11 ■ OROPHARYNX CANCER

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QUICK HIT ■ SCC of the oropharynx is currently the most common H&N cancer in the United States. Its incidence continues to rise with increasing prevalence of HPV. There are two etiologies: those associated with tobacco and alcohol, which are often HPV negative, and those associated with HPV infection. These are classified as two distinct diseases per the AJCC 8th edition staging system. Both are currently treated with the same approach, but treatment paradigms are evolving to account for differences in outcome.

Table 11.1 General Treatment Paradigm for Oropharynx Cancer

	Treatment Options
T1–2N0–1	Definitive IMRT Or TORS (or other function-preserving surgery), neck dissection, and risk-adapted adjuvant therapy (Chapter 17)
T3–4 and/or N1–3	Definitive chemoRT Or Surgery (select patients) with risk-adapted PORT ± CHT

EPIDEMIOLOGY: Estimated 35,610 tongue and pharynx cases in 2020 with 6,470 deaths.[1] Male-to-female ratio approximately 4:1.[2] In the United States, incidence of HPV-associated OPC increased by 225% from 1988 to 2004 and HPV-negative cancer declined by 50% in the same time frame.[3] Prevalence of HPV was 39.5% on RTOG 9003, which increased to 68% on RTOG 0129 and further to 73% on RTOG 0522.[4–6] Peak prevalence of oral HPV DNA is bimodal: 7% for ages 30 to 34 and 11% for ages 60 to 64.[4]

RISK FACTORS: Age, high-risk sexual behavior (HPV+), tobacco, alcohol (HPV–).[4,7]

ANATOMY: Oropharynx consists of base of tongue (lingual tonsil), vallecula, palatine tonsil, soft palate, and posterior oropharyngeal wall. The superior border of the OPX is the soft palate and the inferior border is the hyoid–lingual surface of the epiglottis. The base of tongue is separated from the oral tongue by the circumvallate papillae. The base of tongue is the posterior one third of the tongue and composed of lingual lymphatic tissue. The palatine tonsils sit between an arch formed by the anterior and posterior tonsillar pillars.

Table 11.2 Oropharynx Borders

Site	Boundaries
BOT	Anteriorly by circumvallate papillae, laterally by glossopalatine sulci, and inferiorly by vallecula. Includes pharyngoepiglottic and glossoepiglottic fold.
Tonsillar complex	Composed of anterior and posterior tonsillar pillars, true palatine tonsil, and tonsillar fossa. Tonsillar pillars are mucosal folds over glossopalatine and pharyngopalatine muscles. Tonsillar fossa is a triangular region bounded by pillars, inferiorly by glossotonsillar sulcus and pharyngoepiglottic fold and laterally by pharyngeal constrictor muscles.
Soft palate	Defined anteriorly by hard palate, laterally by palatopharyngeal and superior pharyngeal constrictor muscles and posteriorly by palatopharyngeal arch/uvula. Forms roof of oropharynx and floor of nasopharynx.
PPW	Spans area defined by soft palate, epiglottis, posterior edge of tonsillar complexes, and lateral aspects of pyriform sinuses inferiorly. Inferior to oropharyngeal PPW is PPW of hypopharynx, one of the three subsites of hypopharynx.

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PATHOLOGY: Approximately 95% of OPC are SCCs.[8] Remaining 5% of cases consist of lymphoma, minor salivary cancers (e.g., mucoepidermoid, adenoid cystic; see Chapter 15), and rare sarcomas. HPV-positive and -negative cancers appear different pathologically. HPV-positive tumors often originate from the lymphoid tissue of tonsil or BOT and are more likely to be poorly differentiated/nonkeratinizing and basaloid in appearance. HPV-negative tumors have no predilection for location and are often keratinizing. *HPV 16* serotype accounts for ~90% of HPV-associated cases. HPV viral proteins E6 and E7 bind p53 and Rb respectively with subsequent loss of tumor suppression. When E7 binds to Rb, transcription factor E2F is released and allows cyclin to bypass G1/S checkpoint. Reflexive expression of p16 protein inhibits cyclin D-CDK4 complex in an effort to prevent uncontrolled cell cycling. Overexpression of p16 protein serves as a surrogate marker of HPV integration into DNA. p16 protein can be detected by IHC. HPV DNA is detected by FISH. p16 is more sensitive but less specific than HPV16 DNA. On RTOG 0129, 19% of HPV-negative patients were p16+ but only 3% of p16– were HPV16–. In HPV-endemic areas such as the United States, PPV of p16 status in OPC is high (~90%), but in HPV-uncommon disease sites or in the developing world, PPV of p16 status is poor (<40%). EGFR is more commonly amplified in HPV-negative tumors and is associated with poor prognosis.[2,9]

Table 11.3 Factors Associated With HPV Status in OPC

HPV+	HPV–
- Younger - Non/light smoker - Caucasian - High-risk sexual behavior - More likely tonsil/base of tongue - Nonkeratinizing - Basaloid - p16 upregulated - Poorly differentiated	- Older - Heavy smoking/drinking - Non-Caucasian - Not related to sexual behavior - No tissue preference - Keratinizing - p53 mutation - EGFR amplified

CLINICAL PRESENTATION: Most common presentation of OPC is painless neck mass. Other symptoms related to local invasion include dysphagia, odynophagia, or otalgia referred from cranial nerve IX via tympanic nerve of Jacobson. Oral tongue fixation (unable to protrude tongue) suggests deep musculature involvement. Trismus suggests medial pterygoid invasion.[2]

WORKUP: H&P with careful attention to H&N including palpation of BOT, dental exam, neurologic exam, mirror exam, and/or flexible laryngoscopy.

Labs: CBC and BMP with attention to renal function. Measurement of HPV-circulating tumor DNA, obtained at baseline and posttreatment, is an evolving strategy for surveillance.[10]

Imaging: CT of neck with contrast is most helpful for primary tumor delineation; PET/CT is also recommended for staging and evaluation of lymphadenopathy. Consider MRI if concerns exist for perineural or skull base invasion.[2,11] After chemoRT, it is more cost effective to perform PET/CT at 12 weeks and proceed to neck dissection if positive than to perform planned neck dissection.[12]

Procedures: Initial biopsy via FNA of lymphadenopathy acceptable although confirmatory biopsy of primary via tonsillectomy or BOT biopsy with detailed exam under anesthesia is recommended. Tumor HPV testing recommended per NCCN.

Other: Nutrition, speech and swallowing evaluation/therapy, and audiogram as clinically indicated. EUA with endoscopy as clinically indicated. Smoking cessation counseling should also be advised as appropriate.

PROGNOSTIC FACTORS: Age, smoking (both 10 and 20 pack-year cutoffs have been used for stratification, may be less relevant than current/former smoking status[13]), comorbidities, performance status, stage, HPV status, PET SUV.[14–16] Staging and prognostic stratification of HPV-positive patients is rapidly evolving (see Tables 11.4 and 11.5).

NATURAL HISTORY: Nodal involvement is common and initial site of drainage from oropharynx is to neck level II and subsequently down jugular chain to levels III to IV. Levels IB, V and retropharyngeal nodes can be involved but are less common.[8] Historically, locoregional recurrence was responsible for

the majority of cancer-related morbidity and mortality.[17] While this remains true for HPV-negative disease, locoregional recurrence of HPV-positive disease is generally uncommon. Distant metastases, however, develop in both subgroups at similar rates. Most common sites of distant metastases are lung and bone.[14,18]

Table 11.4 AJCC 8th Edition (2017): Staging for Oropharynx (p16–)

T/M \ N		cN0	cN1	cN2a	cN2b	cN2c	cN3a	cN3b
T1	• ≤2 cm	**I**						
T2	• 2.1 to 4 cm	**II**	**III**		**IVA**			
T3	• >4 cm • Extension							
T4a	• Invasion[1]							
T4b	• Invasion[2]	**IVB**						
M1	• Distant metastasis	**IVC**						

Notes: Extension = extension to lingual surface of epiglottis. Invasion[1] = invasion into larynx, extrinsic musculature of tongue, medial pterygoid muscle, hard palate, or mandible. Invasion[2] = invasion into lateral pterygoid, pterygoid plates, lateral nasopharynx, skull base or encases carotid artery.
cN1, single ipsilateral LN (≤3 cm) and –ENE; cN2a, single ipsilateral LN (3.1–6 cm) and –ENE; cN2b, multiple ipsilateral LN (≤6 cm) and –ENE; cN2c, bilateral or contralateral LN (≤6 cm) and –ENE; cN3a, LN (>6 cm) and no ENE; cN3b, clinically overt ENE.
pN1, single LN (≤3 cm) and –ENE; pN2a, single ipsilateral or contralateral LN (≤3 cm) and –ENE or single ipsilateral LN (3.1–6 cm) and –ENE; pN2b, multiple ipsilateral LN (≤6 cm) and –ENE; pN2c, bilateral or contralateral LN (≤6 cm) and –ENE; pN3a, LN (>6 cm) and –ENE; pN3b, LN (>3 cm) and + ENE.

Table 11.5 AJCC 8th Edition (2017): Staging for HPV-Mediated (p16+) Oropharyngeal Cancer

T/M \ N		cN0	cN1	cN2	cN3
T1	• ≤2 cm	**I**		**II**	**III**
T2	• 2.1 to 4 cm				
T3	• >4 cm • Extension				
T4	• Invasion				
M1	• Distant metastases	**IV**			

Notes: Extension = Extension to lingual surface of epiglottis. Invasion = invasion into larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or beyond.
cN1, one or more ipsilateral LN (≤6 cm); cN2, contralateral or bilateral LN (≤6 cm); cN3, LN (>6 cm).
pN1, ≤4 LNs; pN2, >4 LNs.

TREATMENT PARADIGM

Surgery: Classic oncologic surgery for OPC consists of radical tonsillectomy (simple tonsillectomy performed for biopsy is generally not sufficient for oncologic control), glossectomy (often requiring mandibulotomy), palatectomy, or pharyngectomy with ipsilateral or bilateral neck dissection depending on nodal status and laterality of primary tumor. Because of functional deficits left by these procedures, nonoperative approaches became standard in the 1970s and beyond. Over the past decade, however, minimally invasive procedures such as TLM and TORS have reduced morbidity of surgery and are now standard options for T1–2 and select T3 lesions (see Evidence-Based Q&A).[11] Only one historical trial has compared surgery with RT to definitive RT (RTOG 7303) and with small numbers found similar OS for both approaches; this is the same with the modern ORATOR trial (see following).[19] See Chapter 17 for details on adjuvant RT. Radical neck dissection: levels IB to V with sacrifice of internal and external jugular veins, SCM, omohyoid, CN XI, and submandibular gland. Modified radical neck dissection: levels IB to V but leaves one or more of jugular veins, SCM, omohyoid, or CN XI. Selective neck dissection: modified radical but leaves one or more of levels IB to V. Supraomohyoid neck dissection: resection of levels I to III. Recently, SLNB (followed by neck

dissection if positive) has been found to be oncologically equivalent to neck lymph node dissections for patients with operable oral and oropharyngeal cT1–T2N0 cancer. There is also lower morbidity associated with SLNB during the first 6 months after surgery.[20]

Chemotherapy: Concurrent cisplatin is standard for eligible patients receiving definitive RT with stage III to IV disease. Cisplatin can be given concurrently with RT as 100 mg/m^2 weeks 1, 4, and 7 (NCCN Category 1) or 40 mg/m^2 weekly (NCCN Category 2B).[11] Carboplatin/infusional 5-FU is also considered an NCCN category 1 recommended regimen to be administered concurrently with RT. Cetuximab given concurrent with RT for nonplatinum candidates can be considered, though it has inferior outcomes without overall decreased toxicity for patients who are eligible to receive cisplatin (NCCN category 2B; see Evidence-Based Q&A).[21] Cetuximab starts 1 week prior to RT as loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly during RT.[22] Other less common concurrent regimens include carboplatin/paclitaxel, cisplatin/5-FU, and 5-FU/hydroxyurea. Induction CHT consists of cisplatin, 5-FU, and docetaxel (TPF) every 3 weeks for 4 cycles completing 4 to 7 weeks prior to RT alone or with cetuximab or carboplatin (see Evidence-Based Q&A).[11,23] Cisplatin-based induction CHT has not been proven to increase overall survival as compared to proceeding directly to concurrent chemoradiation regimens.

Radiation

Indications: RT is indicated for definitive treatment of OPC or in postoperative setting (see Chapter 17).

Dose: In a definitive setting, standard dose is 70 Gy/35 fx. Various elective nodal doses have been used including 56 Gy/35 fx (simultaneous boost) and 50 Gy/25 (sequential boost to 70 Gy). RTOG 1016 used a third lower dose to "low-risk" neck to 50 to 52.5 Gy/35 fx. For cT1-2N0-1 OPC, 66 Gy/30 fx RT alone with elective dose of 54 Gy/30 fx (simultaneous) is reasonable based on RTOG 0022 (see Evidence-Based Q&A). Dose reduction for HPV+ patients is the subject of clinical trials.

Toxicity: Acute: Fatigue, mucositis, dysphagia, odynophagia, xerostomia, dermatitis, aspiration. Chronic: Dysphagia, neck fibrosis, xerostomia, trismus, osteoradionecrosis, hypothyroidism, brachial plexopathy (rare but take care with gross disease in low neck).

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 4.[24]

■ EVIDENCE-BASED Q&A

■ Can definitive RT lead to similar control and survival compared to radical surgeries?

This was a key question in the 1970s, when surgery was the definitive treatment of choice, often requiring mandibulotomy for BOT access and subsequent functional deficits. RTOG 7303 is the only historical PRT addressing this question; definitive RT has subsequently become the standard option to preserve functional outcomes.

Kramer, RTOG 7303 (*Head Neck Surg* 1987, PMID 3449477): Advanced SCC of oropharynx or oral cavity randomly assigned to preoperative RT, PORT, or definitive RT (65–70 Gy). Larynx or hypopharynx cancers randomized to either preoperative (50 Gy) or PORT (60 Gy). For oral cavity or OPC patients, 4-year OS was similar between all groups: 30% preoperative, 36% postoperative, 33% definitive. 4-year LRC was 43% preoperative, 52% postoperative, and 38% definitive. **Conclusion: Definitive RT is an ethically justified alternative compared to radical surgery.**

■ Can the efficacy of RT be improved by altering fractionation?

SCC is known to undergo accelerated repopulation and is sensitive to reoxygenation, so fractionation was thought to play an important role in outcomes with definitive RT. Multiple trials and meta-analysis demonstrated improved LRC and OS with AF for treating locoregionally advanced patients.

Horiot, EORTC 22791 (*Radiother Oncol* 1992, PMID 1480768): PRT of 356 patients randomized to 70 Gy/35 to 40 fx or hyperfractionation of 80.5 Gy/70 fx. T2–3 oropharynx (excluding BOT) cancers,

N0–1 were included from 1980 to 1987. Hyperfractionation demonstrated LRC benefit and trend toward OS in T3N0–1 patients but not T2.

Fu, RTOG 9003 (*IJROBP* 2000, PMID 10924966; Update Beitler *IJROBP* 2014, PMID 24613816): PRT 1,073 patients with stage III to stage IV SCC of oral cavity, oropharynx, supraglottic larynx or stage II to stage IV of BOT or hypopharynx randomized to one of four arms: (a) standard fractionation to 70 Gy/35 fx, (b) hyperfractionation to 81.6 Gy/68 fx at 1.2 Gy/fx BID with 6-hour interfraction interval, (c) split-course accelerated hyperfractionation to 67.2 Gy/42 fx given 1.6 Gy/fx BID with 6-hour interfraction interval and 2-week rest after 38.4 Gy, or (d) accelerated hyperfractionation with concomitant boost to 72 Gy/42 fx given at 1.8 Gy/fx 5 days a week with 1.5 Gy/fraction to boost field as second daily treatment given 6 hours apart for last 12 treatment days. Primary end point was 2-year LRC. Results at initial report: At MFU of 23 months, both hyperfractionation (2) and concomitant boost (4) arms showed improved LRC but no significant difference in OS. All 3 AF arms showed increased acute effects but only concomitant boost arm showed increased late effects. In final update, hyperfractionation (2) and concomitant boost (4) decreased 5-year LRR compared to standard fractionation, but hyperfractionation did not increase late effects. When using only 5-year follow-up, hyperfractionation improved OS (HR: 0.81, $p = .05$) but not when all follow-up data were included. **Conclusion: AF improves disease control in locoregionally advanced squamous carcinoma of H&N.**

Table 11.6 Results of RTOG 9003

	Regimen	2-Yr LRC	2-Yr OS
1. Standard	70 Gy/35 fx daily	46%	46%
2. Hyperfractionation	81.6 Gy/68 fx BID	54%*	54.5%†
3. Split course	67.2 Gy/42 fx BID with 2-week break	47.5%	46.2%
4. Concomitant boost	72 Gy/42 fx (BID final 12 days)	54.5%‡	50.9%

*Statistically significant difference in original and final reports.
†Statistically significant difference (only when limited to 5-year follow-up).
‡Statistically significant difference compared to standard arm in original report.

Overgaard, DAHANCA 6 and 7 Combined Analysis (*Lancet* 2003, PMID 14511925): Combined analysis of two trials performed from 1992 to 1999 including 1,485 patients with stage I to stage IV SCC; DAHANCA 6 of glottis carcinoma testing fractionation and DAHANCA 7 of supraglottic, pharynx, and oral cavity cancers testing fractionation and radiosensitizer nimorazole. RT given to 62 to 68 Gy at 2 Gy/fx and randomized to either 5 or 6 fractions per week. Overall 5-year LRC was improved with acceleration (70% vs. 60%, $p = .0005$). Disease-specific survival but not OS was also improved by acceleration. **Conclusion: Six fractions weekly became standard in Denmark. This result was independent of p16 status**.[25]

Bourhis, MARCH Meta-Analysis (*Lancet* 2006, PMID 16950362; Update Lacas, *Lancet Oncol* 2017, PMID 28757375): Patient-level meta-analysis of 11,969 patients from 34 trials with MFU 6 years, 75% oropharynx and larynx cancers and 75% stage III to stage IV. AF was associated with a significant OS benefit of 3.1% at 5 years ($p = .003$). The significant survival benefit was attributed to hyperfractionation alone, which had the most OS benefit (8.1%). OS was significantly worse (5.8% decrement at 5 years) with AF RT alone compared with concurrent chemoRT (HR: 1.22, $p = .01$). **Conclusion: AF, specifically hyperfractionation, improves OS in H&N cancer. The comparison between hyperfractionated RT and concurrent chemoRT remains to be specifically tested.**

■ Does CHT add benefit to conventionally fractionated RT?

Adelstein, H&N Intergroup (*JCO* 2003, PMID 12506176): PRT of 271 of planned 362 patients between 1992 and 1999 with stage III to stage IV unresectable SCC (all sites except sinus, nasopharynx, or salivary) randomized to (a) RT alone (70 Gy/35 fx); (b) cisplatin with RT (100 mg/m^2 weeks 1, 4, and 7); or (c) split-course chemoRT (cisplatin 75 mg/m^2 with 5-FU 1,000 mg/m^2 every 4 weeks with 30 Gy/15 fx 1st course followed by surgical evaluation and if CR or unresectable, another 30–40 Gy given with 3rd cycle of CHT). Trial closed early due to slow accrual; 3-year OS for chemoRT (arm B) was superior to that of arm A or arm C; 89% of patients in arm B experienced grades 3 to 5 toxicity. **Conclusion: High-dose cisplatin when added to conventionally fractionated RT improves OS.**

Table 11.7 Results of H&N Intergroup			
	CR	**3-Yr OS**	**Grades 3 to 5 Toxicity**
Arm A: RT	27.4%	23%	52%
Arm B: CRT	40.2%	37%*	89%*
Arm C: split-course CRT	49.4%*	27%	77%*

**Statistically significant relative to arm A.*

Calais, GORTEC 94-01 (*JNCI* 1999, PMID 10601378; Denis *JCO* 2004 PMID 14657228): PRT of 226 patients with stage III to stage IV SCC of oropharynx randomized to RT alone (70 Gy/35 fx) with or without concurrent carboplatin and 5-FU for 3 cycles. OS (22% vs. 16%), DFS (27% vs. 15%), and LRC (48% vs. 25%) were all improved by statistically significant amount. Grade 3 or higher late effects occurred in 30% vs. 56% ($p = .12$). **Conclusion: CHT improved survival without increasing late toxicity.**

■ Does CHT add benefit to hyperfractionated RT?

Although hyperfractionated RT adds benefit over conventional fractionation, CHT remains beneficial.

Brizel, Duke (*NEJM* 1998, PMID 9632446): PRT of 116 patients with T3–4 N0–3 SCC of H&N (and T2N0 BOT) treated to 75 Gy/60 fx BID and randomized to either no concurrent therapy or concurrent cisplatin (60 mg/m^2) and 5-FU (600 mg/m^2) weeks 1 and 6. At MFU of 41 months, 3-year OS 55% in CHT arm vs. 34% in hyperfractionated group ($p = .07$). LRC was also improved (44% vs. 70%, $p = .01$). Toxicity was comparable**. Conclusion: CHT adds benefit to hyperfractionated RT with similar toxicity.**

Bourhis, GORTEC 99-02 (*Lancet Oncol* 2012, PMID 22261362): Three-arm PRT of stage III to stage IV SCC of H&N randomized to standard chemoRT (70 Gy/35 fx with carboplatin and 5-FU), accelerated chemoRT (70 Gy in 6 weeks with carboplatin and 5-FU), or very accelerated RT alone (64.8 Gy/36 fx BID in 3.5 weeks). Standard chemoRT and accelerated chemoRT were similar in terms of PFS ($p = .88$). Conventional chemoRT improved PFS compared with very accelerated RT ($p = .04$). **Conclusion: Acceleration alone cannot completely compensate for absence of CHT.**

■ Does hyperfractionated RT add benefit to chemoRT?

This question is the inverse of the previous question and was partially addressed by GORTEC 99-02 earlier, but was also addressed by the RTOG (although this was not the most significant finding from RTOG 0129; see HPV section later).

Nguyen-Tan, RTOG 0129 (*JCO* 2014, PMID 25366680): PRT of 721 patients with SCC of oral cavity, oropharynx, larynx, or hypopharynx to either 70 Gy/35 fx or 72 Gy/42 fx over 6 weeks with concomitant boost schedule (see RTOG 9003 earlier). Both arms received cisplatin 100 mg/m^2 every 3 weeks (2 cycles for accelerated arm, 3 for standard arm). After MFU 7.9 years, no differences were observed in any end point (OS, PFS, LRC, or DM). **Conclusion: No benefit to acceleration in presence of concurrent CHT.**

■ What is the overall summary of chemoRT trials?

Pignon, MACH-NC Meta-analysis (*Lancet* 2000, PMID 10768432; Update Pignon *Radiother Oncol* 2009, PMID 19446902; By Disease Site: Blanchard *Radiother Oncol* 2011, PMID 21684027): Patient-level meta-analysis of over 17,000 patients from 93 trials demonstrated OS benefit to addition of CHT of 4.5% at 5 years. Concurrent chemoRT showed absolute benefit of 6.5% at 5 years (SS); induction 2.4% at 5 years (NS). Patients above 70 years of age did not benefit in terms of OS. Both concurrent and induction CHT improved distant control (update: HR 0.73 and 0.88, $p = .0001$ and .04 but not different when compared to each other).

■ Is cetuximab of benefit compared to RT alone?

An EGFR inhibitor, cetuximab is active against H&N cancer and improved OS compared to RT alone.

Bonner (*NEJM* 2006, PMID 16467544; Update *Lancet Oncol* 2010, PMID 19897418): PRT of 424 patients from 1999 to 2002 with stage III to stage IV SCC of oropharynx, hypopharynx, or larynx

randomized to either RT alone (3 regimens permitted: daily, BID, and concomitant boost) or RT with cetuximab given 400 mg/m^2 loading dose 1 week before RT and 250 mg/m^2 weekly during RT. Primary end point was LRC. Cetuximab improved LRC and OS (MS 29 vs. 49 months, p = .03). Toxicity was not different with exception of infusion reactions and acneiform rash. Subsequent analyses did not show interaction with HPV status.[26] Survival was improved in cetuximab patients who developed grade 2 or higher acneiform rash compared to those without rash. **Conclusion: Cetuximab improves OS compared to RT alone.**

■ **Does cetuximab improve survival when added to cisplatin?**

Ang, RTOG 0522 (*JCO* 2014, PMID 25154822): PRT of 891 patients with stages III to IV H&N cancer randomized to RT with cisplatin with or without cetuximab. Addition of cetuximab did not improve OS, DFS, LRC, or DM but did increase toxicity. EGFR expression did not predict outcome. **Conclusion: No benefit to addition of cetuximab to cisplatin.**

■ **Is concurrent cetuximab directly comparable and less toxic than concurrent cisplatin?**

It was hypothesized that concurrent cetuximab may provide similar oncologic outcomes to cisplatin but with reduced toxicity. Three phase III RCTs directly compared RT with concurrent cetuximab vs. concurrent cisplatin among patients with HPV+ oropharyngeal cancer; each demonstrated reduced survival with cetuximab without dramatic reductions in toxicity.

Gillison, RTOG 1016 (*Lancet* 2019, PMID 30449625): PRT of HPV+ oropharyngeal cancer (AJCC 7th edition: T1–2, N2a–N3 or T3–4, N0–3) treated with accelerated IMRT (70 Gy/35 fx, 6 fx/week) with either concurrent cisplatin (100 mg/m^2 days 1 and 22) or concurrent cetuximab. Primary end point OS. Of 805 patients with 4.5-year MFU, OS with cetuximab was not non-inferior to cisplatin (HR: 1.45, p = .5). Furthermore, cetuximab was associated with significantly inferior OS, PFS, and LRF, but not DM; 5-year OS was 84.6% with cetuximab vs. 77.9% with cetuximab (p = .016); 5-year LRF was 9.9% with cisplatin vs. 17.3% with cetuximab (p = .0005). Moderate to severe acute and late toxicities were similar. **Conclusion: For HPV + oropharyngeal cancer, concurrent cetuximab has inferior OS compared to concurrent cisplatin without a dramatic reduction in toxicity.**

Mehanna, De-ESCALATE (*Lancet* 2019, PMID 30449623): PRT with HPV+ low-risk (p16+ and <10 smoking pack-years) oropharyngeal cancer treated with RT (70 Gy/35 fx) with either concurrent cisplatin (100 mg/m^2 days 1, 22, and 43) or concurrent cetuximab. Primary end point was overall G3–5 toxicity at 2 years, and of 334 patients, it was not significantly different (p = .98); 2-year OS worse with cetuximab vs. cisplatin (89.4% vs. 97.5%; p = .001), as was 2-year any-recurrence (16.1% vs. 6%, p = .0007). Giving cetuximab instead of cisplatin was estimated to lead to 1 extra death at 2 years for every 12 patients treated. **Conclusion: For low-risk HPV + oropharyngeal cancer, concurrent cetuximab showed no benefit in terms of reduced toxicity, but instead showed inferior OS and disease control compared to cisplatin.**

Gebre-Medhin, ARTSCAN III (*JCO* 2021, PMID 33052757): Swedish PRT of 291 patients; about 15% were non-OPC and 10% p16-negative. Randomized to weekly cisplatin 40 mg/m^2 vs. cetixumab. Second randomization for cT3–4 tumors to 68 Gy vs. 73.1 Gy. Stopped early due to inferiority of cetixumab; 3-year OS was 88% for cisplatin and 78% for cetuximab (p = .086). LRC and EFS inferior in cetuximab arm, DM not different. Escalation to 73.1 Gy not clearly beneficial. **Conclusion: Cetuximab is clearly inferior to cisplatin.**

■ **Can induction CHT improve survival by reducing rate of distant metastases?**

This subject has been extensively studied and is controversial. In summary, TPF is the preferred induction regimen but superiority of induction CHT has not been established compared to concurrent chemoRT.

Vermorken, TAX 323 (*NEJM* 2007, PMID 17960012): PRT randomized 358 stage III to stage IV H&N cancer to 4 cycles of induction cisplatin/5-FU (PF) with or without docetaxel (TPF) followed by RT alone. TPF demonstrated OS benefit (MS 14.5 vs. 18.8 months). **Conclusion: TPF is induction CHT regimen of choice.**

Posner, TAX 324 (*NEJM* 2007, PMID 17960013; Update Lorch *Lancet Oncol* 2011, PMID 21233014): PRT randomized 501 stage III to stage IV H&N cancer to 3 cycles of induction cisplatin/5-FU

(PF) with or without docetaxel (TPF) followed by RT with concurrent carboplatin. Updated results continued to show survival benefit (MS 34.8 vs. 70.6 months). **Conclusion: TPF is induction CHT regimen of choice.**

Haddad, PARADIGM (*Lancet Oncol* 2013, PMID 23414589): PRT of patients with T3–4 or N2–3 SCC comparing 3 cycles of TPF followed by chemoRT with either docetaxel or carboplatin vs. chemoRT with 2 cycles of cisplatin 100 mg/m^2. Trial closed early after 145 patients were enrolled. No differences observed in terms of OS or PFS. Induction patients experienced more febrile neutropenia. **Conclusion: No clear benefit to induction CHT compared to concurrent cisplatin.**

Cohen, DeCIDE (*JCO* 2014, PMID 25049329): PRT of patients with N2–3 H&N cancer treated with either concurrent CHT (docetaxel, 5-FU, and hydroxyurea) or 2 cycles of TPF induction CHT with same concurrent chemoRT. RT was 74 to 75 Gy given BID. Trial closed early due to slow accrual; 285 patients included. MFU 30 months. No difference in OS, RFS, or distant failure-free survival. **Conclusion: TPF cannot be routinely recommended for N2–3 patients.**

■ Which tonsil tumors can be treated with unilateral neck RT?

O'Sullivan published the classic series defining unilateral RT to be safe for T1–2N0 lateralized tonsil tumors with ≤1 cm of soft palate or superficial base of tongue invasion. Subsequent series have expanded indications to well-lateralized node-positive patients, although this is more controversial.[27–29] *Modern trials (NRG HN-002) recommend unilateral RT for cT1–3 tonsil tumors, well lateralized (<1 cm soft palate, base of tongue invasion) with minimal nodal disease (N0–2a, no ECE) with unilateral RT optional for N2b patients confined to level II without ECE. Guidelines exist on this topic for clarity.*[30]

O'Sullivan, PMH (*IJROBP* 2001, PMID 11567806): RR of 228 patients with carcinoma of tonsillar region treated with unilateral RT between 1970 and 1991; 84% were T1–2, 58% N0. Crude rate of contralateral failure was 3.5%: T1 0% (0/67), T2 1.5% (2/118), T3 10% (3/30), T4 0% (0/7). Risk was >10% if involving medial one-third of soft palate or base of tongue involved. **Conclusion: Unilateral RT is safe in select tonsil cancers >1 cm from midline. Extension to BOT is considered relative contraindication to ipsilateral RT.**

Huang, PMH (*IJROBP* 2017, PMID 28258895): RR of 379 patients treated with unilateral RT. T1–T2N0–N2b tonsil cancer treated between 1999 and 2014 stratified by HPV status. MFU 5.03 years. Regional control was not statistically different compared between HPV+ or HPV− patients. Overall, 5-year contralateral neck failures were 2%. **Conclusion: Ipsilateral RT to selected T1–T2N0–N2b tonsil patients results in equally excellent outcomes regardless of tumor HPV status. When considering ipsilateral RT, ≤1 cm superficial involvement of soft palate or BOT is safe, but suspicion of deeper invasion should be approached cautiously.**

■ When is it necessary to irradiate levels IB and V?

With modern imaging, it is likely safe to spare levels IB and V for T1–2 OPC if not involved on imaging.

Sanguineti, Johns Hopkins (*IJROBP* 2009, PMID 19131181): RR of 103 patients with T1–2, clinically node-positive OPC staged with CT imaging who underwent initial neck dissection. Overall, if CT was negative, levels IB, IV, and V were involved in 3%, 6%, and 1%, respectively. Levels IB and V were <4% regardless of pathologic involvement of II to IV. Level IV was 5% if level III was not involved but 11% if level III was involved. **Conclusion: Levels IB and V are low risk and can be spared in cT1–2 OPC.**

Sanguineti, Johns Hopkins (*Acta Oncol* 2014, PMID 24274389): RR of 91 patients with HPV+ OPC and clinically positive neck nodes who underwent ipsilateral neck dissection between 1998 and 2010. Pathology was reviewed to determine risk of subclinical disease at each neck level (not evident on CT). Risk of subclinical disease in both levels IB and V is <5%, while it is 6.5% (95% CI: 3.1–9.9) for level IV. Level IB subclinical involvement >5% when 2+ ipsilateral levels besides IB are involved. Risk of occult disease in level IV is <5% when level III is not involved. Low number of events in level V did not allow analysis of predictors of involvement. **Conclusion: Consider electively covering level IB if 2+ other levels are involved. Level IV may be spared when level III is negative.**

■ **What prospective data guided the adoption of IMRT for OPC in the United States?**

Although IMRT is now standard in the treatment of H&N cancer, RTOG 0022 is one of the few prospective trials investigating safety and efficacy in cooperative group setting. It is also a trial that demonstrates good outcomes for T1–2N0–1 OPC treated with RT alone.

Eisbruch, RTOG 0022 (*IJROBP* 2010, PMID 19540060): Initial RTOG multi-institutional trial demonstrating safety and efficacy of IMRT. Prospective phase II trial of 69 T1–2 N0–1 OPC treated with RT alone to 66 Gy/30 fx with IMRT; 2-year LRF was 9%. LRF was increased in those with major deviations: 2/4 patients with deviations (50%) vs. 3/49 without (6%, $p = .04$). **Conclusion: IMRT is feasible with encouraging acute and late toxicity. Quality of IMRT is important to avoid LRF.**

■ **What are expected outcomes with TORS? Who are ideal candidates?**

TORS (and TLM) has transformed morbidity associated with surgical resection of OPC. FDA approval was obtained for DaVinci robot in resection of T1–2 OPC in 2009 and NCCN guidelines allow for TORS as option for select patients.[10] *Series from multiple institutions have established the safety and efficacy of TORS.*[31–38] *For now, TORS remains institution- and surgeon-dependent and comparative data are limited to QOL, as shown in ORATOR trial in the following.*

Nichols, ORATOR (*Lancet Oncol* 2019, PMID 31416685): Multicenter phase II PRT of 68 patients with T1–2N0–2 (≤4 cm) OPX SCC comparing TORS + neck LND vs. RT (70 Gy/35 fx). CHT added to RT if N1–2; PORT with 60 Gy/30 fx (<2 mm margin, pT3/4, N+, LVSI) or CRT with 64 Gy/30 fx and concurrent CHT (positive margins or ECE) added to TORS based on pathology. Primary end point was swallowing-related QOL at 1 year using MDADI score, powered to detect "clinically meaningful" improvement in TORS group compared to RT group. MDADI scores at 1 year for TORS vs. RT did not meet clinically meaningful thresholds, although patients treated with RT demonstrated statistically significant improvement in swallowing-related QOL scores. Of the TORS patients, 47% received PORT and 24% received adjuvant CRT. Worse hearing loss, tinnitus, and neutropenia in the RT group, whereas worse trismus in the TORS group. One death was recorded due to bleeding after TORS. **Conclusion: Patients treated with RT did not have a clinically meaningful change in swallowing compared to those who underwent TORS. Discussion of toxicity profiles of TORS and RT/CRT should take place with patients considering options.**

■ **Do HPV-positive tumors behave differently than HPV-negative tumors?**

HPV+ OPC is now classified as distinct disease.

Ang, RTOG 0129 (*NEJM* 2010, PMID 20530316): Retrospective analysis of RTOG 0129 (see Nguyen-Tan 2014 in the preceding) investigating role of HPV. HPV status was determined by both FISH for HPV DNA and IHC for p16; 64% of patients had HPV-positive tumors and 3-year OS was markedly improved for these patients (82% vs. 57%, $p < .001$); 3-year rate of local–regional disease lower for patients with HPV+ tumors vs. HPV− tumors: 13.6% vs. 35.1% ($p < .001$). Smoking and nodal stage were prognostic. RPA for OS divided patients into 3 classes based on HPV status, smoking, T and N stages: low risk (HPV-positive and ≤10 pack-years or HPV-positive, >10 pack-years, and N0–2a), intermediate risk (HPV-positive, >10 pack-years, and N2b–3 or HPV-negative, ≤10 pack-years, and T2–3), or high risk (HPV-negative, ≤10 pack-years, and T4 or >10 pack-years). **Conclusion: This trial defined impact of HPV status on prognosis for oropharynx patients.**

Fakhry, RTOG 2nd Analysis (*JCO* 2014, PMID 24958820): Second analysis of RTOG 0129 and 0522 including patients with initially locally advanced oropharyngeal SCC (206 HPV+, 117 HPV−) who developed recurrent disease after primary treatment. Investigated effect of HPV status on survival after disease progression. Median time to progression 8.2 months for p16+ vs. 7.3 months for p16− (NS); 55% of patients had LRR only, 40% had DM only, 5% had both. MFU time after first event of disease progression was 4 years. p16+ patients had significantly improved OS after disease progression when compared to p16− patients (2.6 years vs. 0.8 years). Salvage surgery reduced risk of death after disease progression. **Conclusion: Patterns of failure do not differ based on p16 status (similar time to disease progression and anatomic site involvement), but p16+ patients have improved survival after first recurrence.**

O'Sullivan, PMH (*JCO* 2013, PMID 23295795): RR of 505 OPC patients; 382 HPV-positive. Although OS, LC (94% vs. 80%), and regional control (95% vs. 82%) were improved in HPV+ patients, distant control was similar (90% vs. 86%). RPA for distant control divided patients into 4 classes: HPV+ low (N0–N2c and T1–3) or high risk (N0–2c and T4 or N3) and HPV− low (N0–2c and T1–2) or high risk (N0–2c and T3–4 or N3). CHT seemed to reduce distant metastases for HPV+ low-risk category patients with N2b–N2c disease. **Conclusion: HPV+ patients with low risk of distant metastases (T1–3N0–2a) may be candidates for treatment de-intensification.**

■ **Are there opportunities to de-intensify treatment for HPV-positive patients?**

No standard regimen has been identified to date, but multiple trials are ongoing investigating de-intensification for low-risk HPV-positive patients. Given the inferior results of the three preceding cetuximab trials, de-escalation should be reserved for patients treated on protocol until phase III data is available.

Chera, UNC/UF/Rex Trial (*JCO* 2019, PMID 31411949): Prospective phase II trial of HPV-positive patients with T0–3N0–2c and ≤10 pack-years or 10 to 30 pack-years but abstinent for >5 years. This was a FU trial to initial phase II where pCR was the end point;[39] in this study, the primary end point was 2-year PFS and PET/CT guided surgery. Patients received 60 Gy/30 fx with weekly cisplatin 30 mg/m^2 (no CHT for cT0–2N0–1). Results: 114 enrolled, MFU 31.8 months. Clinical CR on PET was 93% at primary; 6 were observed without recurrence, 2 biopsied, and 1 had persistence who died. CR in the neck was 80%, neck dissection positive in 4 of 11. PFS was 86% at 2 years, LRC 95%, DMFS 91%. **Conclusion: De-intensification is likely safe for low-risk HPV-positive patients. Further trials are ongoing.**

Marur, ECOG 1308 (*JCO* 2017, PMID 28029303): Phase II trial of 80 patients evaluating whether cCR to induction CHT could select patients with HPV+ OPC who could receive de-intensified therapy with goal of sparing late sequelae. Eligibility criteria: Stage III to stage IV, T1–3N0–N2b OPC, p16+ or HPV+, ≤10 pack-year smoking history. Treated with 3 cycles of induction CHT with cisplatin, paclitaxel, and cetuximab. If cCR of primary site, went on to receive IMRT to 54 Gy with weekly cetuximab. If PR at primary site or nodes, patients went on to receive 69.3 Gy to involved site and cetuximab. Primary end point was 2-year PFS; 70% had primary site cCR and received low-dose arm; these patients had 2-year PFS 80%. At 12 months, patients treated with RT ≤54 Gy had less difficulty swallowing solids (40% vs. 89%, $p = .011$) or impaired nutrition (10% vs. 44%, $p = .025$); 8 of 9 failures in reduced-dose arm were locoregional. **Conclusion: For patients who respond to induction CHT, reduced-dose IMRT with concurrent cetuximab for favorable HPV-associated patients may have improved swallowing and nutritional status.**

Chen, UCLA (*Lancet Oncol* 2017, PMID 28434660): Single-arm phase II trial with biopsy-proven stage III to stage IV (AJCC 7th edition) HPV+ OPC received carboplatin/paclitaxel x2 cycles. CR or PR received 54 Gy/27 fx, less than PR received 60 Gy/30 fx, both concurrent with paclitaxel. Primary end point PFS; 45 patients, MFU 30 months; 3 LRF, 1 DM; 2-year PFS 92% (95% CI: 77–97); 39% grade 3 toxicity (mostly during induction CHT); 2% feeding tube dependence at 3 months, 0% at 6 months. **Conclusion: Reduced-dose chemoRT is associated with high PFS.**

Yom, NRG HN002 (*JCO* 2021, PMID 33507809): Phase II PRT of 306 patients with T1–2N1–2b or T3N0–2b (AJCC 7th edition) OPC with ≤10 pack-year smoking history, randomized to 60 Gy/30 fx + weekly cisplatin (IMRT + C) vs. modestly accelerated IMRT alone 60 Gy/30 fx with 6 fx/week. Powered to detect acceptable prespecified 2-year PFS of ≥85% without worse swallowing QOL at 1 year per MDADI as coprimary end point. MFU 2.6 years, 2-year PFS for IMRT + C was 90.5% (84.5–94.7, $p = .04$), which met prespecified PFS end point, while it was 87.6% (81.1–92.5, $p = .228$) for IMRT-alone arm, which failed to meet prespecified PFS end point. Both arms passed MDADI dysphagia threshold. Similar rates of mucositis, but higher rates of acute dysphagia and hematologic toxicity in IMRT + C arm. No difference in late toxicity or 2-year OS. **Conclusion: De-intensification of chemoradiotherapy for HPV+ OPC with 60 Gy/30 fx and weekly cisplatin warrants phase III comparison with 70 Gy, which is currently ongoing in NRG HN-005.**

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