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Clinical Practice Guideline

Radiation Therapy for HPV-Positive Oropharyngeal Squamous Cell Carcinoma: An ASTRO Clinical Practice Guideline

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Purpose: Human Papilloma Virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is a distinct disease from other head and neck tumors. This guideline provides evidence-based recommendations on the critical decisions in its curative treatment, including both definitive and postoperative radiation therapy (RT) management.

Methods: ASTRO convened a task force to address 5 key questions on the use of RT for management of HPV-associated OPSCC. These questions included indications for definitive and postoperative RT and chemoradiation; dose-fractionation regimens and treatment volumes; preferred RT techniques and normal tissue considerations; and posttreatment management decisions. The task force did not address indications for primary surgery versus RT. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: Concurrent cisplatin is recommended for patients receiving definitive RT with T3-4 disease and/or 1 node >3 cm, or multiple nodes. For similar patients who are ineligible for cisplatin, concurrent cetuximab, carboplatin/5-fluorouracil, or taxane-based systemic therapy are conditionally recommended. In the postoperative setting, RT with concurrent cisplatin (either schedule) is recommended for positive surgical margins or extranodal extension. Postoperative RT alone is recommended for pT3-4 disease, >2 nodes, or a single node >3 cm. Observation is conditionally recommended for pT1-2 disease and a single node ≤3 cm without other risk factors. For patients treated with definitive RT with concurrent systemic therapy, 7000 cGy in 33 to 35 fractions is recommended, and for patients receiving postoperative RT without positive surgical margins and extranodal extension, 5600 to 6000 cGy is recommended. For all patients receiving RT, intensity modulated RT over 3-dimensional techniques with reduction in dose to critical organs at risk (including salivary and swallowing structures) is recommended. Reassessment with positron emission tomography-computed tomography is recommended approximately 3 months after definitive RT/chemoradiation, and neck dissection is recommended for convincing evidence of residual disease; for equivocal positron emission tomography-computed tomography findings, either neck dissection or repeat imaging is recommended.

Conclusions: The role and practice of RT continues to evolve for HPV-associated OPSCC, and these guidelines inform best clinical practice based on the available evidence.

Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.			
Strength of Recommendation	**Definition**	**Overall QoE Grade**	**Recommendation Wording**
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"
Overall QoE Grade	**Type/Quality of Study**	**Evidence Interpretation**	
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.	
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.	
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.	
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.	

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades are not assumed to extend to the implementation remarks.

confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Introduction

Human Papilloma Virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) continues to increase worldwide, with approximately 21,000 new cases in 2020 in the United States alone, reflecting an age-adjusted rate of 5.0 per 100,000 people. It is the most common HPV-associated cancer among men and second only to cervical cancer in women.[3] The incidence of HPV-associated (referred to as HPV-positive in this guideline) oropharynx cancers are projected to increase over the next decade despite the availability of high-risk HPV vaccination, partly owing to the long-latency between oral HPV infection and detectable cancer and low uptake of vaccination in certain countries, including the United States, particularly among men.[4] Not only is HPV-positive OPSCC, one of the few head and neck squamous cell carcinomas (HNSCC), increasing in incidence as smoking and tobacco-related head and neck cancers decrease, but also patients with HPV-positive OPSCC are often younger and have a better prognosis than those with non−HPV-related HNSCC.[5,6] Because of the increasing number of long-term survivors of OPSCC, prospective studies have focused on reducing the long-term effects of treatment by "deintensifying" standard therapies, including surgery, radiation therapy (RT), and systemic therapy. The goal of such studies is to maintain cure rates and minimize the acute and long-term effects of treatment on multiple functions ranging from swallowing, speech, vascular health, and others.

In 2017, the ASTRO oropharyngeal cancer guideline did not focus specifically on HPV-positive OPSCC.[7] At that time, the evidence base comprised prospective clinical trials conducted before the recognition of HPV-positive OPSCC as a clinically distinct disease from non-HPV OPSCC, and HPV status was infrequently assessed in the literature. Since then, several prospective clinical trials were published that further inform management of HPV-positive OPSCC,[8,9] although many seminal previous studies preceding identification of HPV status are still used in decision making.[10,11] This guideline focuses specifically on HPV-positive OPSCC, incorporating data from clinical trials and high-quality retrospective studies on choice and sequences of systemic therapy, optimal postoperative management, RT-specific treatment considerations, and posttreatment response assessment. The task force makes recommendations on optimal management of HPV-positive OPSCC, recognizing that not every clinical presentation can be addressed. Clinical trial enrollment is an essential mechanism to further improve outcomes.

Methods

Task force composition

The task force consisted of a multidisciplinary team of radiation and medical oncologists; head and neck surgeons; a medical physicist; a patient representative; and an information specialist (C.J.A., also a radiation oncologist) who led search strategy development and execution. This guideline was developed in collaboration with the American Society of Clinical Oncology and the American Academy of Otolaryngology-Head and Neck Surgery, which nominated representatives and peer reviewers.

Document review and approval

The guideline was reviewed by 14 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from October to November 2023. The final guideline was approved by the ASTRO Board of Directors and endorsed by the European Society for Radiotherapy and Oncology and the Royal Australian and New Zealand College of Radiologists.

Evidence review

KQs were developed by the ASTRO guideline subcommittee in conjunction with the guideline chairs and then reviewed by the full task force. Using the PICOTS framework (Table 2 and Appendix E3A), a systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English-language publications between January 2000 and May 24, 2023. Allowable publication types included prospective studies including randomized controlled trials (RCTs), individual patient data meta-analyses, retrospective studies, and dosimetric/contouring studies. The population of interest was adults (age ≥18 years) with a diagnosis of HPV-positive OPSCC. Trial size required for inclusion was ≥50 patients for prospective studies and ≥100 patients if retrospective. Universal exclusion criteria included preclinical and nonhuman studies; publication types including abstract only, review articles, comments, or editorials; study types such as health economics/cost analysis studies or large registry/database studies (eg, Surveillance, Epidemiology, and End Results; National Cancer Database); and treatment of recurrent disease/secondary primaries. Studies were excluded if

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**For patients receiving definitive RT for HPV+ OPSCC, what are the indications for systemic therapy?**			
	Adult patients with HPV+ and/or p16+ OPSCC	• Systemic therapy • Chemotherapy • Biological therapy • Immunotherapy	• RT alone • RT + other concurrent regimens	• Overall survival • Progression-free survival • Locoregional control • Distant metastasis • QoL and toxicities • Disparities in oncologic & QoL outcomes
2	**Following curative-intent surgery for patients with HPV+ OPSCC, what are the indications for postoperative RT with or without systemic therapy?**			
	Same as KQ1	• Postoperative RT alone • Postoperative chemoradiation (or biological therapy) + RT	• Surgery alone • Postoperative RT alone	Same as KQ1
3	**For patients receiving definitive or postoperative RT with or without systemic therapy for HPV+ OPSCC, what are the optimal dose-fractionation regimens and treatment volumes?**			
	Same as KQ1	• Altered fractionation • Dose de-intensification • Definitions of primary tumor and neck volumes	• Standard fractionation • Standard dose (6600-7200 cGy for definitive RT, 6000-6600 cGy for postoperative RT) • Conventional fields	Same as KQ1
4	**For patients receiving definitive or postoperative RT with or without systemic therapy for HPV+ OPSCC, what are the preferred RT techniques and appropriate normal tissue considerations?**			
	Same as KQ1	• IMRT • Proton beam therapy • Alternative thresholds for OARs	• Differential organ sparing across techniques (IMRT, protons, 3-D CRT)	• Locoregional control • QoL • Patient-reported outcomes and toxicities • Disparities in oncologic & QoL outcomes
5	**Following definitive or postoperative RT with or without systemic therapy for patients with HPV+ OPSCC, what are the preferred approaches for initial posttreatment restaging and management of the neck?**			
	Same as KQ1	• Imaging • Biopsy • Circulating HPV tumor DNA • Neck dissection	• Clinical follow-up	• Overall survival • Progression-free survival • Regional/neck control • Distant metastasis • QoL and toxicities • Disparities in oncologic & QoL outcomes

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; IMRT = intensity modulated radiation therapy; KQs = key questions; OARs = organs at risk; PICO = Population, Intervention, Comparator, Outcome; QoL = quality of life; RT = radiation therapy.

their patient population comprised <30% OPSCC for all KQs except KQ2 because postoperative studies are less likely to include a majority or plurality of patients with oropharyngeal cancer. For KQ1, induction chemotherapy studies that lacked initial chemoradiation as a comparator were excluded. For specific subquestions where limited data were available, expert opinion was relied on to support recommendations. Full-text articles were assessed by the task force to determine the final included study list, resulting in 186 studies (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram showing the number of articles screened, excluded, and included in the evidence review). This systematic review is reported using Cochrane and PRISMA 2020 methodology (see Appendix E3B for the full search strategy, Appendix E3C for the search strategy key, and Appendix E3D for a checklist of the completed essential elements).[12]

The data used to formulate recommendations are summarized in evidence tables available in Appendix E4.

References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables but included in the text were not used to support the evidence-based recommendations but may have informed expert opinion.

Scope of the guideline

This guideline addresses the following KQs for patients with OPSCC treated with curative intent: the use of systemic therapy for patients treated with definitive RT; indications for adjuvant RT and chemoradiation for patients treated with primary surgery; dose-fractionation regimens and volumes for treatment with definitive and postoperative RT and chemoradiation; preferred treatment techniques and normal tissue constraints for definitive and postoperative RT; and initial posttreatment restaging and management of the neck (Table 2). There are several important questions in the management of HPV-positive OPSCC that are outside the scope of this guideline, including selection of primary therapy, treatment of recurrent disease, and biomarker-based surveillance after initial response assessment. Most of the evidence informing this guideline used the American Joint Committee on Cancer staging system seventh edition (AJCC-7)[13] or earlier to report patient characteristics and results. To make the recommendations consistent with the current AJCC-8 staging system,[14] lymph node size and number are provided in the recommendations.

This guideline's recommendations pertain to patients with previously untreated, HPV-positive OPSCC with no distant metastases (M0), treated with curative intent. HPV status was typically assessed directly with in situ hybridization or indirectly with p16 immunohistochemistry. The evidence base excludes studies of exclusively p16-negative OPSCC but includes studies of patients with unknown HPV status or a mix of both HPV-positive and HPV-negative OPSCC. Patients who are not the subject of this guideline include those with nonsquamous cell carcinoma histology, p16-negative disease, nonoropharynx subsites, and HPV-positive squamous cell carcinoma of unknown primary with cervical nodal metastases. The guideline focuses on the 3 main treatment modalities for OPSCC: RT, surgery, and systemic therapy. For systemic therapy recommendations, intra-arterial chemotherapy studies were out of scope. For RT, the guideline focuses on external beam RT, not stereotactic body RT or brachytherapy.

The key outcomes of interest are oncologic results including overall survival and locoregional control, toxicity, and quality of life metrics. Disparities were evaluated as an outcome but were rarely provided in the evaluated literature.

KQs and Recommendations

KQ1: Indications for systemic therapy with RT (Table 3)

See evidence tables in *Supplementary Materials*, Appendix E4 for the data supporting the recommendations for KQ1 and Fig. 1.

For patients receiving definitive RT for HPV+ OPSCC, what are the indications for systemic therapy?

The task force only considered currently available systemic regimens that were included in the evidence base. In the definitive setting, indications for concurrent chemoradiation are based on T and N category as defined by AJCC-7 criteria[13] because trial eligibility was based on these characteristics.[8-11,27,30] A patient's ability to undergo treatment (eg, adequate performance status and medical fitness) was not defined but is rather at the discretion of the clinician.

Concurrent systemic therapy with RT is recommended for all fit patients with T3-4 disease, ≥2 positive nodes, or a single node measuring >3 cm because there is a demonstrated overall survival and/or locoregional control benefit in multiple trials of such patients with AJCC-7 stages III and IV,[13] which is essentially equivalent to AJCC-8[14] T1-2N1-3 and T3-4N0-3.[8-11,15,16] Recommendations for T1-2N1 (single lymph node ≤3 cm) disease were discussed at length by the task force owing to the limited data specific to this presentation (Table 4). For patients with T1 N1 (single lymph node ≤3 cm) disease, RT alone is recommended because of the limited data for concurrent systemic therapy in this population. For patients with T2N1 (single lymph node ≤3 cm) disease, either RT alone or RT with concurrent systemic therapy is considered appropriate.[9,11,17-19] A multidisciplinary team evaluation and a discussion of the potential risks and benefits of each option are critical to aid patients in making an informed treatment decision.

For patients receiving definitive RT for HPV-positive OPSCC who warrant systemic therapy, it should be delivered concurrently and not sequentially. Multiple RCTs[11,16] and a high-quality meta-analysis[15] demonstrated an overall survival benefit with concurrent systemic therapy versus RT alone, but there is no survival benefit to induction systemic therapy.[15,20-22] The rare scenario in which patients with locally advanced OPSCC may require rapid initiation of therapy for cytoreduction and symptom relief is not addressed in this guideline.

HPV status is prognostic of survival outcomes in patients with OPSCC.[32] However, the available high-quality evidence does not support the use of HPV status to guide the choice of systemic therapy. Seminal data

Table 3 Indications for systemic therapy with RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence
1. For patients with HPV+ OPSCC and either T3-4 disease, ≥2 positive nodes, or a single node >3 cm receiving definitive RT, concurrent systemic therapy is recommended.	Strong	High [8-11,15,16]
2. For patients with HPV+ OPSCC and T1-2 node-negative disease, or T1 disease and a single positive node ≤3 cm receiving definitive RT, RT alone is recommended.	Strong	Low [17-19]
3. For patients with HPV+ OPSCC and T2 disease with a single positive node ≤3 cm receiving definitive RT, either RT alone or concurrent systemic therapy is recommended. Implementation remark: Weigh the potential benefits of concurrent systemic therapy against toxicity risks given limited data regarding its efficacy in this population.	Strong	Low [9,11,17-19]
4. For patients with HPV+ OPSCC who will receive definitive RT with or without concurrent systemic therapy, induction systemic therapy is **not** recommended.	Strong	High [15,20-22]
5. For patients with HPV+ OPSCC who warrant definitive RT and concurrent systemic therapy, cisplatin is recommended. Implementation remark: Either 100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly cisplatin is appropriate.	Strong	High [8,9,11,23,24]
6. For patients with HPV+ OPSCC who warrant definitive RT and concurrent systemic therapy but are not candidates for cisplatin, cetuximab or carboplatin/5-fluorouracil are conditionally recommended.	Conditional	Moderate [16,25-27]
7. For patients with HPV+ OPSCC who warrant definitive RT and concurrent systemic therapy but are not candidates for cisplatin, taxane-based regimens are conditionally recommended.	Conditional	Expert Opinion
8. For patients with HPV+ OPSCC who will receive definitive RT, immunotherapy (either neoadjuvant, concurrent, or adjuvant) is **not** recommended regardless of PD-L1 status.	Strong	High [28,29]

Abbreviations: HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; PD-L1 = programmed death ligand 1; RT = radiation therapy.

demonstrated a survival benefit of adding concurrent cisplatin chemotherapy to conventionally fractionated (200 cGy once daily fraction) definitive RT in the era before intensity modulated radiation therapy (IMRT) for locally advanced HNSCC.[11] The Radiation Therapy Oncology Group (RTOG) 0522 study showed that intensification of systemic therapy with the addition of epidermal growth factor receptor-directed therapy, such as cetuximab, to cisplatin did not improve survival.[33] Despite the hypothesis that concurrent cetuximab could replace either high-dose or weekly cisplatin as the radiosensitizer, RCTs demonstrate the inferiority of concurrent cetuximab compared with cisplatin for outcomes of disease recurrence and overall survival.[8,9,23,24] As such, cisplatin is recommended as standard of care until RCTs support noninferiority of treatment outcomes with alternative agents. While triweekly (every 3 weeks) high-dose cisplatin (100 mg/m^2 every 3 weeks) was established by the Intergroup study as the de facto standard cisplatin regimen,[11] subsequent data suggest that the weekly regimen (40 mg/m^2) is a viable alternative.[23,24,34] These studies, including ARTSCAN III (A randomized phase III study comparing chemoradiotherapy with cisplatin versus cetuximab in patients with locoregionally advanced head and neck squamous cell cancer),[23] NRG-HN002,[34] and Trans-Tasman Radiation Oncology Group (TROG) 12.01 (Randomized trial of radiotherapy with weekly cisplatin or cetuximab in low-risk HPV-associated oropharyngeal cancer),[24] demonstrate favorable locoregional control with weekly cisplatin. The latter 2 studies focus on patients with favorable HPV-positive OPSCC, and the former includes approximately 75% of patients with HPV-positive OPSCC, 70% of whom had a smoking history. There is no head-to-head comparison of the triweekly versus weekly cisplatin regimens in the definitive setting, but this is the subject of an ongoing trial *(NCT 05050162)*.

Many patients with locally advanced HPV-positive OPSCC are not candidates for cisplatin for various reasons (eg, peripheral neuropathy, pre-existing hearing loss or tinnitus, and renal impairment) yet require systemic therapy. In these populations, cetuximab or carboplatin/5-fluorouracil are conditionally recommended regimens shown in phase III RCTs to improve survival in locally advanced HNSCC when added to definitive RT.[16,25-27] Taxane-containing regimens, including weekly docetaxel or carboplatin plus paclitaxel, are also conditionally recommended based on the expert opinion of the task force, but their efficacy in published studies are limited to nonrandomized trials or studies with a low proportion of

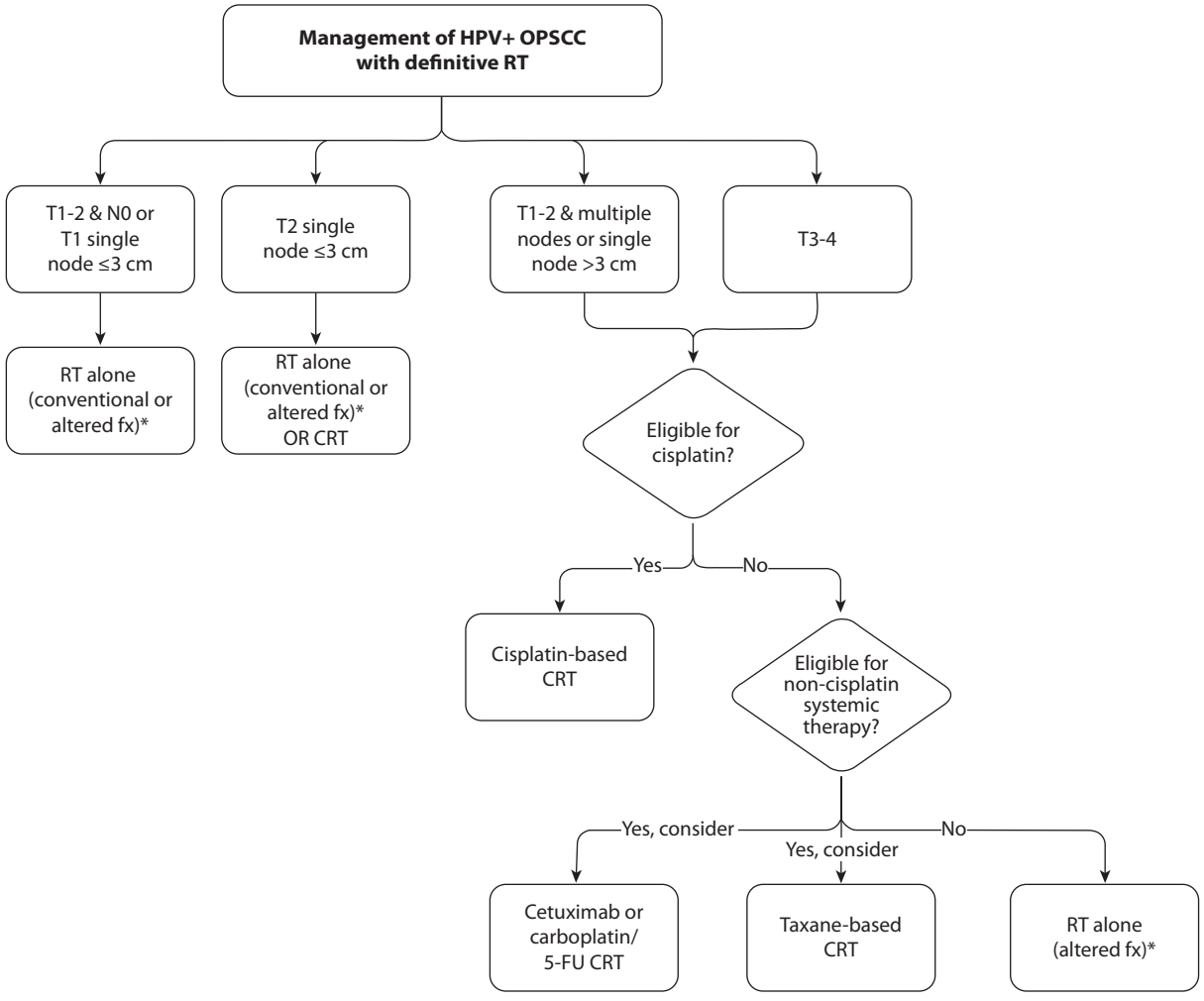

Figure 1 Management of HPV+ OPSCC with definitive RT.
Abbreviations: CRT = RT with concurrent systemic therapy; fx = fractionation; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; RT = radiation therapy; 5-FU = 5-fluorouracil.
*See "KQ3: Dose-fractionation regimens and treatment volumes" section for recommendations on altered fractionation.
Where the strength of a recommendation is conditional, the term "consider" is used.

known HPV-positive OPSCC.[35-37] No prospective data exist regarding the best means to triage patients who are cisplatin-ineligible to alternative regimens, nor are there direct comparative data between regimens (ie, carboplatin/fluorouracil vs cetuximab vs taxane regimens). Patient clinical characteristics including comorbidities and functional status are considered when making treatment decisions, as well as the treatment team's familiarity with the different agents.

The role of immunotherapy for locally advanced HPV-positive OPSCC is not clearly defined. There are 2 published RCTs evaluating the role of immunotherapy in locally advanced HNSCC, including patients with HPV-positive OPSCC.[28,29] JAVELIN Head and Neck 100 (A randomized double-blind phase 3 study of avelumab in combination with standard of care chemoradiotherapy [cisplatin plus definitive radiation therapy] versus standard of care chemoradiotherapy in the front-line treatment of patients with locally advanced squamous cell carcinoma of the head and neck) is an RCT evaluating the effect of concurrent and adjuvant avelumab in addition to cisplatin-based drugs for the treatment of locally advanced head and neck cancer.[28] The trial was stopped after a preplanned interim analysis found no improvement in progression-free survival with the addition of avelumab. Additionally, more severe toxicities were noted in the avelumab arm.[28]

In the GORTEC (Groupe Oncologie Radiotherapie Tête et Cou) 2015-01 PembroRad (Pembrolizumab versus cetuximab concurrent with radiotherapy in patients with locally advanced squamous cell carcinoma of head and neck unfit for cisplatin) phase II RCT, RT was evaluated in combination with pembrolizumab versus cetuximab in patients with locally advanced squamous cell carcinoma not eligible for cisplatin.[29] There was no significant difference in either progression-free survival or overall survival

Table 4 Percentage of patients with AJCC-7 clinical stage T1-2N1 (T1-2 with a single involved lymph node ≤3 cm) included in clinical trials of RT and concurrent systemic therapy

Study	Percentage of Patients With AJCC-7 T1-2 N1	Comments
Maddalo et al[30]	T1 N1 excluded (0%)	AJCC-7 Stage III (20%)
RTOG 1016[8]	T1 N1 and T2 N1 excluded (0%)	AJCC-7 Stage III (7%)
De-ESCALaTE HPV[9]	T1-2 N-any 65%, T3-4 N0, or T1-4 N1 24%	T1-2 N0 excluded
RTOG 0129[10]	T1 N-any, T2 N1 excluded (0%)	AJCC-7 Stage III (22%)
Fallai et al[27]	T1 N1 and T2 N1 excluded (0%)	N/A
Adelstein et al[31]	5%	AJCC-7 Stage III (28%)
H&N Intergroup[11]	1%	AJCC-7 Stage III (<7%)

Abbreviations: AJCC-7 = American Joint Committee on Cancer, seventh edition; De-ESCALaTE HPV = Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in HPV-positive oropharyngeal squamous cell carcinoma; H&N = head and neck; N/A = not applicable; RTOG = Radiation Therapy Oncology Group.

with the use of pembrolizumab as a radiosensitizer, but it was less toxic.[29] There are several either closed or ongoing RCTs evaluating the efficacy of immunotherapy added to RT alone or cisplatin-RT using different sequences (eg, NRG-HN004 [*NCT03258554*], KEYNOTE-412 [A randomized phase III study of pembrolizumab given concomitantly with chemoradiation and as maintenance therapy versus chemoradiation alone in subjects with locally advanced head and neck squamous cell carcinoma; *NCT03040999*], ECOG-ACRIN 3161 [Nivolumab versus observation in patients with locally advanced, intermediate risk HPV-positive OPSCC; *NCT03811015*], and IMVoke010 [Randomized phase III study of atezolizumab vs placebo after chemoradiation; *NCT03452137*]), but the evidence base does not support immunotherapy for curative-intent treatment of patients with HPV-positive OPSCC.

KQ2: Indications for postoperative RT after curative-intent surgery (Table 5)

See evidence tables in *Supplemental Materials*, Appendix E4 for the data supporting the recommendations for KQ2 and Fig. 2.

Following curative-intent surgery for patients with HPV+ OPSCC, what are the indications for postoperative RT with or without systemic therapy?

Surgical expertise and careful patient selection are of the utmost importance to achieve optimal oncologic and functional outcomes. Transoral surgical approaches, using either robotic surgery or laser surgery, have gained credibility in the upfront management of this disease, particularly as ECOG-ACRIN 3311 (Phase II randomized trial of transoral surgery and low-dose intensity modulated radiation therapy in resectable p16+ locally advanced oropharynx cancer) demonstrated feasibility of transoral surgery by credentialed surgeons in a multi-institutional setting.[38] Patients with HPV-positive OPSCC commonly present with metastatic cervical nodal involvement from small primary tumors. Precise surgical technique and specimen processing are critical in determining any risk factors for disease relapse, which inform decisions for postoperative treatment. The generation of evidence-based, postoperative management recommendations is challenged by the absence of high-quality evidence, including a limited number of prospective randomized and nonrandomized trials focused on HPV-positive OPSCC. However, there are many retrospective studies of HNSCC in general, which explains the preponderance of moderate and expert opinion quality of evidence.

The benefit of postoperative concurrent chemoradiation compared with postoperative RT alone was tested in 2 RCTs.[40,41] Adding concurrent cisplatin to postoperative RT is recommended for all patients with pathologic T3-4 or node-positive disease demonstrating extranodal extension (ENE) or positive margins, inclusive of patients with T1-2 node-positive disease.[38-42] The results of 1 RCT[40] and a combined analysis of 2 RCTs[42] demonstrate an overall survival benefit of concurrent chemoradiation versus RT alone in these populations, although these studies were performed before testing HPV status. The definition of "positive margin" in the literature is highly variable and controversial because patients with specimen margin widths as wide as 5 mm were eligible for the European Organisation for Research and Treatment of Cancer (EORTC) 22931 trial,[40] but tumor on ink was required for inclusion in RTOG 9501.[39,41] Tumor on ink was also the positive margin definition for ECOG-ACRIN 3311, recognizing the challenge of obtaining margins wider than 2 mm in the oropharynx with transoral surgery.[38] After much discussion, the task force chose to define positive margins as tumor on ink while also highlighting the importance of communication between the pathologist,

Table 5 Indications for postoperative RT after curative-intent surgery

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence
1. For patients with resected HPV+ OPSCC and pT3-4 or pathologic node-positive disease, and either a final microscopically positive margin (tumor on ink) or ENE, postoperative RT with concurrent cisplatin is recommended. Implementation remark: Either 100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly cisplatin is appropriate.	Strong	High [38-42]
2. For patients with resected HPV+ OPSCC and pT1-2 node-negative disease with a final microscopically positive margin (tumor on ink), either RT alone or RT with concurrent cisplatin is recommended. Implementation remark: Either 100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly cisplatin is appropriate.	Strong	Expert Opinion
3. For patients with resected HPV+ OPSCC and node-positive disease with either pT3-4 disease, ≥2 positive nodes, or a single positive node >3 cm, postoperative RT is recommended.	Strong	Moderate [38-46]
4. For patients with resected HPV+ OPSCC and pT3-4 node-negative disease, postoperative RT is recommended.	Strong	Expert Opinion
5. For patients with resected HPV+ OPSCC and pT1-2 disease with either no positive nodes or a single positive node ≤3 cm without ENE, postoperative RT is conditionally recommended for perineural invasion and/or lymphovascular invasion.	Conditional	Expert Opinion
6. For patients with resected HPV+ OPSCC and microscopically close final margins, postoperative RT is conditionally recommended.	Conditional	Moderate [38,40,43,47]
7. For patients with resected HPV+ OPSCC and pT1-2 disease with a single positive node ≤3 cm without other pathologic risk factors, observation is conditionally recommended. Implementation remark: Considerations before observation include the dissected nodal levels and number of dissected nodes.	Conditional	Moderate [38,46,48-52]

Abbreviations: ENE = extranodal extension; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; RT = radiation therapy.

surgeon, and radiation and medical oncologists to interpret the surgical specimens.

For patients receiving postoperative concurrent chemoradiation, cisplatin remains the standard of care, and either triweekly bolus or weekly cisplatin are appropriate regimens.[40,42,53] The use of concurrent cisplatin in resected HPV-positive OPSCC is primarily based on the results of RTOG 9501[39,41,42] and EORTC 22931,[40,42] which included patients with HNSCC. Both studies used bolus cisplatin (100 mg/m^2 delivered every 3 weeks during RT), whereas the 40 mg/m^2 weekly cisplatin schedule is supported by an RCT by the Japanese Clinical Oncology Group.[53] This trial compared concurrent weekly cisplatin (40 mg/m^2) with bolus cisplatin in a heterogeneous group of patients with HNSCC and showed noninferiority of the weekly regimen, though it only accrued a small number of patients with OPSCC. However, another trial testing a lower dose of weekly cisplatin (30 mg/m^2) versus the triweekly schedule in a non−HPV-positive OPSCC population showed superiority of bolus cisplatin, highlighting the importance of cisplatin dose.[54] Given the results of the Japanese Clinical Oncology Group trial, either cisplatin schedule is recommended provided the starting weekly dose is 40 mg/m^2.[38-42] A trial comparing these regimens in the postoperative setting in HPV-positive OPSCC is unlikely; however, proponents of weekly cisplatin (40 mg/m^2) are further supported by the results of ECOG-ACRIN 3311, which shows excellent clinical outcomes in patients with high-risk features undergoing postoperative chemoradiation with weekly cisplatin.[38]

Further research with a higher volume of patients is needed to determine the impact of limited ENE (≤1 mm) on recurrence following RT alone. While ECOG-ACRIN 3311 treated patients with limited ENE (≤1 mm) using RT alone, there were only 38 such patients.[38] The oncologic safety of RT alone for patients with ENE may be confirmed in the ongoing PATHOS (Postoperative adjuvant treatment for HPV-positive tumours [*NCT02215265*]) trial.[55]

For patients with pathologic T1-2 node-negative disease and positive margins, there was no task force consensus on optimal management, and either postoperative RT or postoperative chemoradiation is considered appropriate. Patients may be appropriately managed with definitive RT alone because they have microscopic disease that is comparable with patients with small volume gross

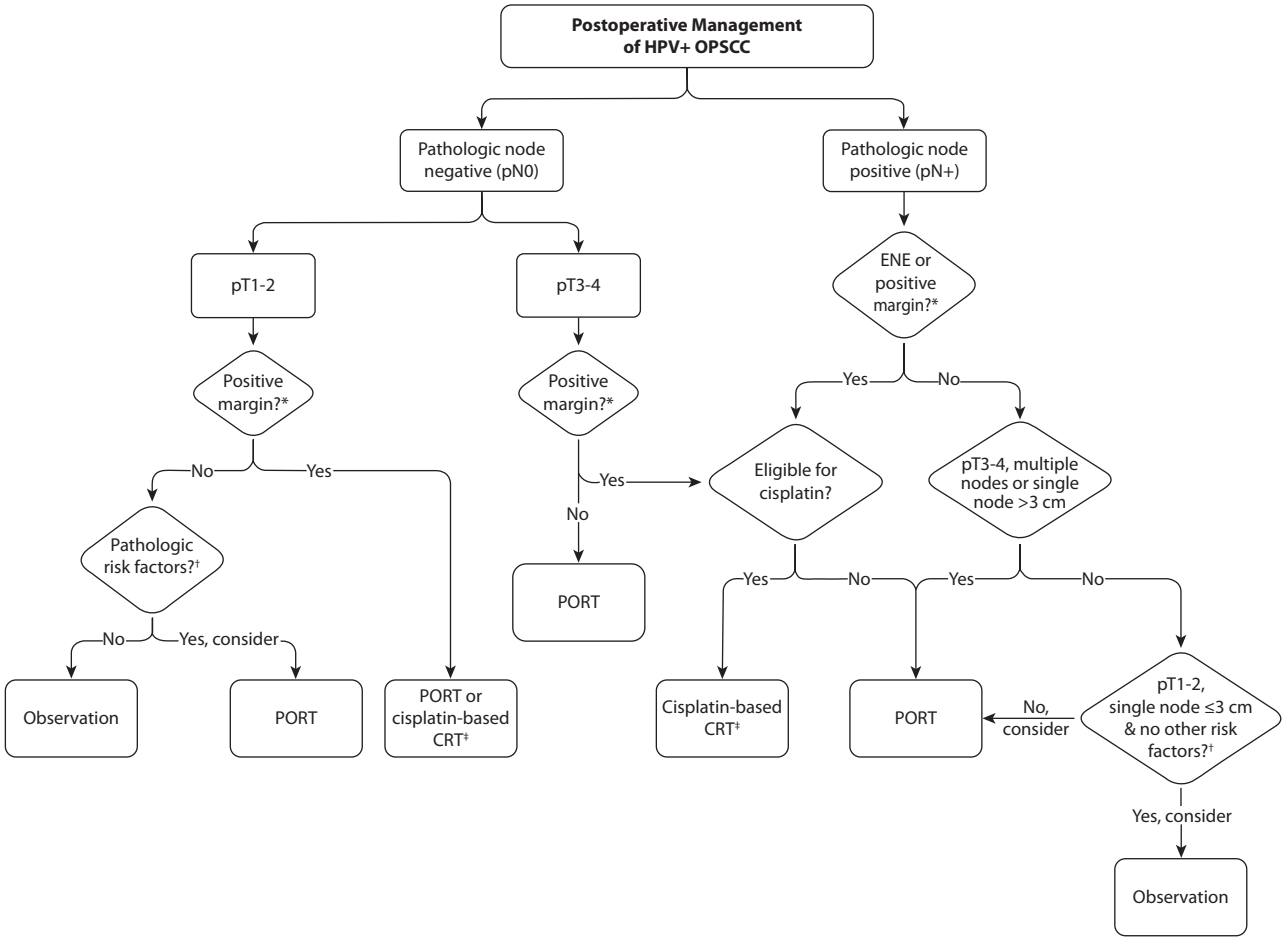

Figure 2 Postoperative management of HPV+ OPSCC.
Abbreviations: CRT = RT with concurrent system therapy; ENE = extranodal extension; HPV+ OPSCC =HPV-positive oropharyngeal squamous cell carcinoma; LVI = lymphovascular invasion; PNI = perineural invasion; PORT = postoperative radiation therapy; RT = radiation therapy.
*Positive margin is defined by the task force as tumor on ink. †Pathologic risk factors include close margins, LVI, and PNI. ‡100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly.
Where the strength of a recommendation is conditional, the term "consider" is used.

disease who can be treated with definitive RT alone, but the presence of a positive surgical margin may portend a higher risk of local recurrence. This discrete population is poorly represented in prospective trials, and thus, the potential benefits of concurrent systemic therapy must be weighed against toxicity risks to inform decision making.[40,42]

For patients with resected high-risk HPV-positive OPSCC that have a contraindication to concurrent cisplatin because of comorbidities or advanced age, there is no clear standard of care as RCTs showing a benefit to an alternative systemic regimen are lacking. For example, the use of concurrent carboplatin alone showed no benefit over RT alone in the postoperative setting.[56] Pending the published results of RCTs with noncisplatin agents including cetuximab (ie, RTOG 0920), no recommendation is made on concurrent systemic therapy for patients ineligible for cisplatin in the postoperative setting.

While there are no randomized studies comparing postoperative RT versus observation following surgical resection of OPSCC, there is a longstanding volume of evidence supporting indications for its use. For patients with more advanced disease, including those with pathologic T3-4 disease, an involved lymph node measuring >3 cm, or multiple lymph node involvement, postoperative RT is recommended based on multiple studies.[38-46] Postoperative RT is conditionally recommended for patients with perineural invasion (PNI) or lymphovascular invasion (LVI) given these factors' association with locoregional recurrence in historical studies that included non−HPV-associated HNSCC and their use as inclusion criteria for postoperative RT.[38,40] However, the task force recognizes the limited evidence that postoperative RT improves outcomes when PNI or LVI are the only indications for treatment, which was the rationale for the conditional strength of recommendation.

Historically, close margins (<5 mm from ink) have been an indication for postoperative RT for HNSCC.[40,43] Yet, this is controversial in the era of transoral approaches because of the anatomic constraints in achieving classic 5 mm margins with these surgeries. In the ECOG-ACRIN 3311 trial, which included only patients with HPV-positive OPSCC, postoperative RT was recommended for all patients undergoing transoral surgery with margins <3 mm from ink.[38] Retrospective series suggest that negative margins, no matter how close (tumor not on ink), may not compromise oncologic outcomes in patients with HPV-positive OPSCC.[48,57,58] Given the controversy surrounding close margins, the decision for postoperative RT with close but negative margins as a sole indication should be made in a multidisciplinary discussion with the resecting surgeon who can provide information regarding the anatomic and functional significance of the margin.

The nonrandomized evidence suggests that surgery alone is effective as a single-modality definitive therapy for most patients with pathologic T1-2 margin-negative disease and no more than 1 involved node measuring ≤3 cm without ENE, provided there are no pathologic risk factors including LVI, PNI, and close margins.[38,46,48-52] While this population is relatively small in comparison with all patients treated with primary surgical therapy, these studies of surgery alone in this cohort suggest highly favorable locoregional control outcomes.

KQ3: Dose-fractionation regimens and treatment volumes (Table 6)

See evidence tables in *Supplementary Materials*, Appendix E4 for the data supporting the recommendations for KQ3.

For patients receiving definitive and postoperative RT with or without systemic therapy for HPV+ OPSCC, what are the optimal dose-fractionation regimens and treatment volumes?

Although total dose de-escalation is an active research topic in HPV-positive OPSCC, no phase III RCT has demonstrated noninferiority of doses lower than 7000 cGy for gross disease. Multiple phase II trials explored dose de-escalation, using doses as low as 5400 cGy in an attempt to identify low-risk patient subsets by using restrictive inclusion criteria (eg, <10 pack-years of smoking or <T4 or N3 disease) and/or by using treatment response (eg, induction chemotherapy) to select patients for dose de-escalation.[34,76,77] Some trials used concurrent cetuximab,[77] which has since proven inferior to cisplatin.[8] Given the limitations of extrapolating from phase II trials, when treating with concurrent systemic therapy, the recommended dose for gross disease remains 7000 cGy (Table 7). An alternative approach of 6500 cGy in 30 fractions has been used in RCTs to determine the benefit of parotid[78] or dysphagia organs at risk (OAR) sparing,[79] but this regimen has not been compared with the established 7000-cGy regimen. An RCT, NRG-HN005 (*NCT03952585*), investigating de-escalation to gross disease is ongoing. The phase II portion of the trial randomized patients to 7000 cGy plus cisplatin versus 6000 cGy plus cisplatin versus 6000 cGy with nivolumab. However, in early 2023, the 6000-cGy plus cisplatin arm was closed after an interim futility analysis comparing it with 7000 cGy plus cisplatin did not achieve noninferiority; the specifics of this analysis have not been released. Of note, on both NRG Oncology RTOG 1016[8] and NRG-HN005, 7000 cGy was delivered in 6 fractions per week with concurrent cisplatin. It is therefore reasonable to consider either conventional fractionation in 5 fractions per week or moderately accelerated 6 fractions per week regimens used in these trials.

Patients with early-stage disease are often treated without systemic therapy. There is a range of acceptable dose-fractionation regimens for this population owing to the lack of high-quality data supporting the superiority of one regimen over another. Numerous trials have compared dose and fractionation regimens for patients being treated with RT alone, but none were limited to subsets of early-stage patients.[62] EORTC 22791 compared hyperfractionation with conventional fractionation in the pre-IMRT era and was limited to oropharyngeal cancer with more early-stage patients than most altered fractionation trials, but the benefit with hyperfractionation was only observed in larger primaries (T3 vs T2).[80] Most other trials of altered fractionation primarily include locally advanced patients because they were designed before the demonstrated benefit of concurrent cisplatin for this population.[62] The altered fractionation meta-analyses that suggest superiority of specific dose-fractionation regimens therefore cannot be generalized to the small subset of included patients with early-stage disease. Evidence for other dose-fractionation regimens come from nonrandomized phase II studies, which were later generalized to broader clinical practice.[18] A range of doses with conventional, hypofractionation, or accelerated fractionation is therefore considered acceptable for patients with early-stage disease receiving RT alone (Table 7).

Nodal levels that are clinically uninvolved yet at high risk of microscopic disease should be treated with RT, regardless of whether patients receive systemic therapy or not. However, there are limited prospective data that define the optimal dose to elective nodal regions[81] and variability in institutional practice as reported in retrospective studies.[70,74,82] Published RCTs in the IMRT era use doses as low as 4600 cGy EQD2 to clinically uninvolved nodal levels, justifying the lower dose in the current recommendation.[8,64] One RCT examined delivering 4000 cGy versus 5000 cGy EQD2 to elective nodal levels but was not powered for noninferiority.[81] This RCT

Table 6 Dose-fractionation regimens and treatment volumes

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence
Definitive treatment		
1. For patients with HPV+ OPSCC receiving definitive RT with concurrent systemic therapy, 7000 cGy in 33-35 fractions to gross disease is recommended.	Strong	High [8,10,23,59-62]
2. For patients with HPV+ OPSCC and T1-2 disease with either no positive nodes or a single positive node ≤3 cm receiving definitive RT alone, either 6600-7000 cGy with altered fractionation (accelerated or hypofractionated) or 6800-7000 cGy with conventional fractionation to gross disease is recommended.	Strong	Low [18,23,61,63,64]
3. For patients with HPV+ OPSCC receiving definitive RT, an EQD2 of at least 4600 cGy to clinically uninvolved nodal levels at risk for microscopic disease is conditionally recommended.	Conditional	Moderate [8,10,23,59,64]
4. For patients with HPV+ OPSCC and T1-2 disease with a single positive node >3 cm or multiple nodes receiving definitive RT alone, altered fractionation (accelerated or hyperfractionated) is conditionally recommended.	Conditional	Moderate [62,65]
5. For patients with HPV+ OPSCC and T3-4 disease with any nodal presentation receiving definitive RT alone, altered fractionation (accelerated or hyperfractionated) is recommended.	Strong	High [60-62,65,66]
Postoperative treatment		
6. For patients with HPV+ OPSCC receiving postoperative RT, 6000-6600 cGy with daily fractionation to regions of microscopically positive primary site surgical margins (ie, tumor on ink) and/or ENE is recommended.	Strong	High [38-43]
7. For patients with HPV+ OPSCC receiving postoperative RT, 5600-6000 cGy with daily fractionation to the postoperative primary bed and the pathologically involved nodal levels is recommended.	Strong	High [38,42,43,67]
8. For patients with HPV+ OPSCC receiving postoperative RT, an EQD2 of at least 5000 cGy to pathologically uninvolved nodal levels in the dissected pathologically node-positive neck is conditionally recommended.	Conditional	Expert Opinion
Treatment volumes: definitive and postoperative		
9. For patients with HPV+ OPSCC, eliminating areas with a low risk of microscopic disease from CTV targets is recommended.	Strong	Moderate [63,68-72]
10. For patients with HPV+ T1-2 palatine tonsil OPSCC confined to the tonsillar fossa and either no positive nodes or a single positive node ≤3 cm without ENE treated with definitive or postoperative RT, unilateral RT is recommended.	Strong	Low [17,19,73-75]
11. For patients with HPV+ T1-2 palatine tonsil OPSCC without base of tongue involvement treated with definitive or postoperative RT, unilateral RT is conditionally recommended for: • Disease involving minimal soft palate and/or • A single positive node >3 cm but ≤6 cm or multiple positive nodes, without evidence of ENE in all nodes. Implementation remark: Consideration for unilateral RT may include the number and size of involved nodes and extent of involved nodal levels.	Conditional	Low [17,19,74,75]

Abbreviations: CTV = clinical target volume; ENE = extranodal extension; EQD2 = equivalent dose in 2 Gy fractions, assuming α/β =10; GTV = gross tumor volume; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; RT = radiation therapy.

demonstrated a numerically higher, but not statistically significant, regional recurrence rate in the lower-dose arm but importantly, the same 2% rate of in-field regional recurrence was seen in both the 4000-cGy and 5000-cGy arms. Selection of the optimal dose for microscopic disease is also limited by the inability to accurately quantify doses delivered in the 2-dimensional (2-D) era. For example, 1 RCT using cobalt-60 and 2-D planning compared 5 with 6 fractions per week and allowed a minimum of 4400 cGy as elective dosing.[65] However, anatomic variation within and between patients means that the delivered dose could have varied substantially from the prescribed dose at depth and makes it challenging to use historic data to identify optimal microscopic dose paradigms. Given these considerations

Table 7 Fractionation types for definitive radiation therapy

Type	Dose per Fraction	Total Dose to Gross Disease	Total Time	Fraction Number	Fractions per Week
Conventional[10,23,59]	200 cGy	6800−7000 cGy	7 weeks	34-35	5
Hyperfractionation[60,62]	120 cGy	7440−8160 cGy	7 weeks	62-68	10
Accelerated[8,60,61]	150-200 cGy	6800−7200 cGy*	6 weeks	34-42	Varies (5-10)*
Hypofractionation[18]	210-220 cGy	6600−7000 cGy	6-6.5 weeks	30-33	5

*The most common schedule uses 200 cGy for all fractions with 6 fractions per week. If delivered, the 7200-cGy regimen should emulate the accelerated concomitant boost schedule (180 cGy once daily fraction, 5 days per week, and 150 cGy to a boost field as a second daily treatment for the last 12 treatment days to a total dose of 7200 cGy in 42 fractions over 6 weeks).[60]

and that dose to elective nodal regions is rarely a primary study question, the strength of the recommendation is conditional.[8,10,23,59,64]

For patients with locally advanced disease who are ineligible for concurrent systemic therapy, altered fractionation is recommended (Table 7).[60,61,63,66] The MARCH (Meta-analysis of radiotherapy in carcinomas of head and neck) meta-analysis demonstrates an overall survival benefit with hyperfractionation but no other altered fractionation regimens.[62] Despite the superiority of hyperfractionation in the meta-analysis, there are several research and practice limitations that preclude recommending hyperfractionation over other regimens. First, the altered fractionation trials included in the MARCH meta-analysis were heterogeneous with respect to many factors, including cancer site. In general, trials of moderately accelerated fractionation (eg, 7000 cGy in 6 fractions per week) included larger proportions of patients with larynx cancer than hyperfractionation trials.[62] As recurrences in laryngeal cancer are more likely to be salvageable than cancers in other sites, benefits in locoregional control may be less likely to translate to an overall survival benefit.[62] However, the magnitude of the locoregional control benefit was larger for hyperfractionation than moderate acceleration, suggesting hyperfractionation might be superior in clinical trial settings.[62] In clinical practice, the twice daily treatment of hyperfractionated regimens, with the requirement of at least 6 hours between fractions, can be logistically challenging if not prohibitive for patients. The patient population now eligible for such treatment (eg, ineligible for systemic therapy) differs from patients enrolled on trials of altered fractionation because most trial patients had good performance status and lacked severe comorbidities. They were enrolled on altered fractionation trials at the time simply because the benefit of concurrent systemic therapy had not been demonstrated yet. Data also suggest increased short-term toxicity with hyperfractionation, which makes tolerance more difficult for patients who are not candidates for systemic therapy.[80]

Given the logistical issues and potential for increased short-term toxicity with hyperfractionation, moderately accelerated regimens such as 6 fractions per week are an acceptable alternative. The updated p16-specific analysis of the DAHANCA 6/7 trials confirms a benefit to this regimen in patients with p16-positive disease.[61] Fractionation trials also suggest altered fractionation in general, and moderately accelerated fractionation specifically, may be more beneficial for locally advanced primary sites than for nodal disease.[60-62,65,66] Both the original and the updated MARCH meta-analyses found lower (ie, superior) hazard ratios for local versus locoregional control.[62,83] Given this, altered fractionation is recommended for T3-4 disease and is conditionally recommended for earlier T-stages with advanced nodal stage.[60-62,65,66]

In the postoperative setting, landmark RCTs examining postoperative chemoradiation for ENE or positive margins include a range of doses between 6000 and 6600 cGy, so this range is considered acceptable.[39,42,43] A foundational RCT from University of Texas - MD Anderson Cancer Center conducted in the pre-IMRT and pre-HPV era shows that doses above 5760 cGy did not improve tumor control, leading to the recommendation of 5600 to 6000 cGy for the resection bed and involved, resected nodal levels.[43] The 5760-cGy dose was delivered over 32 fractions, which is approximately equivalent to 5600 cGy in 28 fractions, after accounting for fractional dose and treatment time. ECOG-ACRIN 3311 randomized patients with resected HPV-positive OPSCC with negative margins, <5 positive nodes, and ≤1mm ENE to postoperative RT with a total dose of 6000 cGy versus 5000 cGy, showing no difference in any oncologic outcome.[38] However, this trial is the only published multi-institutional study using 5000 cGy, which was not powered for noninferiority, and the numbers of patients with commonly seen adverse features (eg, microscopic ENE, multiple positive nodes) are too small to support a recommendation of 5000 cGy at this time. Although single-institutional studies have examined avoidance of the postoperative bed when treating the neck postoperatively, none are RCTs, and RT dose from adjacent nodal levels can result in delivery of higher doses than expected to the postoperative bed.[57,84,85] Treatment to the primary surgical bed is recommended when postoperative RT is delivered.[38,42,43,67] The dose to the dissected, uninvolved

Table 8 Target volume guidance

Margin Type (Refs)	Expansion Size	Requirements/Comments
GTV to high-risk CTV **OR** highest dose level CTV[70-72,86]	≤5 mm	The high-risk CTV expansion does not eliminate the need to treat microscopic disease beyond the visible GTV
CTV to PTV[70,71]	3-5 mm	Daily CBCT is recommended for PTV margins <5 mm
Nodal level that typically can be omitted		
Contralateral high level II (superior to where the posterior belly of the digastric muscle crosses the internal jugular vein), retrostyloid and retropharyngeal[63,68,69]	N/A	• Clinically and/or pathologically node-negative contralateral neck **AND** • No extensive involvement of the soft palate **AND** • No involvement of posterior pharyngeal wall OR nasopharynx **AND** • No involvement of the ipsilateral retrostyloid and/or retropharyngeal nodes
Level IB*[,63,88]	N/A	• Clinically and/or pathologically negative neck **AND** • No oral cavity involvement (includes anterior tonsillar pillar)
Level V*[,89]	N/A	• Clinically and/or pathologically negative neck **AND** • No involvement of nasopharynx and/or hypopharynx

Abbreviations: CBCT = cone beam computed tomography; CTV = clinical target volume; GTV = gross tumor volume; N/A = not applicable; PTV = planning target volume.
*Each side of the neck is considered separately.

neck (5000 cGy EQD2) is higher than that for the clinically negative undissected neck because of the theoretical concerns about hypoxia in the postoperative setting, and this dose was used in each RT arm of ECOG-ACRIN 3311 for negative nodal levels.[38] Moreover, there are limited prospective data supporting the efficacy of elective neck doses below this threshold.

In head and neck RT, the need to treat occult microscopic disease extends to both tissues around the primary cancer and the nodal levels without pathologically enlarged lymph nodes. Minimizing RT dose to normal tissue is expected to improve acute and long-term toxicity. For example, an analysis of the De-ESCALaTE (Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in HPV+OPSCC) trial suggests a 10-mm gross tumor volume (GTV) to high-risk clinical target volume (CTV) (7000 cGy, "CTV7000") margin did not increase recurrence when compared with irradiating the whole oropharynx to full dose.[72] A retrospective study showed reduced toxicity without increased recurrence when reducing the GTV to CTV7000 margin from 10 mm to 6 mm.[71] There are substantial data in other randomized trials[8,34] and studies[86] using ≤5 mm margins from GTV to CTV7000. This approach was endorsed by an international consensus guideline that recommended a 5-mm expansion of the GTV to make the high-risk CTV7000.[87] Some institutions use a 0-mm margin from GTV to high-risk CTV (ie, 7000 cGy). Therefore, GTV to CTV7000 margins may be ≤5 mm.[70] However, there is still a need to treat microscopic disease beyond the radiologically visible primary tumor using a CTV (Table 8).[86]

There are limited prospective data supporting the oncologic safety of sparing elective nodal levels in HPV-positive OPSCC.[86] However, the omission of certain levels—specifically level IB, V, and contralateral retrostyloid/retropharyngeal nodes—is supported by decades of clinical experience combined with modern retrospective series showing a low risk of recurrence.[63,68,69,88-90] The omission of specific nodal levels is specified if all the described conditions are met, with the expectation of a low risk of recurrence and improved ability to spare salivary glands and other normal tissue (Table 8). The risk of nodal recurrence may be low even if only 1 or 2 of the criteria for omitting a specific nodal level are met (eg, omitting level IB in selected cases with no oral cavity involvement but low volume rather than negative ipsilateral nodal disease). However, the task force recommendations reflect the lack of prospective data and the potential for selection bias in the published data.

There is also a lack of randomized data to define the criteria for omission of RT to the contralateral neck in palatine tonsillar cancer. Multiple series suggest that the risk of contralateral involvement is very low if the disease is confined to the tonsillar fossa (ie, not involving the base of tongue or soft palate) and if there is minimal nodal burden (N0 or single node ≤3 cm).[17,19,68-75] A retrospective series demonstrated that the risk of contralateral nodal involvement increases with greater nodal burden or with extension beyond the tonsillar fossa, but quantifying this risk is extremely challenging.[75] This difficulty is acute in the postoperative setting as the radiation oncologist may not have assessed the patient for tongue base and soft palate involvement before surgery. In cases when preoperative assessment is not possible, a detailed discussion with the surgeon about the extent of soft palate or base of tongue involvement is important.

Even when soft palate or tongue base extension can be assessed by the radiation oncologist, the decision to treat unilaterally remains controversial. Although the Princess Margaret series used a cutoff of <1 cm involvement of the soft palate or base of tongue, in practice, it is difficult to obtain accurate measurements of invasion.[17,75] Some series included and quantified soft palate involvement, so there is stronger quality of evidence for considering unilateral treatment when soft palate involvement is minimal.[19,74] Patients with base of tongue involvement are not included in recommendations to avoid the contralateral neck because of its bilateral lymphatic drainage, and the few published series quantifying outcomes when palatine tonsillar cancer involves the base of tongue.

Unilateral treatment of AJCC-7 stage N2a and N2b disease is one of the most controversial topics in tonsillar RT. Although multiple series report lower rates of contralateral recurrence among patients with this nodal burden,[19,74] no series describes delivering unilateral treatment to an unselected cohort of patients with N2a and N2b disease. Furthermore, none of the published institutional series describe reproducible criteria for when unilateral treatment might be acceptable in this population (eg, nodal size cutoffs, number of nodes, and level of nodal involvement). Indeed, the data reflect this variability because 1 series shows that the median and maximum number of nodes involved is nearly identical for patients treated unilaterally versus bilaterally.[91] The data therefore suggest there is a subset of N2a and N2b patients for whom unilateral treatment is acceptable but, unfortunately, that subset cannot be defined further. Given this uncertainty, bilateral treatment in select cases, such as nodes >3 cm with gross extranodal spread, is appropriate. To minimize toxicity in patients treated bilaterally, clinicians can refer to Table 8, which identifies scenarios for omission of uninvolved contralateral levels IB, V, and the retropharyngeal/high level II/retrostyloid nodes, which allows for sparing of the contralateral parotid and submandibular glands.

KQ4: Preferred techniques and appropriate normal tissue considerations (Table 9)

See evidence tables in *Supplementary Materials*, Appendix E4 for the data supporting the recommendations for KQ4.

For patients receiving definitive and postoperative RT with or without systemic therapy for HPV+ OPSCC, what are the preferred techniques and appropriate normal tissue considerations?

For patients with HPV+ OPSCC receiving definitive or postoperative RT, IMRT is recommended over 3-dimensional conformal radiation therapy (3-D CRT) because of improved OAR sparing and dose homogeneity.[59,78] Delivery of RT in the definitive or postoperative setting can be accomplished using a variety of techniques including 3-D CRT, IMRT, or proton therapy (which can include passive scattering, pencil beam scanning, or intensity modulated proton therapy). Four RCTs compared 3-D CRT and IMRT for head and neck cancer and included patients with oropharyngeal cancer, though not exclusively, and all studies showed an improvement in xerostomia outcomes.[59,78,102,103] One trial[59] attempted to see if dose escalation with IMRT (7500 cGy) could improve locoregional control over 3-D CRT (7000 cGy), while the other 3 focused on using IMRT for xerostomia reduction.[78,102,104] Patients included in these trials received a variety of treatments, including hypofractionated RT alone, postoperative RT, or definitive chemoradiation. Importantly, no trial shows a decrement in locoregional control, a concern with the increased conformality and steep dose-gradients of IMRT plans. There are no prospective data comparing outcomes of IMRT with proton therapy, although studies are in progress *(NCT02923570* and *NCT01893307)*.

When planning IMRT for oropharyngeal cancer, balance is needed between sufficient dose coverage to the target and minimizing dose to the OARs. In general, coverage of the high-dose PTV is prioritized, though this may necessitate a balance when gross disease approaches the spinal cord or brainstem. In contrast, it may be appropriate to sacrifice coverage of the lower risk PTV to meet OAR constraints. Minimizing heterogeneity and hotspots within the target volumes is expected to reduce the risk of acute and late toxicity such as mucositis, osteoradionecrosis, and soft tissue injury. Therefore, dose homogeneity of the target volume should be optimized, moderating the maximum dose and constraining it to within the target volume. Physicians should attempt to limit the dose to <107% (preferred) but no more than 110% of the maximum prescription dose.

Optimizing dose to normal tissues is a priority in planning IMRT cases for oropharyngeal cancer, which requires the contouring of all relevant OARs. Consensus guidelines for CT-based delineation of head and neck OARs have been published.[105] Because there remains variation in OARs definitions and reporting, Table 10 includes the most common OARs with guidance on dose constraints and contour considerations for both bilateral and unilateral neck treatment. Because OARs may overlap with targets in the head and neck region, using the entire OAR in the IMRT optimization process could lead to under coverage of targets or inappropriate heterogeneity. Often, a planning structure is created (OAR subtracting the PTV), with either approach considered reasonable during the treatment planning process. Although Table 10 provides guidance for acceptable constraints for most patients, lower doses should be delivered if they are achievable.

In the IMRT optimization process, preserving neurologic function is an important goal. A detailed discussion

Table 9 Preferred techniques and appropriate normal tissue considerations

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence
1. For patients with HPV+ OPSCC receiving definitive or postoperative RT, IMRT over 3-D CRT is recommended.	Strong	High [59,78]
2. For patients with HPV+ OPSCC receiving definitive or postoperative RT, reducing dose to xerostomia OARs is recommended, as target coverage permits. Implementation remark: Xerostomia OARs include parotid glands, submandibular glands, and oral cavity (Table 10).	Strong	High [78,90,92]
3. For patients with HPV+ OPSCC receiving definitive or postoperative RT, reducing dose to dysphagia/swallowing OARs is recommended, as target coverage permits. Implementation remark: Swallowing OARs include pharyngeal constrictors, cervical esophagus, larynx, and oral cavity (Table 10).	Strong	Moderate [93-98]
4. For patients with HPV+ OPSCC receiving definitive or postoperative RT, reducing dose to the mandible to minimize risk of osteoradionecrosis is recommended, as target coverage permits.	Strong	Moderate [99-101]
5. For patients with HPV+ OPSCC receiving definitive or postoperative RT, optimizing RT prescription dose homogeneity in target volumes is recommended.	Strong	Expert Opinion

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; IMRT = intensity modulated radiation therapy; KQ = key question; OARs = organs at risk; RT = radiation therapy.

of toxicity risk and RT dose-volume exposure to the spinal cord and brainstem is found in QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) because prospective data are sparse.[106] There may be value in reducing dose to the spinal cord and brainstem below their absolute tolerances because Lhermitte syndrome[107] and radiation-induced nausea[108] are associated with higher dose to these structures, respectively. Prospective randomized trials demonstrate reducing mean dose to the (contralateral) parotid gland decreases the risk of late xerostomia.[59,78,102,103] In addition, prospective and retrospective data suggest that sparing of submandibular glands and oral cavity (minor salivary glands) may also decrease the risk of late xerostomia and acute mucositis.[90,109] Clinicians should aim to lower doses to OARs as much as reasonably possible without compromising target coverage. It is easier to spare these structures when only treating one side of the neck; differential constraints are proposed in Table 10 for unilateral and bilateral neck treatment.

Dose reduction to swallowing OARs is associated with a reduced risk of dysphagia, as shown in an RCT and multiple retrospective studies.[79,93,95,97,98,110,111] Swallowing OARs include the oral cavity, pharyngeal constrictors, and larynx. Endpoints in studies examining dysphagia following IMRT for HNSCC include patient-reported swallow function,[79,95] observer-reported dysphagia,[93,97,110] aspiration,[95,110] stricture,[95] or gastrostomy tube dependence.[98]

Moderate-to-high doses of RT to the mandible contribute to the risk of osteonecrosis, with the data suggesting that both maximum point doses and lower-dose baths contributing to toxicity.[99-101,112] When possible, minimizing the volume of mandible receiving doses ≥5000 and/or 6000 cGy and avoiding a point dose >105% prescription may reduce risk of any grade osteoradionecrosis, including grade 4 osteoradionecrosis, which requires major surgery.[99-101] Reduction in dose to the mandible is also associated with a lower rate of tooth loss.[113,114]

Tinnitus or hearing loss may be a consequence of cisplatin systemic therapy but can also be affected by the RT dose to the hearing apparatus.[115] Minimizing the dose to the cochlea may reduce the risk of grade 2 or greater tinnitus or hearing loss, particularly when given in combination with concurrent cisplatin.[116] For most patients with oropharyngeal cancer, a mean dose <2000 cGy in the ipsilateral or node-positive neck and dose <500 cGy in the contralateral node-negative neck can often be achieved, based on expert opinion of the task force.

In general, reducing RT dose to normal tissue may lead to less acute and late effects of treatment. This is balanced with the need to provide adequate target coverage. Several anatomic structures including the thyroid gland, carotid arteries, and brachial plexus are in proximity to clinical targets but have less data to guide tissue constraints. Hypothyroidism is a frequent late effect of RT and usually occurs within 1 to 2 years after treatment and is associated primarily with the mean dose to the thyroid, though this may be modified by the thyroid volume.[117-119] Of note, a pooled analysis of 2 RCTs of 3-D CRT compared with IMRT demonstrates an increase in subclinical hypothyroidism with IMRT.[120] However, the thyroid was not constrained in treatment planning of IMRT cases, limiting the utility of this evidence. The brachial plexus may receive high RT doses if in proximity to PTV, which can

Table 10 Guidance on dose constraints for xerostomia, swallowing, mandible, and neurologic OARs*

OARs (Refs)	Dose Constraints†		Contour Considerations	Clinical Endpoint
Xerostomia OARs				
	Bilateral neck treatment	*Unilateral neck treatment*		
Parotid gland[90,124-126]	Contralateral mean 1800-2600 cGy	Contralateral mean ≤700 cGy	• Prioritize sparing of the gland in the node-negative neck • Entire gland	Salivary flow, patient-reported xerostomia
Submandibular gland[90]	Contralateral mean 3000-3900 cGy	Contralateral mean ≤1000 cGy	• Prioritize sparing of the gland in the node-negative neck • Entire gland	Salivary flow, patient-reported xerostomia
Oral cavity[90,92]	Mean 2000-3000 cGy	Mean ≤2000 cGy	• If evaluation metric *excludes* PTV • Includes lips, buccal mucosa, oral tongue, floor of mouth and hard palate	Xerostomia, mucositis, PEG-dependence
	Mean 3000-5000 cGy	Mean ≤3000 cGy	• If evaluation metric *includes* PTV	
Swallowing OARs				
Pharyngeal constrictors (superior & middle)[93,95,97]	Mean 3500-5000 cGy	Mean 2500-4000 cGy	• If evaluation metric *excludes* PTV	Aspiration, dysphagia
	Mean 4500-6000 cGy	Mean 3500-4500 cGy	• If evaluation metric *includes* PTV	
Pharyngeal constrictors (inferior)[97]	Mean 2000-3500 cGy	Mean 1500-2500 cGy	• Evaluation metric *includes* PTV	Aspiration, dysphagia, stricture
Cervical esophagus[93,96]	Mean 2000-3500 cGy	Mean 1500-2500 cGy	• Evaluation metric *includes* PTV • Cervical esophagus structure should not extend to >1 cm below the most inferior PTV	Stricture, dysphagia
Larynx[93,94]	Mean 2500-4000 cGy	Mean 1500-2500 cGy	• Evaluation metric *includes* PTV • Include supraglottic and glottic larynx	Aspiration, dysphagia
Mandible[99-101]	• Max point dose ≤100% highest prescription dose outside PTV, ≤105% prescription inside PTV (avoid hotspots)	• Max point dose ≤100% highest prescription dose outside PTV, ≤105% highest prescription inside PTV (avoid hotspots)	• Whole mandible should be included in the structure	Osteoradionecrosis
	• Minimize V50 and V60 (volume of mandible receiving ≥5000 cGy and ≥6000 cGy, respectively)	• Minimize V50 and V60 (volume of mandible receiving ≥5000 cGy and ≥6000 cGy, respectively)	• Point dose defined to 0.03 cc volume	

(*Continued*)

Table 10 (*Continued*)

OARs (Refs)	Dose Constraints[†]		Contour Considerations	Clinical Endpoint
Neurologic OARs				
Brainstem[‡]	Max point dose 3500-5400 cGy	Max point dose 3500-5400 cGy	Point dose defined to 0.03 cc volume	Myelopathy, nausea
Spinal cord[‡]	Max point dose 3500-4500 cGy	Max point dose 3500-4500 cGy	Point dose defined to 0.03 cc volume	Myelopathy
Cochlea[†]	Mean ≤2000 cGy	Contralateral mean ≤500 cGy	N/A	Hearing loss

Abbreviations: Max = maximum; N/A = not applicable; OARs = organs at risk; PEG = percutaneous endoscopic gastrostomy; PTV = planning target volume.

[*]Dose ranges are provided to reflect typical achievable doses given variation in tumor extent, and to encourage limiting dose to OARs while preserving adequate target coverage. This table is a combination of evidence-based constraints and expert opinion, assuming 28 to 35 once daily fractions given with or without systemic therapy.

[†]Exceeding these maximum constraints may be necessary to adequately treat the targets of therapy, according to the clinical judgment of the treating physician.

[‡]Planning risk volumes with a 3 to 5 mm expansion are often employed in the planning process, with a max point dose of ≤5000 cGy for the spinal cord and ≤5600 for the brainstem.

increase the risk of brachial plexopathy.[121] RT to the neck is associated with carotid artery stenosis and stroke.[122,123] In a large retrospective study, there was no clear dose-response between carotid dose and risk of carotid artery stenosis as evaluated by ultrasound.[122] Dose reduction to the carotid arteries is often limited by the proximity to the elective nodal basins at risk. Future work may identify novel paradigms to screen and treat survivors for carotid stenosis.

KQ5: Preferred approaches for initial posttreatment restaging and management of the neck (Table 11)

See evidence tables in *Supplementary Materials*, Appendix E4 for the data supporting the recommendations for KQ5.

Following definitive or postoperative RT with or without systemic therapy for patients with HPV+ OPSCC, what are the preferred approaches for initial posttreatment restaging and management of the neck?

After completion of definitive RT with or without concurrent systemic therapy, imaging is recommended to assess treatment response at the primary site and neck.[127-135] Historically, patients with node-positive OPSCC received a planned neck dissection, which was associated with both acute and chronic morbidity. This practice waned as retrospective studies showed that patients with a complete response by contrast-enhanced CT and/or fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) have low rates of recurrence without a neck dissection.[139-141] For patients with node-positive disease, prospective studies demonstrated a high negative predictive value (92%-97%)—a low false negative rate—of a PET-CT 3 months after completion of definitive chemoradiation.[130,142] The PET-NECK (A multicentre randomized Phase III non-inferiority trial comparing a positron emission tomography-computerised tomography-guided watch-and-wait policy with planned neck dissection in the management of locally advanced [N2/N3] nodal metastases in patients with squamous cell head and neck cancer) RCT showed PET-CT could be used to select patients who do not require a neck dissection after definitive chemoradiation.[127] This study included a large proportion of patients with HPV-positive OPSCC, all with AJCC-7, N2-3 disease (ie, a single node >3 cm or multiple positive nodes). Patients were randomized to receive a planned neck dissection or a PET-CT 3 months after completion of chemoradiation. Those with a complete response on PET-CT did not undergo neck dissection. The PET-CT arm had noninferior overall survival, similar locoregional control, and lower rates of surgery and was more cost effective.[127] Notably, in PET-NECK, <5% of patients had N3 disease, and therefore, direct extrapolation of the results to this subgroup is controversial.

For patients with node-negative disease, there is less evidence demonstrating superiority of one imaging modality over another for response assessment at the primary site. PET-CT has a negative predictive value for response at the primary site of greater than 90%,[135] like that of the negative predictive value for nodal disease.[143] A prospective study showed that the sensitivity of PET-CT was greater at the primary site (82%) than at the lymph nodes (45%), suggesting that PET-CT may be particularly useful for identifying residual disease at the primary.[143] These data support the role of PET-CT as a useful imaging modality for response assessment.

Table 11 Preferred approaches for initial posttreatment restaging and management of the neck

KQ5 Recommendations	Strength of Recommendation	Quality of Evidence
1. For patients with HPV+ OPSCC and node-positive disease receiving definitive RT with or without concurrent systemic therapy, reassessment with PET-CT approximately 3 months after completing treatment is recommended.	Strong	Moderate [127-133]
2. For patients with HPV+ OPSCC and node-negative disease receiving definitive RT with or without concurrent systemic therapy, reassessment with cross-sectional imaging approximately 3 months after completing treatment is recommended. Implementation remark: Imaging modalities include PET-CT and/or contrast-enhanced CT or MRI.	Strong	Low [128,129,131,132,134,135]
3. For patients with HPV+ OPSCC who undergo surgery with or without postoperative RT, reassessment with cross-sectional imaging approximately 3-6 months after completing treatment is recommended. Implementation remark: Imaging modalities include PET-CT and/or contrast-enhanced CT or MRI.	Strong	Expert Opinion
4. For patients with HPV+ OPSCC and node-positive disease receiving definitive RT with or without systemic therapy, neck dissection is recommended when PET-CT approximately 3 months after treatment reports convincing evidence of residual or progressive isolated regional disease.	Strong	Moderate [127,130]
5. For patients with HPV+ OPSCC and node-positive disease receiving definitive RT with or without systemic therapy, either neck dissection or short interval repeat imaging is recommended when PET-CT approximately 3 months after treatment reports an equivocal response in regional disease. Implementation remark: Repeat imaging in 2-3 months with PET-CT and/or contrast-enhanced CT or MRI may avoid unnecessary surgical intervention.	Strong	Moderate [127,133,136-138]

Abbreviations: CT = computed tomography; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; RT = radiation therapy.

Prospective and retrospective data also suggest that PET may be more accurate than contrast-enhanced CT or magnetic resonance imaging (MRI) at diagnosing recurrence at the primary site.[129,134] However, a meta-analysis did not find superiority of PET over MRI.[144] Cross-sectional imaging with PET-CT and/or contrast-enhanced CT or MRI is recommended for patients with node-negative disease because of the limited data supporting one modality over another in assessing response at the primary site for patients with node-negative disease.[128,129,131,132,134,135]

The timing of PET-CT influences the frequency of a reported inconclusive or equivocal response CT.[131,143,145,146] The diagnostic accuracy increased and proportion of inconclusive results declined from 26% to 8.4% when PET was done 0 to 3 months versus 3 to 6 months after treatment.[131] If imaging is done prematurely, there is an increased risk of equivocal and false-positive findings that can lead to unnecessary biopsies or surgical procedures.[147] Therefore, posttreatment imaging assessment at approximately 3 months after completion of definitive RT and/or chemoradiation is recommended, provided the clinical follow-up and examination is reassuring (eg, decreasing nodal size and symptom burden).[127-134]

The optimal method of defining an equivocal radiologic response to treatment is not yet standardized.[146] The PET-NECK trial defined an equivocal response as persistently enlarged nodes and mild-to-no FDG uptake or mild FDG uptake in normal nodes.[127] Use of standardized PET-CT reporting criteria, such as the Hopkins criteria, reduces the number of equivocal reports and improves interreader agreement.[130,148] Discussion of the optimal method of reporting is beyond the scope of the guideline.

For patients treated with definitive surgery with or without postoperative RT, there are no prospective studies addressing the optimal timing or modality of imaging reassessment. Several studies identified in the literature search include patients treated with definitive surgery.[131,132,149] However, there is insufficient evidence to routinely recommend one imaging modality over another. After surgery and postoperative RT, false-positive findings can occur at the primary site or neck when imaging is performed too early.[149] Despite the limited data, there was consensus based on expert opinion that obtaining baseline imaging 3 to 6 months after completion of all local therapy is important, with cross-sectional imaging including PET-CT and/or contrast-enhanced CT

neck or MRI. This time frame provides baseline posttreatment imaging, and it may minimize the risk of false-positive findings because of acute posttreatment changes.

Neck dissection is recommended when patients with initially positive nodes have convincing evidence of residual or progressive neck disease on restaging imaging.[127,133,150] However, an equivocal response to treatment based on PET-CT requires more nuance in clinical decision making and therefore the task force made a conditional recommendation for a neck dissection or repeat imaging in this scenario.[127,133,136-138,150] In the PET-NECK trial, patients with an equivocal PET-CT received a neck dissection, and based on this study and a preference to minimize the risk of undertreating residual disease, surgery is one of the conditional recommendations when faced with equivocal findings.[127,133,136-138,150] However, there is variability in practice regarding management of the equivocal PET-CT response because lymph nodes for HPV-positive OPSCC frequently take >3 months to return to normal size. One retrospective study showed that 51% of patients with HPV-positive OPSCC had persistently enlarged nodes >1.0 cm on CT or MRI beyond 12 weeks after chemoradiation.[151] Only a quarter of the patients subsequently selected for neck dissection had pathologically positive nodes. Similarly, another study showed that among patients with an incomplete or equivocal PET-CT response in the nodes, only 28% selected for neck dissection had residual disease.[152]

Published alternative approaches to the equivocal PET response include careful follow-up imaging with repeat CT neck or PET-CT in 2 to 3 months to avoid unnecessary interventions.[137,145,153] Careful imaging and clinical follow-up are essential to ensure resolution of equivocal findings if immediate neck dissection is deferred. Although a PET-CT provides valuable functional imaging, a contrast-enhanced CT and/or MRI offers enhanced anatomic detail. Retrospective data suggest that the combination of a contrast-enhanced CT and PET can increase diagnostic accuracy after chemoradiation.[154] Therefore, repeat imaging within 2 to 3 months is also considered an appropriate response to equivocal findings on restaging PET-CT.

There is significant interest in alternative or complementary paradigms to restage patients with HPV+ OPSCC using circulating tumor DNA. The presence of viral-specific gene sequences allow for rapid assessment of cell-free plasma circulating tumor HPV DNA (ctHPVDNA) using polymerase chain reaction[155,156] or HPV sequencing.[157] Approximately 90% of patients with HPV-positive OPSCC have detectable plasma ctHPVDNA for the 5 most common HPV strains (16, 18, 31, 33, and 35) at diagnosis.[158,159] Potential future applications of ctDNA include response assessment, response-prediction, and surveillance.

Before routine integration in the clinic, prospective studies are needed to define the kinetics of ctHPVDNA clearance and demonstrate utility in clinical decision making after treatment. Baseline ctHPVDNA is not detectable in approximately 10% of patients with HPV-positive OPSCC, limiting its use in such patients.[156,158] Additionally, assay standardization is needed before widespread incorporation into clinical management. The diagnostic performance of ctHPVDNA for accurate initial treatment response assessment has not been compared with that of imaging-based response assessment in prospective data. Therefore, posttreatment imaging alone remains the recommended method of response assessment after curative-intent treatment.[127-132,134,135]

Conclusions and Future Directions

The multidisciplinary team faces a broad range of management decisions in determining the optimal treatment of a patient with HPV-positive OPSCC. One of the important decisions in treating any patient with OPSCC is whether to use concurrent systemic therapy and, if so, which regimen. For patients receiving definitive or postoperative RT with concurrent systemic therapy, the long-established standard of cisplatin remains the evidence-based recommendation, but additional trials are needed for cisplatin-ineligible patients.[8,9,11,23,24,38-42] For patients with locally advanced disease, active multicenter RCTs are evaluating the optimal cisplatin dosing regimen (*NCT05050162*) and the role of concurrent immunotherapy with RT for definitive management (eg, NRG-HN005 [*NCT03952585*] and Keynote 412 [*NCT03040999*]). For patients with early-stage HPV-positive OPSCC treated with definitive RT, there is debate over which patients benefit from systemic therapy, and in the absence of pending clinical trials, such decisions will likely remain highly individualized. Ongoing work to determine the lowest acceptable definitive and postoperative RT doses (eg, NRG-HN005 [*NCT03952585*] and PATHOS [*NCT02215265*]), especially in the context of published data from de-escalation studies, has the potential for significant impact in this patient population.[34,38] In the postoperative setting, ECOG 3311 opened the door to reducing the dose of postoperative RT, but confirmatory data are needed before establishing a new standard of care.[55] An ongoing RCT aims to test lowering the postoperative RT dose and omitting cisplatin chemotherapy for patients with traditional indications of positive margins and/or ENE.[55] The proverbial stakes are high with dose reduction because the potential improvement in acute and late toxicity may not offset an increased risk of locoregional progression and unknown salvage outcomes. Given these concerns and the absence of successful phase III RCT data on lower definitive and postoperative doses, "standard" doses are still recommended for patients treated with RT (Table 6).

One of the most exciting innovations in managing HPV-positive OPSCC is the ability to measure ctHPVDNA, which holds the potential to reimagine not only surveillance protocols but also definitive and postoperative treatment decisions as a function of viral clearance.[158] Although biomarkers may play a role in future management of HPV-positive OPSCC, the existing data are either retrospective or insufficient to draw definitive conclusions; the task force looks forward to additional data in this space to guide future recommendations.

The preferred primary treatment modality is inadequately evaluated with prospective data. The competing therapeutic ratios of definitive RT versus surgery are continuously evolving because de-escalation approaches may constantly alter the relative risks and benefits of one local therapy over another. In the absence of a phase III comparison, the optimal choice of local therapy will likely remain highly personalized. Finally, trials of HPV-positive OPSCC have largely enrolled White male patients. Patients in RTOG 1016[8] and HN002[34] comprised 90% male, 93% White patients and 84% male, 92% White patients, respectively. Based on these data, it is unclear how and to what extent these prospective data can be extrapolated to other racial, sex, and socioeconomic settings. Additional work is clearly needed to understand the impact of and optimal treatments for HPV-positive OPSCC in diverse populations.

Disclosures

All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

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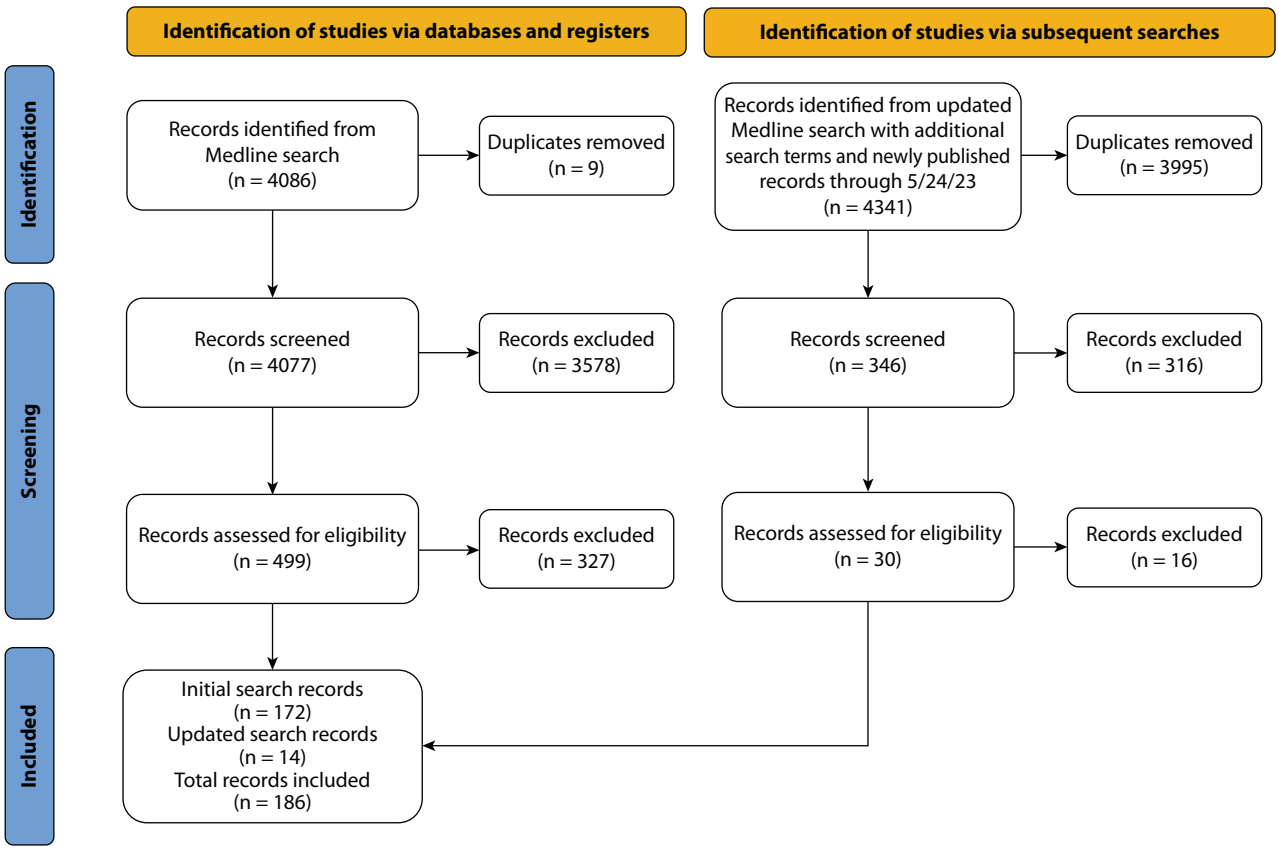

PRISMA 2020 study selection flow diagram.[12]
Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2024.05.007.

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