonstrable extent and location of the tumour. All examinations and imaging modalities, which provide information on the extent and location of the tumour should be used, e.g. clinical examination, anatomic imaging and functional imaging.

Literature review and evidence description

23. All steps in immobilisation, scanning, image reconstruction, image transfer and co-registration should be quality assured (D)

24. All scans used for target delineation in radical radiotherapy should be less than 3 weeks old (D)

25. The responsible oncologist should take part in all parts of the target definition in complex cases (D).

The extension of disease outside what is defined as GTV with the available information may be evaluated by three distinctly different methods, that supplements each other: 1) Pathology examination of surgical specimens, e.g. Cambell et al. [6] and Apisarnthanarax et al [7]. 2) macroscopic tumour extension on surgical specimens with respect to different imaging modalities e.g. Daisne et al [8] and Ligtenberg et al[9], and finally 3) the recurrence pattern with respect to target definition and dosimetry[10][1][11][12][13].
With the available evidence, it is not obvious that geographical miss is the dominant problem on a population basis. This is important to keep in mind when target delineation and margins are discussed. Larger treatment volumes may impede treatment intensification, or reduce compliance due to side effects[1][14]. Nevertheless, optimal GTV definition remains critical for optimal radiotherapy of the individual patient.

In radiotherapy, the planning CT is the reference imaging modality, as this is the basis for correct dose planning and treatment setup. Information from other scanning procedures must therefore be evaluated with respect to anatomical and geographical precision. That is, co-registration must be evaluated whether it is performed rigidly or deformable.
Imaging acquired in non-treatment position, e.g. diagnostic MRI or PET-CT scans can be used for target delineation. The scans should not be more than 3 weeks old (consensus), otherwise they must be repeated or used with caution.

Ideally, the same oncologist should be involved in the entire patient trajectory, from staging at the multi-disciplinary team conference (MDT), to patient information and discussion of expected and accepted side effects in relation to target definition. This is especially important in case of advanced disease or potentially serious side effects, e.g. double-sided blindness or brainstem injury.

Planning CT

26. A planning CT scan of optimal quality with the use of metal artefact reduction should be acquired with a maximal slice thickness of 2 mm (D).

The optimal scan quality of the CT is important and metal artefact reduction should be used [15]. Slice thickness should not be larger than 2 mm. Intra-venous contrast should be used for nodal evaluation, if a MRI in treatment position is not available. Field of view settings and pixel size should be evaluated since this can potentially change margins.

Recommended MRI sequences for delineation

27. MRI sequences for target delineation should be T1 with and without contrast + T2 with and without fat suppression (STIR/ Dixon)(D).

The recommended MRI sequences should be optimized to the local hardware such as scanner and coils. Priorities should be geometric stability, image quality, patient convenience and scanning in treatment position i.e. in immobilisation as well as resources. If available, 3D scans should be considered for geometric stability, but it will often be necessary to add axial scans for optimal image quality. Sequences optimized for image quality only can lead to serious geometric distortions [16].
The recommended sequences are T1 with and without contrast + T2 with and without fat suppression (STIR/ Dixon). Adding fat suppression sequences to T1 with contrast is recommended in cases of suspected intracranial or intraorbital spread. Diffusion weighted imaging including ADC maps may be added. The order of sequences should be prioritized so that the most important sequences are done first in case the patient tolerates the scanning poorly (e.g., T1, T1+contrast, T2, DWI).

PET-CT

28. The procedures related to PET/CT should follow EANM guidelines from 2015[17] **(D).**

PET-CT scans can be used to detect a primary tumour, to distinguish between solid matter and effusions, distant metastasis, or other primaries. In the latter situation, the patient is scanned from the vertex to the proximal thigh. In case the patient has been evaluated below the clavicles, the scan area does not need to be as large. Metal artefact reduction algorithms should be used, especially if the CT is used as the planning CT, and not only attenuation correction. A flat table couch and an immobilisation mask should be used.

Nuclear medicine specialist, a radiologist and an oncologist participates in the target delineation process, ideally at a multidisciplinary team conference with the purpose of target evaluation.

Nuclear medicine specialists and the radiologist create a written description of the target, and this is stored together with the images in RIS/PACS archiving system.

Pharynx and oral cavity

29. PET-CT and MRI should be used for target delineation of cancers in the oral cavity and pharynx(D).

Areas of special attention are perineural invasion, bone and skull base invasion

Larynx

30. PET-CT and MRI should be used for target delineation of cancers in the larynx(D)

31. In case of tumours not visible on the diagnostic scans (e.g. T1N0 larynx cancer), PET and MRI are not indicated (D)

32. Examination in general anaesthesia, drawings or photos should be used for the delineation of superficially spreading tumours (D).

Areas of special attention are cartilage invasion and superficially spreading tumours.

Cancer of nasal cavity, paranasal sinuses and the salivary glands

33. PET-CT and MRI should be used for target delineation of sinonasal and salivary gland cancers(D).

Areas of special attention are perineural invasion, bone, orbital and skull base invasion

Nodal metastases

34. The choice of imaging modality follows the primary tumour. In case of unknown primary it follows either the guidelines for post-operative radiotherapy (MRI only) or radical radiotherapy (PET-CT + MRI) (D).

The normal anatomical nodal characteristics should be considered: small size, kidney or bean shape, presence of hilus, homogenous cortex and hilar vascularity. Some of these characteristic are superiorly assessed with ultrasound, which should be considered. Deviations from these characteristics should be considered an indication for malignancy.

The malignancy criterion concerning size is measured in the shortest axis [18]. The sensitivity, using this criterion alone is not high, and the morphological criteria should be weighted as well[19]:

Neck nodes in general: 10 mm

Angular nodes (upper jugulo-carotid): 11 mm [20]

Retropharyngeal nodes 6 mm. [21][22]

Using functional imaging, other malignancy criteria might be used.

Post-operative radiotherapy

35. The indication for postoperative radiotherapy is decided at a multidisciplinary team conference(D).

36. All cases of T3/T4, ENE, high risk histology and non-radical surgery, must be discussed at the multidisciplinary team conference(D).

Tasks to be clarified at the MDT conference

The indication for post-operative radiotherapy should be discussed at the MDT conference between the operating surgeon and an oncologist as soon as the final pathology report becomes available. Hereafter, the conclusion is presented to and discussed with the patient. Ideally, all post-operative cases should be discussed at the MDT, with respect to the indication of postoperative radiotherapy. As a minimum, all cases of T3/T4, ENE, high-risk histology and non-radical surgery must be discussed between an oncologist and a surgeon. Lack of information in the pathology report and e.g. ambiguous nomenclature of specimens and large specimens with several nodal levels are other issues that must be clarified at the MDT conference.

The target should be described in the medical report from the MDT conference.

Target definition

37. Also for postoperative radiotherapy, all available information must be used for target delineation (D).

38. Optimal naming and marking of the surgical specimen is essential for optimal delineation of e.g. ENE or R1 resections (D).

39. Complicated targets should be defined with the operating surgeon (D).

Except in case of macroscopic non-radical surgery/ debulking surgery, there is no GTV in post-operative radiotherapy. Nevertheless, it is of advantage for accurate target delineation, that a pre-operative tumour volume (pre-operative GTV) can be defined [23]. Furthermore, the surgical bed should be defined with optimal accuracy irrespective of any reconstruction. Any area of non-radical surgery should also be defined with optimal precision. With all these considerations in mind, it is strongly recommended that the operating surgeon takes part in the target delineation, as a minimum for complex cases. Post-operative oedema and altered anatomy are typical issues that need special attention. The oncologist participating in the MDT conference and defining the target should be the same.

Other considerations for postoperative target delineation

To ensure optimal workflow and quality of the target definition, the operating surgeon should take preoperative photographs or make a tumour drawing, and make a thorough description of tumour extension, evaluated with the patient in general anaesthesia. Optimally, areas of anticipated narrow margins or e.g. ENE, should be marked with surgical clips. Clips can also be used to mark the entire surgical bed [24].

Imaging

40. MRI should be used for target delineation in post-operative radiotherapy, except when there was no visible pre-operative target and no reconstruction, e.g. T1 glottic larynx (D).

41. There is no indication for PET-CT in immediate post-operative radiotherapy, unless macroscopic tumour is suspected, or the neck needs evaluation (D).

MRI has superior soft-tissue contrast that can be utilized to delineate the surgical bed. Furthermore, MRI for target delineation allows for comparison with pre-operative MRI's.

Patient values and preferences

Not relevant.

Rationale

Optimal delineation of the target is essential for high quality radiotherapy. All errors in this part of planning will result in systematic errors and therefore inferior quality radiotherapy.

Comments and considerations

The guidelines for GTV delineation has recently (January 2020) been discussed among the DAHANCA Radiotherapy Quality Assurance group and imaging specialist from all centres. The present guidelines is the result of these discussions and will provide us with an opportunity to evaluate target delineation on a national level in the future.

Definition of volumes beyond the GTV

42. The nomenclature of volumes by the ICRU should be applied, and the definitions of nodal levels according to international consensus guidelines should be followed (D).

Literature review and evidence description

Clinical target volumes (CTVs) and organs at risk (OARs) must be defined in the dose planning system for CT-based radiotherapy. The terminology for these volumes is defined by ICRU. The relevant editions are ICRU 50 (1993), ICRU 62 (1999) and ICRU 83 (2010). The definitions in ICRU 83 and ICRU 62 are the same, but in the latter edition, the 'Remaining volume at risk' (RVR) – defined as CTV + OAR subtracted from the patient contour – is reported as an important volume for IMRT dose planning in order to avoid high dose areas outside the targets and to avoid unexpected late morbidity, including secondary cancer. The use of an internal margin in head and neck cancer radiotherapy is considered irrelevant according to ICRU 83 as a defined volume, but the internal margin should be included in CTV.

Definition of volumes according to ICRU

1. GTV = gross tumour volume includes all verified tumour extensions from clinical examinations and all available scanning modalities. Other volumes such as ”GTV_preop”, ”GTV_MR” or ”GTV_PET” may be defined.
2. CTV = clinical target volume includes GTV if present and subclinical tumour extension to the vicinity of the primary or lymph nodes. The CTV should also include margin for internal changes and uncertainties e.g. shape, size and organ movement, rarely relevant for head and neck radiotherapy.
3. PTV = planning target volume is a geometrical volume defined to secure dose delivery to the CTV. The PTV includes uncertainties related to dose delivery including setup and mechanical uncertainties. The size of PTV-margin is dependent on systematic and random uncertainties related to a specific treatment technique, local quality assurance and other locally dependent factors. It should ideally be defined based on local measurements. The size of the PTV is defined by adding the square of the single independent uncertainties (ICRU 62). Notice: PTV is not used for proton therapy. See the chapter on proton therapy.
4. OAR = organ at risk
5. PRV = planning risk volume =OAR + margin for internal movements and setup margin as described above. The PRV is mainly relevant for serial organized and for small OAR volumes (lacrimal glands).
6. RVR = remaining volume at risk = CTV and OAR subtracted from the total patient volume
7. TV = treated volume = the volume receiving the prescribed dose.
8. IV = irradiated volume = volume receiving a dose relevant for normal tissue effects

DAHANCA principles for target delineation

DAHANCA uses the following volumes and definitions for radiotherapy: GTV is delineated based on examinations, imaging, pathology reports, drawings and other information. Elective regions are selected based on estimations of the risk of subclinical spread. There are two risk levels: high risk (CTV2) and low risk (CTV3). Low risk is defined as elective nodal regions with as risk for subclinical spread of at least 10%. The risk

estimations, and thereby the recommended elective regions, are significantly different between the N0 and N+ neck.

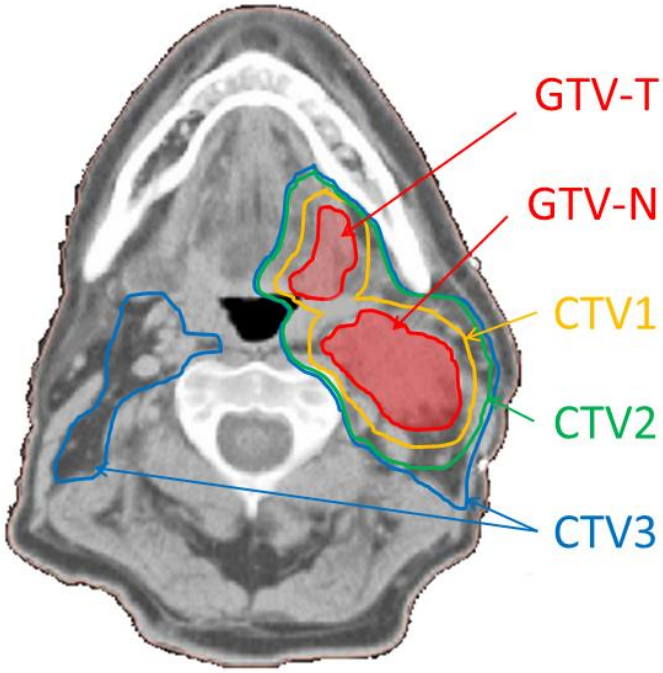

Figure 1. Principles for target delineation and nomenclature

GTV and CTV in radical radiotherapy

GTV: Gross tumour in both T (GTV-T) and N (GTV-N) site evaluated by clinical examination and imaging (see above)

CTV1*:* Includes the primary tumour (GTV-T), involved nodes (GTV-N) with an isotropic margin of 5 mm, though larger if the tumour is poorly defined and smaller if the margin extends into air, uninvolved bone or other natural borders for tumour spread. That is; uninvolved bone is not included in the CTV1.

CTV2: Includes CTV1 and the surrounding volume outside CTV1 with the highest risk of subclinical tumour extension. It is defined as GTV with an isotropic margin of 10 mm. The margin may be less if it extends into air or surpasses natural borders such as bone. The total geometrical margin from GTV to CTV2 should not be larger than 12 mm. Furthermore, a disease specific high-risk anatomical region could be added. See the guidelines for the specific regions for details.

CTV3: Contains CTV2 and regional elective lymph nodes without margin. The CTV3 definition is highly dependent on nodal status. N0 and N+ are treated as recommended in Grégoire 2003[25], Grégoire 2006[26] and Grégoire 2014[27], respectively. For the N+ patients, the elective nodal regions are extended 2 cm cranial and caudal from any pathological lymph nodes (GTV-N). The sternocleidomastoid muscle is included 2 cm above and below any pathological nodes in case of suspected muscle involvement.

GTV and CTV in postoperative radiotherapy

Preoperative-GTV: As defined from pre-operative clinical examination and imaging (See above).

CTV1*:* Includes the pre-operative non-radical operated tumour (R1 or R2) with an isotropic margin of 5 mm, though larger if the tumour is poorly defined and smaller if the margin extends into air, uninvolved bone or other natural borders for tumour spread. That is; uninvolved bone is not included in the CTV1.

CTV2: After R0 resection, CTV2 includes the preoperative GTV with an isotropic 10 mm margin. In case of non-radical resection the CTV2 includes CTV1 with 5 mm margin. The margin may be larger in case of poorly defined tumour and less if it extends into air or surpasses natural borders such as bone. Furthermore, a

disease specific high-risk anatomical region could be added. See the guidelines for the specific regions for details.

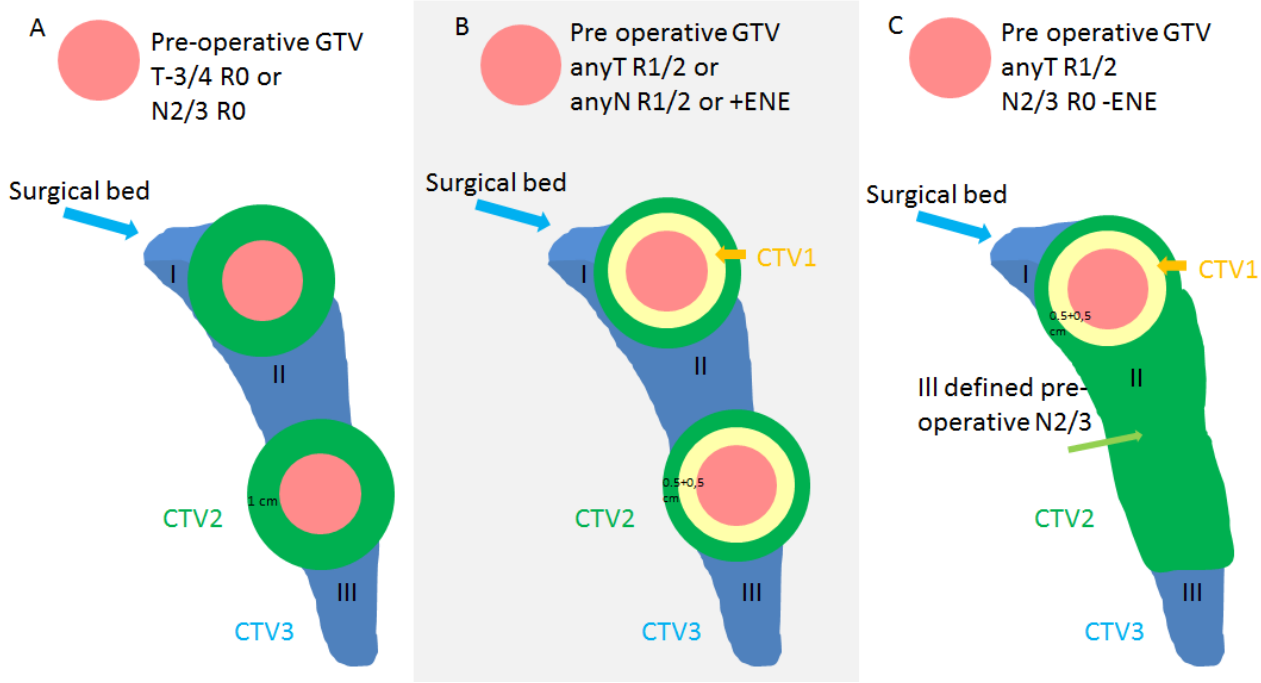

Figure 2: *Examples of postoperative radiotherapy scenarios. I, II and III refers to elective nodal regions. Scenario A: Stage is the only indication for post-operative radiotherapy (R0) and thus, no CTV1 is present. Scenario B: Volumes with insufficient margins or ENE is included in CTV1. If there is only indication of post-operative radiotherapy in the T-site, but N0 disease, elective nodal regions are not treated. Scenario C: Well defined pre-operative primary tumour GTV with R1 or R2 resection. Nodal areas with R0 resection and no ENE, but ill defined, e.g. several smaller positive nodes. In general: In case of well-defined pre-operative volumes, geometrical margins are applied. In case of ill-defined volumes or diffuse soft tissue invasion; entire nodal volumes or anatomical regions (e.g. entire tongue) may be used as an anatomical margin.*

CTV3: Contains CTV2 and the surgical bed of the primary tumour site outside preoperative GTV + 10 mm + regional elective lymph nodes without margin. The CTV3 definition is highly dependent on nodal status. See references above.

PTV

PTV1, PTV2, PTV3: Contains corresponding CTVs with set-up margins (SM) that may vary with field localisation, patient immobilisation and the use of Image guided adaptive radiotherapy (IGRT). It is recommended that all departments gather data for their respective SM. PTV can be further divided into sub-volumes, e.g. close to surfaces or in case of overlaps with OAR and PRV.

In proton planning, the PTV margin is not used.

Example of workflow

1. When present, GTV-T and GTV-N are delineated on basis of the above mentioned recommendations

2. CTV1 is generated from GTV by adding an isotropic margin of 5 mm.

3. CTV2 is generated from GTV by adding an isotropic margin of 10 mm. CTV2 is modified for bone, air, skin and specific anatomical consideration

4. CTV1 outside CTV2 is erased.

5. CTV3 is delineated according to atlases, available at DAHANCA.oncology.dk.

6. Organs at risk are defined according to the treatment area and delineated according to atlases (defined in Appendix 1). The spinal cord must always be delineated, and the brain stem should be delineated at least in all cases with a defined CTV3.

7. Targets and organs at risk should be visualized in beams eye view to identify target and OAR irregularities and inconsistencies. The CTVs are modified to represent clinical and biological relevant volumes.

8. The volumes are transferred to the dose planning process and considerations concerning bolus and priorities are discussed with the treatment planner.

9. Target definition and dose prescription used for the dose planning process is formally approved and documented.

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored

Comments and considerations

Adherence to the guidelines may influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

Normal tissues

43. The nomenclature (D), dose-volume constraints (C) and definition of volumes (D) should follow the guidelines of Table 1 and Appendix 1.

Literature review and evidence description

Atlas of relevant normal tissues

Knowledge on normal tissue anatomy in the head and neck area can be acquired from the anatomy/ radiology literature. The definition of organs at risk does not always follow the strict anatomical or functional definition of an organ, but it is aimed for the organs at risk to be defined in a safe and operational manner, e.g. the location of the division from the spinal cord to the brainstem. See Appendix 1 for delineation guidelines of OAR.

Dose volume constraints

The dose volume constraints relevant for head and neck cancer are listed below in Table 1. Data is mainly acquired from studies of conventional radiotherapy of adults without concomitant chemotherapy. Normal tissue tolerance can be different for other fractionation schedules, and the table is only applicable for fraction sizes of 2 Gy and below and is not applicable for children or hypo-fractionation. For some normal tissues, other models and other parameters are available. For other organs, no or limited data are available, and the dose-volume constraints are products of discussions and consensus among the members of the DAHANCA Radiotherapy Quality Assurance Group. The models and constraints are selected from the available evidence, with emphasis on being operational, simple and relevant for the dose levels used in head and neck cancer radiotherapy.

For the optimization process, it is important to have in mind that the risk of toxicity is not dependent on a single dose-volume (DVH) parameter, but on a complex dose-volume interplay. All tissues should be spared to doses "as low as reasonable possible", - considering and prioritizing competing organs at risk.

If over-dosage is unavoidable due to prioritization of target coverage, some guidance to over-dosage of critical normal tissues, with low risk of severe side effects, are provided. The violation of these constraints should be discussed with the patient, and consent should be recorded (BrainStem, SpinalCord and optical structures). The nomenclature follows Santanam, when applicable[28]. Suffixes for L=left / R=right should be applied. D_{max} means $D_{0.027\ cm^3}$ (3x3x3 mm^3). For delineation guidelines; see Appendix 1.

Table 1. Dose Constraints

	Structure (alphabetically within groups). Nomenclature and explanation	Dose constraint OAR [Gy]	Dose constraint PRV [Gy]	Comments. Endpoint in bold	References
ABSOLUTE	BrainStem	D_{max} ≤ 54Gy	D_{max} ≤ 60Gy	Treating ≤10 cm^3 of the OAR to a maximum of 59 Gy results in a low risk of **neurological damage.** If over-dosage is unavoidable due to target coverage, it may be done. In the peripheral 3 mm rim of the brain stem, 64 Gy causes a low risk of neurological sequelae *.	Mayo [29] *Weber [30] *Debus [31]
	SpinalCord	D_{max} ≤ 45Gy	D_{max} ≤ 50Gy	Risk of **neurological damage** is estimated to 6 % for doses at 60 Gy. Limited over-dosage may therefore be allowed to achieve target coverage.	Kirkpatrick [32]
MUST	Chiasm OpticNerve_L OpticNerve_R	D_{max} ≤ 54Gy	D_{max}≤ 60Gy	Dmax ≤ 55 Gy leads to a low risk of **visual disturbance**. Doses above 60 Gy leads to an estimated risk of above 7%. Dose constraint can be violated in order to achieve target coverage	Mayo [33]
	EyeBack_L EyeBack_R	D_{max}≤ 45Gy	D_{max}≤ 50Gy	**Retinopathy** is seen after doses as low as 30 Gy, and doses must be kept as low as possible. There is a volume effect and e.g. the lateral retina can be spared separately.	Jeganathan [34]
	EyeFront_L EyeFront_R (cornea, iris, lens)*	D_{max}≤30 Gy	D_{max}≤35 Gy	**Conjunctivitis, dry eye syndrome and cataract.** *The lenses have been removed from the list of OARs since it is contained in the anterior eye OAR and side effects may be treated.	Jeganathan [34]
	Lacrimal_L Lacrimal_R (lacrimal gland)	D_{mean}≤25 Gy	D_{mean}≤30 Gy	**Dry eye syndrome.** Even if constraints are not met for other parts of the optic pathways, the anterior eye and lacrimal glands are worth sparing in order to preserve the eye in situ. In case of severe	Jeganathan [34]

				dry eye syndrome, the eye must often be removed.	
SHOULD	Brain	D_{1ccm}<58Gy D_{max}≤ 68Gy Avoid hotspots.		At D_{max}=72 Gy the risk of **necrosis is** 5% at 5 years. **Cognitive disturbances** may be seen at lower doses.	Su [35] Lawrence [36]
	Cochlea_L Cochlea_R	D_{mean} ≤ 45Gy and $D_{5\%}$ ≤ 55Gy	D_{mean} ≤ 50Gy and $D_{5\%}$ ≤ 60Gy	Risk of clinical relevant **hearing loss** may be as high as 15% at mean doses of 47 Gy when using concomitant cisplatin.	Bhandare [37] Chan [38] Hitchcock [39]
	Esophagus (cervical esophagus+ esophagus inlet muscle+ cricopharyngeal muscle)	D_{mean} ≤ 30Gy		Limited data for radiation induced **swallowing problems** for esophagus.	
	LarynxG (glottic larynx)	D_{mean} < 40 Gy,		Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth [40]
	LarynxSG (supraglottic larynx)	D_{mean} < 40 Gy		Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth [40]
	Mandible	D_{max}≤ 72Gy		**Osteoradionecrosis.** Limited data.	*Eisbruch* [41]
	OralCavity	D_{mean} ≤ 30Gy for non-involved oral cavity.		Extended oral cavity according to Brouwer. ***Xerostomia and mucositis***	Beetz [42] Hawkins [43] Dean [44]

	Parotid_L Parotid_R	1) Contralateral parotid: D_{mean}≤ 20Gy 2) Both parotids: D_{mean}≤26Gy	***Xerostomia***	Deasy [45]
	PCM_Low (lower pharyngeal constriktor)	D_{mean} < 55 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth [40]
	PCM_Mid (middle pharyngeal constrictor)	D_{mean} < 55 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth [40]
	PCM_Up (upper pharyngeal constrictor)	D_{mean} < 55 Gy	Different available data for **swallowing problems.** No indications of a steep dose response curve.	Batth [40]
	Pituitary	D_{mean}≤20Gy	No certain threshold. The risk of **hormonal disturbances** increases at >20 Gy	Darzy [46]
	Submandibular_L Submandibular_R	D_{mean} ≤ 35Gy	**Xerostomia**	Deasy [45]
	Thyroid	D_{mean}≤40 Gy	No specific threshold for **biochemical hypothyroidism**	Rønjom [47] Boomsma [48]
CAN	Carotid_L Carotid_R	D_{max}≤40 Gy	Should be spared to avoid **stenosis and cerebral ischemia,** in case no elective volume is irradiated e.g. $T1_{a/b}$ glottic cancer or ipsilateral radiotherapy	Choi [49]

	BuccalMuc_L/R Buccal mucosa	D_{mean} ≤ 30Gy for non-involved OAR	**Xerostomia** (and perhaps mucositis) Data only available as a part of oral cavity	Dean [44] Hawkins [43]
	Lips	D_{mean} ≤ 20Gy	**Mucositis, Cheilitis**	RTOG 1016
	Hippocampus	D40% < 7.2Gy [EQD2] (i.e. < 11Gy on 33fx with α/β=3)	Risk of **poor memory** at 11% and 66% at doses below and above constraint. The consequences for other OARs resulting from hippocampal sparring should be monitored carefully at dose optimization due to the very low constraint.	*Gondi [50]

ABSOLUTE: Organs of critical importance that must be prioritized over target coverage, as a rule
MUST: Serial organs that must be delineated, but not necessarily prioritized over target coverage.
SHOULD: Organs at risk with some evidence for sparring, and OAR with serious but manageable toxicity.
CAN: Poor evidence, uncertain endpoints or manageable toxicity. Organs may be delineated according to local guidelines/research projects.

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored.

Comments and considerations

Adherence to the guidelines may influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

Radiotherapy dose planning

Literature review and evidence description

44. Dose planning should attempt to comply with the tolerance levels for target-coverage and normal tissue sparring described in Table 2 (D).

The treatment planning process for radiotherapy consists of a series of patient-related procedures and machine work tasks that eventually result in a treatment plan that enables a radiation dose prescription to be applied effectively for tumour control, and safely for the patient. This entails a long string of hardware and software equipment that are involved in application of photon beams, electron beams, and particles, such as

protons.
Economical issues are strongly involved in radiation treatment, and thus, treatment planning and delivery is not only based on clinical experience and scientific evidence, but also on the performance and availability of technical equipment from commercial manufactures. Therefore, Oxford-levels of recommendation are considered D, however, due to patient safety and legal issues, radiotherapy is carried out at the highest level of approval by authorities.

Dose prescription
The prescribed dose for a target (CTV) is the mean dose.

Dose calculation
For *photon* treatment, the mean dose must be the prescribed dose. Dose in $CTV2_{only}$ (CTV2 minus CTV1) and $CTV3_{only}$ (CTV3 minus CTV2) must be as close to prescription dose, for the volume, as achievable.

CTV1 must be covered with 95%-107% of the prescribed dose. CTV2 and CTV3 must be covered with 95% of the prescribed doses. The 95% isodose curve for PTV1, PTV2 and PTV3 must be as close to the delineation of PTV1, PTV2 and PTV3 respectively, as achievable. Adherence to this is defined by QA measures, see Table 2.

A maximum volume of 1.8 cm^3 in the patient may receive >107% of the prescribed dose to CTV1.

Dose calculation for photons must take differences in patient density into account. This applies to both primary and scattered radiation.

For *electrons* the minimal dose for PTV must be 92.5% of the prescribed dose, and the maximum dose should be <107% of the prescribed dose. Dose calculation for electrons should preferably be based on density information of a CT scanning, but for tumours close to the skin, a manual calculation may be performed.

Simultaneous integrated boost (SIB) is used as the standard technique, with different dose levels for CTV1, CTV2 and CTV3, but with all volumes treated at each fraction. The total dose to the elective regions has therefore been increased from 46 Gy (2 Gy/fx) to 50 Gy (1.5 Gy/fx) and 56 Gy (1.0 Gy/fx), see Appendix 2.

Prioritization of treatment goals
The IMRT optimization algorithms and the dose planning systems need a prioritization of the treatment goals. The prioritization listed below is recommended for maximal clinical benefit, but individual prioritization may differ according to patient wishes and the clinical situation. The OARs are not listed by priority within groups.

1. Critical normal tissues, potentially lethal complication

SpinalCord
BrainStem

2. Target coverage

GTV
CTV1

3. Critical serial normal tissues
EyeFront
Chiasm
EyeBack

4. Target coverage
CTV2
CTV3
PTV1
PTV2
PTV3

5. Sensitive normal tissue
Brain
Cochlea
Esophagus
LarynxSG
LarynxG
Mandible
OralCavity
Parotid
PCM
Pituitary
Submandibular
Thyroid
Carotid
BuccalMuc
Lips
Hippocampus

6. Avoid overdosage of PTV2 and PTV3

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored

Comments and considerations

Adherence to the guidelines may influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

Treatment

Literature review and evidence description

Like the treatment planning process for radiotherapy described above, radiation treatment delivery is defines by a series of patient-related procedures and technical aspects related to accelerators and additional equipment. Therefore, the Oxford-levels of recommendation is considered D, however, due to patient safety and legal issues, radiotherapy is carried out at the highest level of approval by authorities.

According to ICRU, the dose rate must be at least 0.1 Gy/min inside CTV, in photon radiotherapy.

Image guidance

Patient positioning should be verified with 2D imaging and/ or CBCT-scans according to local guidelines. Tolerances and imaging frequency should be defined locally with respect to local PTV and PRV margins originating from measurements of random and systematic uncertainties in the whole process of treatment preparation and delivery[51].

The anatomical structures used for matching must be defined with respect to target localisation. For example, emphasis must be put on more cranial structures for nasopharyngeal tumours than for hypopharyngeal tumours. The 'region of interest' (ROI) for the matching process must also take the extent of the elective areas into account. Match structures with limited internal movements should be chosen, e.g. not the hyoid bone, but preferably the cervical spine. Soft tissue matching is often possible when CBCT scans are available. The ROI must be chosen to include both target and critical normal tissue. Both automatic and manual match must be visually verified according to bony anatomy and visible soft tissue.

In case of non-adherence to pre-specified tolerances, target coverage and normal tissue sparring should be prioritized as described above, and the reasons for non-adherence should be documented.

Re-planning

It should be continuously evaluated whether patient anatomy and the effectiveness of the immobilisation device change to a degree that may have significant implication on the dose distribution. In that case, a new CT scan with or without new immobilisation must be performed and the dose distribution evaluated. If necessary, new targets and normal tissues must be delineated and a new treatment plan must be developed. Evaluation during treatment, must be based on regular imaging of the patient in treatment position and e.g. supplied with a CT scan half way through treatment if necessary. The latter is especially relevant for patients with significant weight loss or for patients with large tumours were the CTV1 volume might shrink significantly. Re-planning must always take place in case of risk of critical normal tissue overdose or insufficient target coverage.

Special considerations for proton therapy

Potential candidates for proton therapy are identified at the local departments of oncology, after a comparative dose plan, i.e. comparison of two treatment plans using protons and photons, respectively. The dosimetric

differences are quantified and applied to normal tissue complication models (NTCP) to estimate a potential benefit of proton therapy. If it is decided that the patient should be offered referral to the Danish Centre for Particle Therapy (DCPT), and the patient accepts, further planning will take place at DCPT. The patients are referred to the local department of oncology for follow-up after end of treatment.
The principles regarding dose prescription, definitions of clinical target volumes (CTV1, CTV2 or CTV3), target selection, normal tissue definition, nomenclature and normal tissue constraints are applicable for both photons and protons. Several factors are qualitatively different between proton and photon planning as described below. The advantages, as well as disadvantages of proton therapy are well illustrated by the dose depth curve and the Bragg peak.

Preparation and scanning
There are special considerations regarding homogeneity and blunt edges of the immobilisation devices. The CT-scanners must be calibrated and optimized for the translation of HU to stopping power, using e.g. dual energy CTs. Nevertheless, mono energetic, non-calibrated CTs or even diagnostic MRI scans can be used for comparative dose plans. The dosimetric differences of the comparative dose plan should be quantified using differences in dose and expected NTCPs of specific OARs.

Dose planning
Proton therapy planning includes other solutions than photon therapy regarding choice of field angles, number of fields, techniques for skin coverage, and lateral penumbra. The final treatment plan at DCPT, as well as comparative dose planning, requires special skills and training defined by the DCPT.
The PTV concept is not an optimal solution for uncertainties from immobilization, scanning, setup errors, and dose calculation in proton therapy. In dose optimization, CTV coverage and critical normal tissue sparring are ensured in multiple 'worst-case scenarios' of setup errors and range uncertainties, referred to as robust optimization. Dose to CTV and dose limits to OARs are prescribed and reported for the nominal plan, i.e. the robustly optimized dose plan with no introduced errors.

DCPT will ensure that proton dose plan guidelines are updated.

Intensity modulated proton therapy (IMPT) uses several small beamlets (spots) to deliver the required dose. The volumes of possible spot placement are called beam-specific Robust Target Volumes (RTVs), and are defined by calculation of beam-specific uncertainties regarding setup errors and range uncertainties. To reduce uncertainties, a target, or parts thereof, is covered by more than one field.

The CTV in head and neck cancer is often located close to the skin. The lowest possible energy delivered by the cyclotron at DCPT is 70 MeV, which is equivalent to a Bragg peak depth of 4 cm. Therefore, a range shifter (a water equivalent plastic plate) is introduced between the snout and the patient. This reduces the energy and deposits the dose closer to the surface. Unfortunately, the range shifter also limits the space around the patient and restricts the possible field directions as well as increases the spot sizes, whereby the lateral penumbra is degraded. The dosimetric advantage of proton therapy is thus in the field direction with a lower entrance and exit dose. These characteristics must be exploited to obtain an optimal proton plan.

Treatment
Patient positioning is very similar to photon treatment. CBCTs are used for correction of translational and rotational errors. Nevertheless, proton therapy requires greater attention to changes in depth and density, e.g. shoulder position, immobilization devices and anatomical changes, since the energy deposition of protons relies heavily on these parameters.

Treatment prolongations

All fields must be treated at all fractions. Patients treated with 6 fractions per week must receive a single fraction Monday to Friday and the sixth fraction should be administered during the weekend or as an extra fraction on a weekday. An interval of at least 6 hours between fractions must always be ensured. For patients receiving 10 fractions per week, two daily fractions with an interval of at least 6 hours is used.
Before the first treatment-interruption (e.g. a weekend), at least 4 Gy should be administered, and similarly, not less than 4 Gy should be administered after a weekend.

In case of treatment prolongation, the overall treatment time, from first to last fraction, should be maintained if possible. The missing fraction(s) must be administered as soon as possible and ideally within a week, if clinically applicable. This can be done by delivering an extra fraction during weekends or on the day of a planned fraction (but at least 6 hours apart). Considering acute toxicity, treatment breaks should not be compensated with more than one extra fraction per week, and no more than 13 consecutive treatment days. Furthermore, no more than 3 days of double fractionation must take place within 2 weeks for conventional fraction sizes.
To compensate for longer treatment breaks, hyper-fractionation and dose escalation may be worth considering[52].

Patient values and preferences

Patients may be involved in decision-making if more options of compensating procedures are available.

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored.

Comments and considerations

Adherence to the guidelines might influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

Radiotherapy planning

45. Dose planning should strive to achieve the tolerances for target-coverage and normal tissue sparring mentioned in table 2 (D).

Literature review and evidence description

Treatment methods must be quality assured and reported in clinical trials. QA can be divided into three steps:

Step 1: Preparation including writing guidelines, dose audits and delineation workshops.

Step 2: Daily QA: Technical QA of the performance of the accelerators, verification of delineation, dose plans and setup procedures.

Step 3: Follow-up on the given treatments; reporting, sampling and evaluation according to predefined criteria of minor and major deviations.

Preparation

The principles of Technical QA in DAHANCA refers to ”Practical Guidelines for the Implementation of a Quality System in Radiotherapy” from the European Society for Therapeutic Radiology and Oncology (ESTRO), ”Comprehensive QA for Radiation Oncology”, Reports of AAPM Radiation Therapy Committee Task Group 40, and ”Absorbed Dose Determination in Photon and Electron Beams”, Technical Report Series 398, from the International Atomic Energy Agency (IAEA).

It will be described below how the correct treatment of head and neck cancer is ensured under the auspices of DAHANCA. Also, local guidelines must exist in all centres to ensure adherence to the national guidelines by DAHANCA.

Dose audit

The path from CT scanning, dose planning and treatment delivery is complex, and all steps must be verified. Nevertheless, transitions from one step to another may also introduce errors that may escape a stepwise QA. One way to assure that all steps and transitions are retained is by performing a dose audit: A dose audit includes treating a standardized phantom according to specified guidelines to certain doses. Dose to the phantom is measured and compared to the dose plan produced at the centre. It is recommended that an external dose audit is performed at least every 5 years under the auspices of the DAHANCA Radiotherapy Quality Assurance Group.

Delineation workshops

The basis of dose planning is the delineation of the tumour and clinical target volume. Delineation guidelines for the OARs and CTVs contained in the present guidelines are aimed at increasing consistency and comparability between patients and centres. Nevertheless, no gold standard exists, and delineation practises must be continuously evaluated through participation in national workshops. National delineation workshops will be arranged every 3 years through the DAHANCA Radiotherapy Quality Assurance Group.

Daily quality assurance

A guideline for daily QA must be present at all centres.

Delineation verification and approval
Delineation of targets and normal tissues must be approved by a trained specialist. Delineation must, as a rule, follow the present guidelines, and deviations from the guidelines should be described in the medical records.

Dose planning verification and approval
All dose plans must be verified by an independent dose planner or a physicist. Prescribed dose and target coverage on all CT slices, as well as dose to the normal tissues, must be verified.

Imaging calibration
A procedure for the calibration and QA of the localisation of imaging and treatment isocentre must be available on all centres.

Follow up
A continuous adaptation of QA and guidelines to technical and clinical developments are essential. Reports of the delivered treatment are therefore important.

Reports of radiotherapy
Prescribed dose to CTV1, CTV2 and CTV3, as well as date of first and last fraction should be reported in the "Primary Treatment" charts of the DAHANCA data base.

Central quality assurance
For all patients participating in clinical protocols with planned central QA, dose plans in the DICOM format must be electronically transferred to a central data base according to specific guidelines.

QA Audits
According to pre-defined agreements, QA audits are performed in all DAHANCA protocols, either by sample or for the entire cohort. Appointed experts will audit the clinical data as well as the treatment plans. The evaluations will be graded according to any degree of protocol deviation as minor or major. Major deviations are defined as deviations with potential influence on survival.

Table 2. QA Parameters

	Per protocol	Minor deviations	Major deviations
Dose prescription for the CTV1	66, 68, 70, 76 Gy		
Mean dose to CTV1	±1 %	±2 %	
Minimum dose to CTV1	95% of dose to 99% of CTV1, and 90% of dose to the last 1 % of CTV1	95% of dose to 98% of CTV1, and 90% of dose to the last 2 % of CTV1	< 95% of dose to ≥2% CTV1
Minimum dose to PTV1 (skin excluded)	95% of dose to 98% of PTV1, and 90% of dose to the last 2 % of PTV1	95% of dose to 95% of PTV1, and 90% of dose to the last 5 % of PTV1	< 95% of dose to ≥5% of PTV1
Maximal dose to > 1,8 cm^3 ($D_{1.8cm^3}$)	≤107% of CTV1 dose	≤ 110% of CTV1 dose	> 110% of CTV1 dose

Maximal dose to spinal cord ($D_{0.027\ cm^3}$)	≤ 45 Gy	45-50 Gy	> 50 Gy
Maximal dose to PRV spinal cord ($D_{0.027\ cm^3}$)	≤ 50 Gy	50-55 Gy	> 55 Gy
Maximal dose to brain stem ($D_{0.027\ cm^3}$)	≤ 54 Gy	54-59 Gy	> 59 Gy
Maximal dose to PRV brain stem ($D_{0.027\ cm^3}$)	≤ 60 Gy	60-65	> 65 Gy
Length of the treatment course	Accelerated radiotherapy (6 and 10 fx/week): ≤41 days. 5 fx/weeks: ≤48 days	Accelerated radiotherapy (6 and 10 fx/week): 42-46 days 5 fx/week: 49-53 days	Accelerated radiotherapy (6 and 10 fx/week): >47 day 5 fx/week: > 54 days

Patient values and preferences

Not relevant

Rationale

Adherence to the guidelines may influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored

Comments and considerations

Adherence to the guidelines might influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

Guidelines for specific tumour sites

Oral Cavity

Anatomy: The oral cavity includes buccal mucosa, gingiva, hard palate, anterior 2/3 of the tongue, and floor of mouth. Lateral tumours are defined as tumours of the buccal mucosa, gingiva and retromolar trigone, with no involvement of contralateral nodes. Midline tumours are defined as tumours of the tongue, floor of mouth, and hard palate, *and any tumours with involvement of these structures*. Midline tumours have the propensity of bilateral nodal involvement. Drainage to the lymphatic system from the anterior tongue rarely spreads to level III and IV without involvement of proximal nodes.

Primary treatment is described in the national guidelines (www.dahanca.dk). Shortly, the mainstay of treatment is surgery for resectable tumours whenever a good functional and cosmetic result can be expected. Postoperative radiotherapy is added in case of non-radical surgery (R1 or R2) in N or T-site, pN2-3, and or pT3-4, or any N stage with extranodal extension (ENE). Target delineation is often greatly improved when the operating surgeon takes part in the procedure.

Radical radiotherapy:
CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural anatomical barriers such as bone, unless bone involvement is evident.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins should be cropped for air and natural borders such as bone, unless bone is adjacent to the GTV Here, 2 mm cortical bone is included for T1 and T2 tumours. The CTV2 should not be cropped in case of T3 and T4 tumours adjacent to bone. CTV2 can be individually expanded to include high-risk anatomical areas, e.g. the ipsilateral or whole tongue in case of tongue involvement or ipsilateral floor of mouth.

CTV3: Midline tumours are treated with bilateral elective regions, and lateral tumours with ipsilateral elective regions. Elective nodal regions are:

- N0: level I, II, III
- N1-3: level I, II, III. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle is suspected, the entire muscle is included at least 2 cm above and below GTV-N.

Postoperative radiotherapy:
CTV1: Macroscopic tumour (R2), microscopically non-radically resected (R1), or areas of ENE, with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours, and margins should be cropped for air and natural anatomical barriers such as bone, unless bone involvement is evident

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone.

In case of an absent CTV1, i.e. in radically resected patients (R0), CTV2 is defined as the pre-operative GTV with at least 10 mm margin. In case of uncertainties as to the localization of involved nodes, or if the involved nodes are not identified on a pre-operative scanning, the entire involved level is included. Due to the difficulties

of irradiating a T-site recurrence, the T-site should be included in CTV2, even if the indication for postoperative radiotherapy is in the N-site e.g. non-radically removed nodes, ENE, or N2-N3.

CTV3: Remaining surgical bed and elective nodal levels without a margin. As a rule, bilateral irradiation of elective levels is used, but ipsilateral irradiation only is used in case of primaries in the cheek, lateral gingiva, and retromolar trigone without invasion of the floor of mouth, base of tongue, or hard palate, as well as absence of contralateral pathological nodes.

Note: If the indication for radiotherapy is in the T-site alone, no elective nodal irradiation should be per-formed for pT1-2.

Elective nodal regions are

- pN0: level I, II, III.
- pN1-3: level I, II, III. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle is suspected, the entire muscle is included at least 2 cm above and below GTV-N.
- In case of involvement of macroscopic cranial nerve, the nerve is included to the base of scull.

Nasopharynx

Anatomy: The nasopharynx is limited by the choanae (anteriorly), pre-vertebral muscles (posteriorly), medial border of the parapharyngeal space (laterally), scull base (superiorly), and caudal border of C1 (inferiorly).

The target is defined by both a CT and MRI scan.

CTV1: Includes the primary tumour (GTV-T) and involved nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins are used in case of a poorly defined primary, and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: Includes CTV1 with an isotropic margin of 5 mm, cropped for air and natural barriers such as bone, unless bone is involved. Furthermore, CTV2 includes

A) The remaining nasopharynx
B) Skull base with bilateral foramina ovale, foramina rotunda and foramina lacera
C) Inferior 5-10 mm of the sphenoid sinus, (the entire sinus in case of involvement)
D) Posterior 5 mm of nasal cavity and maxillary sinus (the entire sinus in case of involvement)
E) Anterior one third of clivus, (the entire clivus in case of involvement)
F) The ipsilateral cavernous sinus if invasion is suspected

CTV3: Elective nodes
N0: Bilateral level II-III, Va, VIIb (retro-styloid) , VIIa (retropharyngeal) and the parapharyngeal space.
The parapharyngeal space (PPS) is an inverted pyramidal fat-filled space in the lateral suprahyoid neck, with its base attaching to the skull base and the apex extending to the superior cornus of the hyoid bone. Anatomically, PPS is bordered anteriorly by the pterygo-mandibular raphe, anterolaterally by the medial pterygoid muscle, and posterolaterally by the deep lobe of the parotid gland)[53].

N+: Includes N0 volume plus ipsilateral level IV and Vb. Level Ib is included in case of invasion of the submandibular region, oral cavity or anterior nasal cavity. Elective regions are extended at least 2 cm cranially

and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N.

Oropharynx

Anatomy: Oropharynx is limited by the anterior faucial pillars, macroscopic taste buds (papillae vallatae), soft palate including uvula, and vallecula. The laryngeal surface of the epiglottis belongs to supraglottic region. Oropharynx thereby includes posterior third of tongue, vallecula, tonsils, tonsillar pillars, posterior pharynx and soft palate.

Radical radiotherapy

CTV1: Includes the primary tumour (GTV-T) and involved nodes (GTV-N) with an isotropic margin of 5 mm in all directions. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

After diagnostic tonsillectomy, the tonsillar fossa and pillars are considered as the CTV1. The clinical examination is very important in the evaluation of the extension to soft palate and especially the base of tongue. Base of tongue tumours are often difficult to depict on CT or MRI and it is often necessary to include large part of the base of tongue in CTV1 or CTV2.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas such as the entire or ipsilateral base of tongue in case of base of tongue primary, or invasion from an adjacent tonsillar primary.

CTV3: Tumours confined to the tonsillar fossa and tonsillar pillars are considered lateral tumours and is treated with ipsilateral radiotherapy. Tumours arising in, or extending to, the base of tongue, soft palate or posterior pharyngeal wall are considered midline tumours and should be treated with bilateral elective irradiation.

Elective nodal regions are:

- N0: Level II, III. The retropharyngeal nodes are included in case of posterior pharyngeal wall involvement and level Ib is included in case of oral cavity involvement.
- N1-3: Level II, III. Level IV on the side of nodal involvement. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N. The retropharyngeal nodes are included in case of posterior pharyngeal wall involvement and level Ib is included in case of oral cavity involvement

Postoperative radiotherapy

Indication for postoperative radiotherapy after primary surgery is done in accordance with the DAHANCA 34 protocol:

- T-site: < 2 mm free margin or pT3/ pT4 tumours
- N- site: more than 2 positive nodes, or 2 node metastases both >1 cm. Extranodal extension (ENE). Less than 10 removed nodes in each side of the neck dissection.

CTV1: Any macroscopic tumour (R2), areas of non-radical surgery (R1) or ENE, plus an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone.

CTV2: Includes CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone cropped for air and at natural barriers such as bone.

In case of an absent CTV1, i.e. radiotherapy after radical surgery (R0), CTV2 includes pre-operative GTV with a minimum 10 mm margin. If the indication for postoperative radiotherapy is due to N-site alone, the primary tumour volume (R0) is included in the target, as in oral cavity tumours. In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: The remaining surgical bed and elective nodal areas.

Note: If the indication for radiotherapy is in the T-site alone, no elective nodal irradiation should be per-formed in pT1 or pT2 tumours.

Tumours confined to the tonsillar fossa and tonsillar pillars are considered lateral tumours and should be treated with ipsilateral radiotherapy. Tumours arising in, or extending to, the base of tongue, soft palate or posterior pharyngeal wall are considered midline tumours and should be treated with bilateral elective irradiation.

Elective nodal areas

- pN0: Bilateral level II, III. Retropharyngeal nodes are included in case of posterior wall invasion, and level Ib is included in case or oral cavity involvement.
- N1-3: Level II, III. Level IV on the side of nodal involvement. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N. The retropharyngeal nodes are included in case of posterior pharyngeal wall involvement and level Ib is included in case of oral cavity involvement.

Hypopharynx

Anatomy: Hypopharynx is limited by oropharynx, larynx and oesophagus. *The anterior* wall includes arytenoid cartilage and aryepiglottic fold to the lower cricoid cartilage. *Pyriform sinus* includes pharyngo-epiglottic fold and the upper extension of oesophagus, laterally to the thyroid cartilage and medially from the hypopharyngeal surface of the aryepiglottic fold, arytenoid cartilage and cricoid cartilage. The hypo-pharyngeal posterior wall extends from a level through the hyoid bone (bottom of vallecula) to the lower border of the cricoid cartilage and from apex of one pyriform sinus to the other.

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: Includes CTV1 with an isotropic margin of 5 mm . Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. In case of T1/T2 primaries, the prevertebral fascia and the thyroid cartilage can be considered as a natural barrier.

CTV3: Elective nodal regions are

- N0: bilateral level II, III and IV. The cranial part of level II can be excluded after individual consideration.
- N1-3: bilateral level II, III and IV. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N. In case of subglottic or oesophageal involvement level VI is included.

Supraglottic larynx

Anatomy: Supraglottic larynx includes larynx above the vocal folds i.e. the suprahyoid part of epiglottis (lingual and laryngeal surface above hyoid bone), aryepiglottic folds, infrahyoid epiglottis, ventricular folds and sinus of Morgagni.

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. For T1 tumours the thyroid cartilage and prelaryngeal muscle is considered a natural barrier. For T2 tumours the pre-laryngeal muscles are considered as a natural barrier.

CTV3: Elective nodal regions:

- N0: bilaterally level II and III.
- N1-3: bilaterally level II and III. Level IV on the side of nodal involvement or bilateral in case of hypopharyngeal involvement. Elective regions are ex-tended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N
- In case of subglottic or oesophageal involvement, level VI is included
- The stoma is included in case of tracheostomy

Glottic larynx

Anatomy: The region includes vocal cords, anterior and posterior commissure

For T1N0
CTV1: Includes primary tumour (GTV-T) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers. The thyroid cartilage is considered a natural barrier. There is no CTV2.

For T2N0:
CTV1: Includes primary tumour (GTV-T) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers. The thyroid cartilage is considered a natural barrier.

CTV2: Includes CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers. CTV2 can be individually expanded to include high risk areas. CTV2 could be left out in case of superficial tumours without involvement of the anterior commissure.

CTV3:

- As a rule, no elective irradiation is used.
- Nodal irradiation could be considered in non-superficial T2N0. Elective areas are dependent on areas of involvement. Often level III and caudal level II
- In case of supraglottic extension, elective nodes should be irradiated according to recommendations for that site
- In case of subglottic or oesophageal involvement, level VI is included
- The stoma is included in case of tracheostomy

T3-4N0 and all N+:

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident. Mucosa inside the thyroid cartilage should be included.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas, e.g. supra- or subglottic larynx

CTV3: Elective nodal regions

- N0: bilaterally level II and III.
- N1-3: bilaterally level II and III. Level IV on the side of nodal involvement, or bilateral in case of hypopharyngeal involvement. Elective regions are ex-tended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N
- In case of subglottic or oesophageal involvement, level VI is included
- The stoma is included in case of tracheostomy

Subglottic larynx

Anatomy: The region includes larynx below vocal cords.

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas, e.g. glottic or supraglottic larynx.

CTV3: Elective nodal regions

- N0: bilateral level III, IV, VI, and level II in case of supraglottic extension
- N1-3: bilateral level III, IV, VI, and level II in case of supraglottic extension. Elective regions are ex-tended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N.
- The stoma is included in case of tracheostomy.

Postoperative radiotherapy after primary laryngectomy

Elective nodal treatment can be performed using (chemo)irradiation or surgery in case of primary total laryngectomy. The target is individually defined by the multidisciplinary team.

CTV1: Macroscopic tumour (R2), microscopically non-radical operated areas (R1) or areas of ENE, with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. CTV2 can be individually expanded to include high risk areas.

In case of an absent CTV1, i.e. after radical (R0) surgery, CTV2 includes the pre-operative GTV with at least 10 mm margin. In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: Includes the remaining surgical bed and potentially elective areas. As a rule, elective nodal areas without additional margin and the tracheostoma with a 5 mm margin is included. Nodal areas as mentioned above for the individual sub-sites.

Sinonasal tumours

Anatomy: The region includes nasal cavity posteriorly to the vestibule, the maxillary sinus, ethmoid sinuses, sphenoid sinus and frontal sinus. All areas are bordered by bone except the anterior and posterior extent of the nasal cavity.

Treatment is decided according to national guidelines (www.dahanca.dk). The mainstay of treatment is surgery in all operable patients. Postoperative radiotherapy is indicated in pT3-pT4 tumours even after radical surgery (R0), in case of R1 or R2 resection and in all cases of uncertainty as to the sufficiency of the margins. Furthermore, postoperative radiotherapy can be considered in pT2.
Often, target coverage and normal tissue sparring must be prioritized, based on a case-specific evaluation.

Primary radiotherapy

CTV1: Primary tumour (GTV-T) and involved lymph nodes (GTV-N) with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. Furthermore, the entire involved sinus(es) or ipsilateral nasal cavity is included, as well as other high-risk areas after individual consideration.

CTV3: The elective nodal areas are:

- N0: Elective nodal irradiation is considered only in case of involvement of skin, oral cavity or pharynx. In that case, level Ib and II is included. Level III can be included. Level IV, V, VIIa (retropharyngeal) and VIIb (retrostyloid) are included in case of nasopharyngeal invasion. Ipsilateral radiotherapy can be used in case of limited involvement of e.g. gingiva, without involvement of midline structures. Elective treatment of the neck (surgery or radiotherapy) can be considered in case of T3-T4 tumours, especially in case of squamous cellular tumours of the maxillary sinus.
- N1-3: Involved elective regions including the volumes mentioned above. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected,

the entire muscle is included at least 2 cm above and below GTV-N. Ipsilateral radiotherapy can be used in case of limited involvement, e.g. gingiva, without involvement of midline structures.

Postoperative radiotherapy
CTV1: Includes non-radically operated areas (R2 and R1) with a 5 mm isotropic margin. Margins could individually be enlarged to include high-risk regions and cropped for air and at natural barriers such as bone.

CTV2: Includes CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone. Should also include the entire involved region, i.e. the involved sinus(es) and/or ipsilateral nasal cavity.

In case of an absent CTV1, i.e. after radical surgery (R0), CTV2 includes the pre-operative GTV plus at least 10 mm and the entire region i.e., the entire involved sinus(es) and/ or nasal cavity.
In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: Surgical bed plus elective nodal areas.

- N0: Elective irradiation is given only in case of involvement of skin, oral cavity or pharynx. In that case, level Ib and II is included. Level III can be included. Level IV, V, VIIa (retropharyngeal) and VIIb (retrostyloid) are included in case of nasopharyngeal invasion. Ipsilateral radiotherapy can be used in case of limited involvement of e.g. gingiva, without involvement of midline structures. Elective treatment of the neck (surgery or radiotherapy) can be considered in case of T3-T4 tumours, especially in case of squamous cellular tumours of the maxillary sinus.
- N1-3: In case of pN1 without ENE, no elective irradiation is recommended after neck dissection. In case of pN2-pN3, postoperative radiotherapy is recommended irrespective of the result of the neck dissection. T-site irradiation is considered relative to the possibility of irradiating any local-recurrence. CTV3 includes elective regions mentioned above. Elective regions are extended at least 2 cm cranially and caudally of GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N -N. Ipsilateral radiotherapy can be used in case of limited involvement of e.g. gingiva, without involvement of midline structures.

Salivary gland
Anatomy: Salivary gland tumours arise in the macroscopic glands (parotid, submandibular and sublingual glands) as well as the entire mucous membranes of the head and neck, predominantly in the oral cavity.

DAHANCA has divided salivary gland tumours into prognostic groups based on histology. The treatment principles are determined by national guidelines (www.dahanca.dk). As a rule, surgery is performed as the primary treatment of all operable tumours. Postoperative radiotherapy is recommended after non-radical surgery of the T site (R1 or R2), T≥T3, N+, perineural invasion, recurrences, and high-grade tumours, irrespective of other risk factors.

DAHANCA has divided salivary gland tumours into prognostic groups based on histology:
Low grade: Acinic cell carcinoma, polymorphous low-grade adenocarcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma, high and intermediate grade mucoepidermoid carcinoma, well-differentiated adenocarcinoma NOS (Not Otherwise Specified), well-differentiated non-invasive or minimally invasive carcinoma of pleomorphic adenoma, clear cell carcinoma NOS, sialoblastoma.

High grade: Adenoid cystic carcinoma, intermediate and poorly differentiated adenocarcinoma NOS, intermediate and poorly differentiated carcinoma in pleomorphic adenoma with invasive depth of >1,5 mm, poorly differentiated mucoepidermoid carcinoma, salivary duct carcinoma, primary squamous cell carcinomas, undifferentiated carcinoma (lymphoepithelial carcinoma), large cell carcinoma, mucinous adenocarcinoma, oncocytic carcinoma, carcino-sarcomas, small cell carcinoma, myoepithelial carcinoma.

Perineural invasion (PNI) is a histopathological description and a potential risk factor of loco-regional recurrence and distant metastasis. Perineural spread (PNS) is a clinical /macroscopic concept that describes growth along macroscopic nerves. It is often asymptomatic and observed per-operatively or on MRI scans. PNI does not imply PNS. PNI is an indication for postoperative radiotherapy. PNS is an indication to expand the CTV along macroscopic nerves. See e.g. Biau[54] for delineation guidelines.

Radical radiotherapy:
CTV1: Includes the primary tumour (GTV-T) with a 5 mm isotropic margin plus the entire involved salivary gland. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident.

CTV2: Includes CTV1 with an isotropic margin of 5 mm cropped for air and at natural barriers such as bone.

CTV3: As a rule, elective ipsilateral regions are irradiated only. In case of involvement of midline structures both sides of the neck are irradiated

- Parotid: level Ib + II + III + VIII (parotid group)
- Submandibular: level Ia + Ib + II + III
- For all other glands, the principles for the specific region (often oral cavity) is applied. Elective regions are extended at least 2 cm cranially and caudally of any GTV-N. If extension to nearby muscle involvement is suspected, the entire muscle is included at least 2 cm above and below GTV-N.
- In case of PNS along the major branches of the cranial nerves, these are irradiated to the base of scull.

Postoperative radiotherapy
CTV1: Macroscopic tumour (R2), microscopically non-radical operated areas (R1) or areas of ECE, with an isotropic margin of 5 mm. Larger margins should be used for ill-defined tumours and margins should be cropped for air and natural barriers such as bone, unless bone involvement is evident

CTV2: CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions and cropped for air and at natural barriers such as bone.
If no CTV1 is present in case of radical surgery (R0), CTV2 is the pre-operative GTV with an isotropic margin of 10 mm.
Furthermore, the entire salivary gland should always be included in the CTV2.
In case of uncertainties as to the localization of involved nodes, or if the nodes are not identified on a pre-operative scanning, the entire involved level is included.

CTV3: Includes the surgical bed and elective areas.

- In case of PNS along the main branches of the cranial nerves, these are irradiated to the base of scull.
- pN0: No elective nodal irradiation is performed.
- N+: As a rule, selective ipsilateral regions are irradiated only. In case of involvement of midline structures both sides of the neck are irradiated
- Parotid: level Ib + II + III

- Submandibular: level Ia+ Ib + II + III
- For all other glands the principles for the relevant region (often oral cavity) is applied. Elective regions are extended at least 2 cm cranially and caudally of any GTV-N If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N.

Lymph node metastasis from unknown primary tumour (UP)

Anatomy: Neck metastasis from an unknown primary tumour is defined as an undiagnosed primary tumour after thorough diagnostic procedures, at the beginning of treatment.

Diagnostic procedures and treatment follow national guidelines (www.dahanca.dk).

A distinction is made between squamous cell carcinomas and other histologies.
Neck nodes containing squamous cell carcinoma will often originate from the mucous membranes of the head and neck area. For other histologies, multiple origins may exist. Some can be treated with curative intent, e.g. germ cell tumours, small cell lung cancer, and some are relative treatment resistant such as melanomas.

Radiotherapy for squamous cellular carcinomas
In case of nodal metastasis from a squamous cellular carcinoma there is, as a rule, indication for treatment of regional lymph nodes as well as potential primary tumour sites. This is *not* the case for other histologies. Irradiation of the ipsilateral neck is difficult without irradiation of contralateral regions which makes irradiation of recurrences difficult. Bilateral irradiation is therefore recommended.

CTV1: Includes known macroscopic tumour (non-operated or R2), insufficiently operated areas (R1) or areas of ENE. CTV1 includes involved nodes with an isotropic margin of 5 mm in all direction, cropped for air and at natural barriers such as bone.

CTV2: Includes CTV1 with an isotropic margin of 5 mm. Margins could individually be enlarged to include high risk regions, such as mucosal areas with an increased risk of harbouring a primary and cropped for air and at natural barriers such as bone.

CTV3: The entire mucous membrane of 5 mm depth, in the pharynx and larynx, from the base of scull to below the cricoid cartilage, including tonsillar fossa on both sides. Base of tongue should be included with a 10 mm margin due to its irregular surface. Elective regions include bilateral level II, III, IV. Level V is included if a nasopharyngeal primary is suspected. Elective regions are extended at least 2 cm cranially and caudally of any GTV-N. If extension to nearby muscle involvement is suspected the entire muscle is included at least 2 cm above and below GTV-N.

Radiotherapy for non-squamous cell histologies
In case of adenocarcinoma, treatment depends on the likely localisation of a primary. Localisations include salivary and thyroid glands, nasal cavity and paranasal sinuses, lung, breast, gastro-intestinal canal, uterus, ovary, and prostate. Localisation, immuno-histochemistry, serology and iodine scintigraphy may aid in the search of a primary and guide the treatment. In case of unknown primary after relevant diagnostics, involved field irradiation to curative doses may be indicated, but elective nodal or mucosal irradiation is not recommended.

Patient values and preferences

Not relevant.

Rationale

Adherence to the guidelines might influence both tumour control and side effects. The guidelines are continuously updated and the international literature is closely monitored.

Comments and considerations

Adherence to the guidelines may influence both tumour control and side effects. Data on loco-regional control and side effects are continuously monitored through the clinical DAHANCA database and in clinical protocols.

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5. Methods

Literature search

No formalized literature search has been performed.

Evidence assessment

The evidence levels is in general low, but most often international agreement has been reached on the overlying principles of therapy. Some recommendations rely on international guidelines eg. by the ICRU (International Commission on Radiation Units and Measurements)

Articulation of the recommendations

All recommendations have been reviewed and discussed among the Dahanca radiotherapy quality assurance group with physician and physicist representatives from all centres

Stakeholder involvement

Patient values and preferences are not relevant in this technical aspect and therefore no attempt has been made for establishing a patient panel

External review and guideline approval

No formal peer review process has been performed although the Danish Head and Neck Cancer group have formally also approved the guidelines. This multidisciplinary groups represents all medical specialties and medical physicists involved in the diagnosis, treatment and follow up of head and neck cancer patients

Recommendations which generate increased costs

No new specific resource-demanding recommendations have been proposed in the present guidelines, although all guidelines add to the increasing complexity of treatment.

Need for further research

The target margins and normal tissue sparing are the subject for several projects within the DAHANCA group. The use of imaging for target delineation will be updated in the next version based on a multidisciplinary workshop.

6. Monitoring

Standards and indicators

Adherence to the guidelines are monitored for the large number of patients included in clinical protocols. Many overall quality indicators are monitored in the clinical DAHANCA database and included in the yearly report. Furthermore: See chapter on “Quality assurance”

Plan for audit and feedback

The guidelines are evaluated on each meeting in the DAHANCA quality assurance group, with meetings three times annually. Work has been initiated for the next update.

7. Appendix

Appendix 1: Delineation of organs at risk

Organ	Cranial	Caudal	Anterior	Posterior	Lateral	Medial	Reference delineation*
BrainStem	**Bottom of the 3rd ventricle**	Tip of the dens of C2					Brouwer[55]. Except craniel extended to the bottom of 3rd ventricle.
SpinalCord	tip of the dens of C2						Brouwer[55]
Chiasm			Optic nerve. Ie. chiasma is a Line" not a "H"	Optic tract	A. carotis interna/ cerebri media		Brouwer[55]
OpticNerve_L OpticNerve_R							Brouwer[55]
EyeBack_L EyeBack_R (Eye except EyeFront)			EyeFront				Brouwer[55]
EyeFront_L EyeFront_R (cornea, iris, lens)*			Structures anterior of the vitreous humour				Brouwer[55]
Lacrimal_L Lacrimal_R (gl. lacrimalis)	Supralateral to the eye						Brouwer[55]
Brain	Entire Brain except brainstem						Brouwer[55]
Cochlea_L Cochlea_R	Hypodense volume in temporal bone anterior to canalis auditoria interna						Brouwer[55]
Esophagus (cervical esophagus+ esophagus inlet muscle+ cricopharyn	First slice caudal to the arytenoid cartilages	Sternal notch	Posterior edge of cricoid cartilage. tracheal lumen	Prevertebral muscle	Thyroid cartilage, fatty tissue, thyroid gland. Thyroid cartilage		Cervical esophagus+ esophagus inlet muscle+ cricopharyngeal muscle as in Christianen[56]

geal muscle)							
LarynxG (glottic larynx)	Upper edge of the arythenoid cartilages	Lower edge of cricoid cartilage (if soft tissue is present)	Thyroid cartilage	Inferior PCM, pharyngeal lumen/ cricoid cartilage	Thyroid cartilage	Pharyngeal lumen (lumen excluded)	Christianen[56]
LarynxSG (supraglottic larynx)	Tip of epiglottis	First slice cranial to the upper edge of the arytenoid cartilages	Hyoid bone, pre-epiglottic space, thyroid cartilage	Pharyngeal lumen, inferior PCM	Thyroid cartilage	Pharyngeal lumen (lumen excluded)	Christianen[56]
Mandible	Mandible teeths excluded						Brouwer[55]
OralCavity (=Brouwer extended oral cavity)	Hard palate mucosa and mucosal reflections near the maxilla	The base of tongue mucosa and hyoid posteriorly and the mylohyoid m. and ant. belly of the digastric m. anteriorly	Inner surface of the mandible and maxilla	Post. borders of soft palate, uvula, and more inferiorly the base of tongue	Inner surface of the mandible and maxilla		Brouwer[55]
Parotid_L Parotid_R							Brouwer[55]
PCM_Low (lower pharyngeal constrictor)	First slice caudal to the lower edge of hyoid bone	Lower edge of the arythenoid cartilages	Soft tissue of supraglottic/ glottic larynx	Prevertebral muscle	Superior horn of thyroid cartilage		Christianen[56]
PCM_Mid (middle pharyngeal constrictor)	Upper edge of C3	Lower edge of hyoid bone	Base of tongue, hyoid	Prevertebral muscle	Greater horn of hyoid bone	Pharyngeal lumen	Christianen[56]
PCM_Up (upper pharyngeal constrictor)	Caudal tip of the pterygoid plates (hamulus)	Lower edge of C2	Hamulus of pterygoid plate; mandibula; base of tongue;	Prevertebral muscle	Medial pterygoid muscle	Pharyngeal lumen	Christianen[56]

			pharyngeal lumen				
Pituitary	Gland as seen on MRI or inner part of sella turcica						Brouwer[55]
Submandibular_L Submandibular_R	Med. pterygoid m., mylohyoid m.	Fatty tissue	Lat. Surface mylohyoid m., hyoglossus m.	Parapharyngealspace, sternocleidomastoid m.	Med. surface med. pterygoid m., med. surface mandibular bone, platysma	Lat. surface mylohyoid m.,hyoglossus m., superior and middle pharyngeal constrictor m., anterior belly of the digastric m.	Brouwer[55]
Thyroid							
A_Carotid_L A_Carotid_R							Brouwer[55]
Buccal mucosa	Bottom of maxillary sinus	Upper edge teeth sockets	Lips, teeth	Med. pterygoid m.	Buccal fat	Outer surface of the mandible and maxilla, oral cavity/base of tongue/soft pallate	Brouwer[55]
Lips	Hard palate (lateral), anterior nasal spine (at the midline)	Lower edge teeth sockets, cranial edge mandibular body	Outer surface of the skin	Mandibular body, teeth, tongue, air (if present)	Depressor anguli oris m.buccinator m. levator anguli oris, m./risorius m. (the mentioned mucles are all lateral to the m. orbicularis oris)	Hard palate (lateral), anterior nasal spine (at the midline)	Brouwer[55]
Hippocampus	Bilateral structures. Defined by MRI T1-hypointense signal medial to the temporal horn.						Gondi[57] http://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx

Appendix 2: Applicable dose and fractionation schedules

Using IMRT with simultaneous integrated boost, the following dose and fractionation schedules may be prescribed.

Fractionation schedules DAHANCA 2019	CTV1				CTV2		CTV3	
	Total dose	Dose/fx	fx	Fx/W	Total dose	Dose/fx	Total dose	Dose/fx
Conventional fx	66	2	33	5	60	1.82	50	1.52
Conventional fx	68	2	34	5	60	1.76	50	1.47
Accelerated fx	66	2	33	6	60	1.82	50	1.52
Accelerated fx	68	2	34	6	60	1.76	50	1.47
Accelerated hyperfx	76	1.36	56	10	66	1.18	56	1

Appendix 3: DAHANCA – guidelines 2000-2019

The guideline is to a large extent a product of discussion within the DAHANCA Radiotherapy Quality Assurance Group, through an extended period from the very first guidelines in 2000.

DAHANCA, the Danish Head and Neck Cancer Group, was founded in 1976. The group has a long standing tradition for conducting clinical trials as well as establishing national guidelines for radiotherapy for head and neck cancer. DAHANCA was the first Danish cooperative group to introduce national guidelines for CT-based conformal RT and IMRT.

The first edition of the guidelines was implemented in 2000 after it was approved by the DAHANCA group in December 1999. With that, ICRU compatible terminology was implemented at all Danish referral centres for head and neck cancer.

The second edition (2002) was approved at the DAHANCA meeting on the 13th of December 2001. The following minor adjustments were made:

- The possibility of treating T1a carcinomas of the vocal cord with only 62 Gy was removed.
- The elective target for primaries of the oropharynx was changed from level II-IV to level II, III (+ retro-pharyngeal nodes in case of tumour in the posterior pharyngeal wall, and potentially level IV in case of N2-3.

The third edition (2004) was approved at the DAHANCA Radiotherapy Quality Assurance Group meeting 14th of September 2004. The following major changes were made:

- CTV-T(umour) was redefined to ”Areas of known macroscopic tumour (GTV), microscopically incompletely resected tumour, or areas of known extra-nodal extension” to comply with post-operative radiotherapy recommendations.
- CTV-E(lective) was divided into CTV-E(high-risk) and CTV-E(low-risk). CTV-high-risk was only relevant for post-operative radiotherapy or IMRT and treated to 60 Gy.
- Elective nodal regions were defined according to the Brussels-Rotterdam consensus[25] , instead of Wijers[58]. Tables and figures from the original publication were included as appendices.
- A modification of the inclusion of the upper part of level 2 was allowed for cancers of the larynx and hypopharynx.
- An appendix with guidelines for the use and implementation in IMRT, including fractionation and normal tissue constraints, was included as an appendix.

The fourth edition (2013) was approved at the DAHANCA meeting 10th of December 2012. All chapters were thoroughly revised in order to comply with the ICRU guidelines and to define important parameters of quality assurance. Furthermore,

- A detailed list of sensitive normal tissues and constraints was added
- The terms CTV-T, CTV-N, CTV-E(high-risk), CTV-E(low-risk) were renamed into the new terms CTV1, CTV2 and CTV3, and ITV was included into the definition of CTV.
- The margins around GTV were thoroughly discussed. The existing guideless had been interpreted with large departmental variations. Margins of 0-10 mm from GTV to CTV had been used. The adopted margins were thus a compromise: A 5 + 5 mm margin from GTV to CTV1, and from CTV1 to CTV2, respectively, were suggested.
- A table of minor and major deviations for dose and fractionation for QA, and a table of recommended dose-fractionation schedules were added.

The following minor revisions have been approved May 22nd 2014

- A precision that the added margin, GTV to CTV2, should not exceed 12 mm
- Grégoire [27] added as reference
- It is emphasized that the spinal cord should always be delineated and that the brain stem should be delineated in case of elective irradiation
- The constraint of cochlea is corrected to $D_{5\%} \leq 55Gy$
- All treatment interruptions and prolongations must be compensated. The word “unintended” has been erased.
- Oropharyngeal and supraglottic tumours: Level IV has been excluded in case of N1-3 neck disease and the sentence: “Level IV on the side of nodal involvement” has been inserted in order to avoid level IV irradiation to the non-involved side of the neck.
- Regarding postoperative radiotherapy after laryngectomy: In case of planned primary total laryngectomy, with postoperative (chemo-)radiotherapy, elective nodal areas can be treated with radiotherapy. The treatment plan is made individually by the multidisciplinary team.
- Regarding postoperative radiotherapy for salivary gland tumours: In case of pN0, the elective nodes are not to be irradiated.
- Regarding Unknown primary: The wording has been brought up to date with the “National Guidelines for the Treatment of Lymph Node Metastasis from Unknown Primary”

Fifth edition (2018) was approved at the DAHANCA meeting September 19th, 2018. All chapters were thoroughly revised, with the following major revisions:

- New chapters and sections on proton therapy and perineural spread.
- Normal tissue delineations according to new international guidelines. Among others, the hippocampus was included as a new organ at risk
- The guidelines by Lee [4] has inspired a thorough revision of the guidelines regarding nasopharyngeal CTV
- The guidelines by Grégoire [5] inspired a thorough revision of the guidelines for larynx and pharynx cancer
- The standardized nomenclature for OARs and targets[28] were included and mentioned in an appendix.

In the sixth edition (2020), a separate chapter has been added on postoperative radiotherapy. From, and including the sixth edition, the English version is considered the reference document and the Danish version is the translation." June 2020 a chapter on the GTV delineation was added, and any mentioning of diagnosis and staging was omitted, to conform with the RKKP, clinical guidelines

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