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

Source of support: This work was funded by the American Society for Radiation Oncology.

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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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. The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (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 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.
Table 1 ASTRO recommendation grading classification system

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
<th>Overall QoE Grade</th>
<th>Recommendation Wording</th>
</tr>
</thead>
</table>
| 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.
1. Introduction

HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) continues to increase worldwide, with approximately 21,000 new cases in 2020 in the US alone, reflecting an age-adjusted rate of 5.0 per 100,000 people. It is the most common HPV-associated cancer among males, and second only to cervical cancer in women. 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 due to the long-latency between oral HPV infection and detectable cancer, and low uptake of vaccination, particularly among men. 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 patients with HPV-positive OPSCC are often younger and have a better prognosis than those with non-HPV-related HNSCC. Because of the increasing number of long-term survivors of OPSCC, prospective studies have focused on reducing the long-term effects of treatment by ‘de-intensifying’ 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. At that time, the evidence base was comprised of 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, although many seminal prior studies preceding identification of HPV-status are still used in decision-making. 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 post-treatment response-assessment. The task force makes recommendations on optimal management of HPV-positive OPSCC, recognizing that not every clinical presentation can be addressed with a recommendation. Clinical trial enrollment is an essential mechanism to further improve outcomes.

2. Methods

2.1. 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 (XX, also a radiation...
oncologist) who led search strategy development and execution. This guideline was developed in collaboration
with the American Society of Clinical Oncology (ASCO) and the American Academy of Otolaryngology-Head and
Neck Surgery (AAO-HNS), who nominated representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by XX 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 TBD.

2.3. 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), a systematic search of human
participant studies retrieved from the Ovid MEDLINE database was conducted for English-language
publications between January 2020 through April 15, 2023. Allowable publication types included prospective
studies including randomized controlled trials (RCTs), individual patient data meta-analyses, retrospective
studies, and dosimetric/contouring studies (see Appendix E3 for the full search strategy). 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. For KQ1, induction chemotherapy studies that lacked initial chemoradiation as a
comparator were excluded. Studies were excluded if their patient population was comprised of <30% OPSCC
for all KQs except KQ2. For specific subquestions where limited data was available, expert opinion was relied
upon to support recommendations. Two reviewers independently screened the comprehensive list of articles,
with discrepancies resolved by a third reviewer (CJA). 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] 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; a checklist confirms the completion of essential elements (Appendix E3).

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.

2.4 Scope of the Guideline

This guideline addresses only the subjects specified in the KQs (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 7th edition (AJCC-7) or earlier to report patient characteristics and results. To make the recommendations consistent with the current AJCC-8 staging system, 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 non-squamous 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 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 and not stereotactic body RT or brachytherapy.

The key outcomes of interest are oncologic results including overall survival and locoregional control, and toxicity and quality of life (QoL) metrics. Disparities were evaluated as an outcome but were rarely provided in the evaluated literature. Table 2 describes the PICOs for each KQ, with additional details in Appendix E3).
## Table 2 KQs in PICO format

<table>
<thead>
<tr>
<th>KQ</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 1  | 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  
- 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 and 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 primary RT, 6000-6600 cGy for postoperative RT)  
- Conventional fields | Same as KQ1 |
| 4  | For patients receiving definitive and 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  
- 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 post-treatment 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  
- 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.
# 3. Key Questions and Recommendations

## 3.1. 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 Figure 1.

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

### Table 3 Indications for systemic therapy with RT

<table>
<thead>
<tr>
<th>KQ1 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with HPV+ OPSCC and T3-4 disease, ≥2 positive nodes, or a single node &gt;3 cm receiving definitive RT, concurrent systemic therapy is recommended.</td>
<td>Strong</td>
<td>High 12-17</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
<td>Low 18-20</td>
</tr>
<tr>
<td>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 are recommended.</td>
<td>Strong</td>
<td>Low 13,15,18-20</td>
</tr>
<tr>
<td>Implementation remark: Weigh the potential benefits of concurrent systemic therapy against toxicity risks given limited data regarding its efficacy in this population.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. For patients with HPV+ OPSCC who will receive definitive RT, induction systemic therapy is not recommended.</td>
<td>Strong</td>
<td>High 16,21-23</td>
</tr>
<tr>
<td>5. For patients with HPV+ OPSCC who warrant definitive RT and concurrent systemic therapy, cisplatin is recommended.</td>
<td>Strong</td>
<td>High 12,13,15,24,25</td>
</tr>
<tr>
<td>Implementation remark: Either 100 mg/m² every 3 weeks or 40 mg/m² weekly cisplatin are appropriate.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Moderate 17,26-28</td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Expert Opinion</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
<td>High 29,30</td>
</tr>
</tbody>
</table>

**Abbreviations:** HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; PD-L1 = programmed death ligand 1; RT = radiation 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 7th edition staging criteria, since trial eligibility was based on these characteristics. 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 and/or a single node measuring >3 cm as there is a demonstrated overall survival and/or locoregional control benefit in multiple trials of such patients with AJCC 7 stages III and IV, which is essentially equivalent to AJCC-8 T1-2 N1-3 and T3-4 N0-3. Recommendations for T1-2 N1 (single lymph node ≤3 cm) disease were discussed at length by the task force due 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 T2 N1 (single lymph node ≤3 cm) disease, either RT alone or RT with concurrent systemic therapy are considered appropriate. 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of pts with AJCC-7 T1-2 N1</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maddalo et al</td>
<td>T1 N1 excluded</td>
<td>AJCC-7 Stage III 20%</td>
</tr>
<tr>
<td>RTOG 1016</td>
<td>T1 N1 and T2 N1 excluded</td>
<td>AJCC-7 Stage III 7%</td>
</tr>
<tr>
<td>De-ESCALaTE HPV</td>
<td>T1-2 65%, N0-1 24%</td>
<td>T1-2N0 excluded</td>
</tr>
<tr>
<td>RTOG 0129</td>
<td>T1 N-any, T2 N1 excluded</td>
<td>AJCC-7 Stage III 22%</td>
</tr>
<tr>
<td>Fallaj et al</td>
<td>T1 N1 and T2 N1 excluded</td>
<td>...</td>
</tr>
<tr>
<td>Adelstein et al</td>
<td>5%</td>
<td>AJCC-7 Stage III 28%</td>
</tr>
<tr>
<td>H&amp;N Intergroup</td>
<td>1%</td>
<td>AJCC-7 Stage III &lt;7%</td>
</tr>
</tbody>
</table>

*Abbreviations:* AJCC-7 = American Joint Committee on Cancer, 7th edition; De-ESCALaTE HPV = Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in HPV+ oropharyngeal squamous cell carcinoma; H&N = head and neck; pts = patients; RTOG = Radiation Therapy Oncology Group.

For patients receiving definitive RT for HPV-positive OPSCC who warrant systemic therapy, the drug(s) should be delivered concurrently and not sequentially. Multiple RCTs and a high-quality meta-analysis demonstrated an overall survival benefit with concurrent systemic therapy versus RT alone, but there is no survival benefit to induction systemic therapy. The rare scenario in which patients with locally advanced OPSCC may require urgent/emergent initiation of systemic therapy for rapid cytoreduction and symptom relief is not addressed in this guideline.
HPV-status is prognostic of survival outcomes in patients with OPSCC. However, the available high-quality evidence does not support the use of HPV status to guide the choice of systemic therapy. Seminal data demonstrated a survival benefit of adding concurrent cisplatin chemotherapy to conventionally fractionated definitive RT in the pre-IMRT (intensity modulated radiation therapy) era for locally advanced HNSCC. Since this RCT was published, intensification of systemic therapy with the addition of epidermal growth factor receptor (EGFR)-directed therapy, such as cetuximab, to cisplatin did not improve survival. 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 to cisplatin for outcomes of disease recurrence and overall survival. As such, cisplatin is recommended as standard of care until RCTs support noninferiority of treatment outcomes with alternative agents. While triweekly high-dose cisplatin (100 mg/m²) was established by the Intergroup study as the de facto standard cisplatin regimen, subsequent data suggest that the weekly regimen (40 mg/m²) is a viable alternative. 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), NRG-HN002 (Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002), and TROG 12.01 (Randomized trial of radiotherapy with weekly cisplatin or cetuximab in low risk HPV associated oropharyngeal cancer), demonstrate favorable locoregional control with weekly cisplatin. The latter 2 focus on patients with favorable HPV-positive OPSCC, and the former includes approximately 75% patients with HPV-positive OPSCC, 70% of whom had a smoking history.

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, renal impairment), yet still require systemic therapy. In these populations, both cetuximab or carboplatin/fluorouracil (5-FU) are conditionally recommended regimens shown in RCTs to improve survival in locally advanced HNSCC when added to definitive RT. Taxane-containing regimens, including weekly docetaxel or carboplatin plus paclitaxel, are also conditionally recommended based on the expert opinion of the task force, but its efficacy in published studies is limited to nonrandomized trials or study populations with a low incidence of HPV-positive OPSCC. No prospective data exists regarding the best means to triage patients who are cisplatin-ineligible to alternative regimens, nor is there direct comparative data between regimens (ie, carboplatin/5-FU versus cetuximab versus 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 RCTs evaluating the role of immunotherapy in locally advanced HNSCC, including patients with HPV-positive
OPSCC.\textsuperscript{29,30} 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 chemoradiation using cisplatin with either avelumab or placebo for the treatment of locally advanced head and neck cancer.\textsuperscript{29} 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.\textsuperscript{29}

In the GORTEC-REACH (Groupe Oncologie Radiotherapie Tête et Cou-Randomized trial of avelumab-cetuximab-radiotherapy versus standard of care in locally advanced squamous cell carcinoma of the head and neck) phase II RCT, RT was evaluated in combination with pembrolizumab versus cetuximab in patients with locally advanced squamous cell carcinoma not eligible for cisplatin.\textsuperscript{30} There was no significant difference in either progression-free survival or overall survival with the use of pembrolizumab as a radiosensitizer but it was less toxic.\textsuperscript{30} There are several either closed or ongoing RCTs evaluating the efficacy of immunotherapy added to RT alone or cisplatin-RT (eg, NRG-HN004 [Randomized phase II/III trial of radiotherapy with concurrent MEDI4736 (durvalumab) vs. radiotherapy with concurrent cetuximab in patients with locoregionally advanced head and neck cancer with a contraindication to cisplatin; 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], and ECOG-ACRIN 3161 [Nivolumab versus observation in patients with locally advanced, intermediate risk HPV-positive OPSCC; NCT03811015]) but the use of immunotherapy is not supported for curative-intent treatment for patients with HPV-positive OPSCC.
Figure 1 Definitive Management of Patients with HPV+ OPSCC

Abbreviations: CRT = RT with concurrent systemic therapy; fx = fractionation; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; RT = radiation therapy; 5-FU = 5-fluorouracil.

Where the strength of a recommendation is conditional, the term ‘consider’ is used.
3.2. KQ2: Indications for postoperative RT after surgery (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2 and Figure 2.

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

Table 5 Indications for postoperative RT after surgery

<table>
<thead>
<tr>
<th>KQ2 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with resected HPV+ OPSCC, postoperative RT is recommended for ENE and/or final microscopic positive margins (tumor on ink).</td>
<td>Strong</td>
<td>Moderate 39-45</td>
</tr>
<tr>
<td>2. For patients with resected HPV+ OPSCC and pT3-4 or node-positive disease, concurrent chemoradiation is recommended for ENE or a final microscopically positive margin (tumor on ink).</td>
<td>Strong</td>
<td>Moderate 42-44</td>
</tr>
<tr>
<td>3. For patients with resected HPV+ OPSCC receiving concurrent chemoradiation, cisplatin is recommended. Implementation remark: Either 100 mg/m² every 3 weeks or 40 mg/m² weekly cisplatin are appropriate.</td>
<td>Strong</td>
<td>High 39,41-44</td>
</tr>
<tr>
<td>4. For patients with resected HPV+ OPSCC, postoperative RT is recommended for node-positive disease and at least 1 of the following pathologic features: pT3-4 disease, ≥2 positive nodes, and/or a single positive node &gt;3 cm.</td>
<td>Strong</td>
<td>Moderate 39-44,46,47</td>
</tr>
<tr>
<td>5. For patients with resected HPV+ OPSCC and pT3-4 node-negative disease, postoperative RT is recommended.</td>
<td>Strong</td>
<td>Expert Opinion</td>
</tr>
<tr>
<td>6. For patients with resected HPV+OPSCC and pT1-2 disease with up to a single positive node ≤3 cm without ENE, postoperative RT is conditionally recommended for perineural invasion and/or lymphovascular invasion.</td>
<td>Conditional</td>
<td>Expert Opinion</td>
</tr>
<tr>
<td>7. For patients with resected HPV+ OPSCC, postoperative RT is conditionally recommended for microscopically close final margins.</td>
<td>Conditional</td>
<td>Moderate 39,42,45</td>
</tr>
<tr>
<td>8. 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 nodes.</td>
<td>Conditional</td>
<td>Moderate 39,48-53</td>
</tr>
</tbody>
</table>

 Abbreviations: ENE = extranodal extension; HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; RT = radiation therapy.
credibility in the upfront management of this disease. Surgical expertise is of the utmost importance for ideal patient selection for the best oncologic and functional outcomes. Precise surgical technique and specimen processing are critical in determining any risk factors for disease relapse which inform decisions for postoperative treatment. Surgery alone is effective as a single-modality definitive therapy for most patients with pathologic T1-T2 margin-negative disease and no more than 1 involved node measuring ≤3 cm without extranodal extension (ENE).\textsuperscript{39,48-53} Postoperative RT is conditionally recommended for patients with perineural invasion or lymphovascular invasion 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.\textsuperscript{39,42}

For patients with more advanced disease, including those with pathologic T3-T4 disease, an involved lymph node measuring >3 cm, an involved lymph node with ENE, or multiple lymph node involvement, postoperative RT is recommended based on these same historical studies.\textsuperscript{39-44,46,47,49} Further, postoperative RT is recommended for all patients with final positive margins (tumor on ink) as this implies the presence of residual disease.\textsuperscript{39-45}

Historically, close margins (<5 mm from ink) have been an indication for postoperative RT for HNSCC.\textsuperscript{39,42,45} Yet this is controversial in the era of transoral approaches due to the anatomic constraints in achieving classic 5 mm margins with these surgeries. In the Eastern Cooperative Oncology Group (ECOG) 3311 (Phase II randomized trial of transoral surgery and low-dose intensity modulated radiation therapy in resectable p16+ locally advanced oropharynx cancer) study, which included only patients with HPV-positive OPSCC, postoperative RT was recommended for all patients undergoing transoral surgery with margins <3 mm from ink.\textsuperscript{39} 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.\textsuperscript{54,55} 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.

Adding concurrent cisplatin to postoperative RT is recommended for all patients with T3-4 or node-positive disease and ENE or a positive margin (tumor on ink), inclusive of patients with T1-2 node-positive disease. The results of 1 RCT\textsuperscript{42} and a combined analysis of 2 phase III trials\textsuperscript{44} demonstrate an overall survival benefit of concurrent chemoradiation versus RT alone in these populations. While ECOG 3311 treated patients with limited ENE (≤1 mm) using RT alone, there were only 38 such patients.\textsuperscript{39} The oncologic safety of RT alone for patients with ENE may be confirmed in the ongoing PATHOS (Post-operative adjuvant treatment for HPV-positive tumours) trial.\textsuperscript{56} No recommendations are included on concurrent systemic therapy for patients with pathologic T1-2 node-negative disease and a positive margin as such patients are not represented in the RCTs. Although these patients may be appropriately managed with definitive RT alone as they have microscopic
disease that is comparable to patients with small volume gross disease who can be treated with definitive RT alone, the presence of a positive surgical margin may portend a higher risk of local failure; therefore, there is no consensus on optimal management in this scenario.

For patients receiving postoperative concurrent chemoradiation, cisplatin remains the standard of care, and either triweekly bolus or weekly cisplatin are appropriate regimens. The use of concurrent cisplatin in resected HPV-positive OPSCC is primarily based on the results of Radiation Therapy Oncology Group (RTOG) 9501 and European Organisation for Research and Treatment of Cancer (EORTC) 22931 which included patients with all head and neck cancers. Both studies used bolus cisplatin (100 mg/m² delivered every 3 weeks during RT), whereas the 40 mg/m² weekly cisplatin schedule is supported by an RCT by the Japanese Clinical Oncology Group (JCOG). This study compared concurrent weekly cisplatin (40 mg/m²) to 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. Another trial asking a similar question with a larger percentage of patients with OPSCC did not meet adequate accrual for adequate power, while a third trial testing a lower dose of weekly cisplatin (30 mg/m²) in a non-HPV-positive OPSCC population showed superiority of bolus cisplatin. Given the results of the JCOG trial, either cisplatin schedule is recommended. A trial comparing these regimens in the postoperative setting in HPV-positive OPSCC is unlikely; however, proponents of weekly cisplatin (40 mg/m²) are further supported by the results of ECOG-ACRIN 3311 (Phase II randomized trial of transoral surgery and low-dose intensity modulated radiation therapy in resectable p16+ locally advanced oropharynx cancer) which shows excellent clinical outcomes in patients with high-risk features undergoing postoperative chemoradiation.

For patients with resected high-risk HPV-positive OPSCC but 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. Pending the published results of RCTs with non-cisplatin agents including cetuximab (ie, RTOG 0920 [A phase III study of postoperative radiation therapy (IMRT) +/- cetuximab for locally-advanced resected head and neck cancer]), no comment is made on concurrent systemic therapy for patients ineligible for cisplatin in the postoperative setting.
**Figure 2 Postoperative Management of Patients with 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.

*Pathologic risk factors include close margins, LVI, and PNI.
†The task force did not comment on PORT versus PORT with systemic therapy.
‡100 mg/m² every 3 weeks or 40 mg/m² weekly.
### 3.3. 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?

**Table 6 Dose-fractionation regimens and treatment volumes**

<table>
<thead>
<tr>
<th>KQ3 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitive treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. For patients with HPV+ OPSCC receiving definitive RT with concurrent systemic therapy, 7000 cGy in 33-35 fractions is recommended to gross disease.</td>
<td>Strong</td>
<td>High 12,14,24,62-65</td>
</tr>
<tr>
<td>2. For patients with HPV+ OPSCC and T1-2 disease with up to 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 is recommended to gross disease.</td>
<td>Strong</td>
<td>Low 19,24,64,66,67</td>
</tr>
<tr>
<td>3. For patients with HPV+ OPSCC receiving definitive RT, an EQD2 of at least 4600 cGy is conditionally recommended to clinically uninvolved nodal levels at risk for microscopic disease.</td>
<td>Conditional</td>
<td>Moderate 12,14,24,62,67</td>
</tr>
<tr>
<td>4. For patients with HPV+ OPSCC and T1-2 disease with a single positive node &gt;3 cm or multiple nodes receiving definitive RT alone, altered fractionation (accelerated or hyperfractionated) is conditionally recommended.</td>
<td>Conditional</td>
<td>Moderate 65,68</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
<td>High 63-65,68,69</td>
</tr>
<tr>
<td><strong>Postoperative treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. For patients with HPV+ OPSCC receiving postoperative RT, 6000-6600 cGy is recommended to regions of microscopically positive primary site surgical margins and/or ENE.</td>
<td>Strong</td>
<td>High 40-44</td>
</tr>
<tr>
<td>7. For patients with HPV+ OPSCC receiving postoperative RT, treating the postoperative primary bed and the pathologically involved nodal levels with a dose of 5600-6000 cGy is recommended.</td>
<td>Strong</td>
<td>High 39,40,44,70</td>
</tr>
<tr>
<td>8. For patients with HPV+ OPSCC receiving postoperative RT, an EQD2 of at least 5000 cGy is conditionally recommended to pathologically uninvolved nodal levels in the dissected pathologically node-positive neck.</td>
<td>Conditional</td>
<td>Expert Opinion</td>
</tr>
</tbody>
</table>

**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. (See Table 8 for target volume margins).

10. For patients with HPV+ OPSCC and T1-2 tonsillar carcinoma with up to a single positive node ≤3 cm without ENE treated with definitive or postoperative RT, unilateral RT is recommended for disease confined to the tonsillar fossa.

11. For patients with HPV+ OPSCC and T1-2 tonsillar carcinoma treated with definitive or postoperative RT, unilateral RT is conditionally recommended for disease with no base of tongue involvement and:
   - Disease involving minimal soft palate and/or
   - A single positive node >3 cm but ≤6 cm or multiple positive nodes without evidence of ENE.

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

Although total dose de-escalation is a 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. Some trials used concurrent cetuximab, which has since proven inferior to cisplatin. Given the limitations of extrapolating from phase II trials, when treating with concurrent systemic therapy, the standard of care for gross disease remains 7000 cGy (see Table 7). An RCT, NRG-HN005 (De-intensified radiation therapy with chemotherapy (cisplatin) or immunotherapy (nivolumab) in treating patients with early-stage, HPV-positive, nonsmoking associated oropharyngeal cancer; NCT03952585), is 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 to 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 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 due 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.
compared hyperfractionation to conventional fractionation in the pre-IMRT era and was limited to oropharyngeal cancer with more earlier stage patients than most altered fractionation trials, but the benefit with hyperfractionation was only observed in larger primaries (T3 versus T2). Most other trials of altered fractionation primarily include locally advanced patients, as they were designed prior to the demonstrated benefit of concurrent cisplatin for this population. 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. A range of doses with either conventional 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 for microscopic disease should be treated with RT, regardless of whether patients receive systemic therapy or not. However, there is limited high-quality data that define the optimal dose to elective nodal regions. Published RCTs and other studies use doses as low as 4600 cGy EQD2 to clinically-uninvolved nodal levels, justifying the lower dose in the current recommendation. One RCT examined delivering 4000 cGy versus 5000 cGy EQD2 to elective nodal levels but was not powered for noninferiority. This RCT also demonstrated a numerically higher, but not statistically significant, regional recurrence rate in the lower-dose arm. Selection of the optimal dose for microscopic disease is also limited by the inability to accurately quantify doses delivered in the 2-dimensional era. 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 and that dose to elective nodal regions is rarely a primary study question, the strength of the recommendation is conditional.

For patients with locally advanced disease who are ineligible for concurrent systemic therapy, altered fractionation is recommended (Table 7). 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. 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 heterogenous 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. As failures 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. However, the magnitude of the locoregional control benefit was larger for hyperfractionation than moderate
acceleration, suggesting hyperfractionation might be superior in clinical trial settings. In clinical practice, the
twice daily treatment of hyperfractionated regimens 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.81

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 DAHANACA 6/7 trials confirms a benefit to this regimen in patients with p16-positive
disease.64 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.63-
65,68,69 Both the original and the updated MARCH meta-analyses found lower (ie, superior) hazard ratios for
local versus locoregional control.65,84 Given this, altered fractionation is recommended for T3-4 disease and is
conditionally recommended for earlier T-stages with advanced nodal stage.63-65,68,69

In the postoperative setting, landmark RCTs examining postoperative chemoradiation for extranodal
extension or positive margins include a range of doses between 6000 to 6600 cGy, so this range is considered
acceptable.40,41,44 A foundational RCT from 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.40 The ECOG 3311 phase II trial
randomized patients with resected HPV-positive OPSCC to postoperative RT with a total dose of 6000 cGy
versus 5000 cGy, showing no difference in any oncologic outcome.39 However, this trial is the only published
multi-institutional study using 5000 cGy, 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, none are RCTs, and RT dose from adjacent nodal levels can result in delivery of higher
doses than expected to the postoperative bed.54,85,86 Treatment to the primary surgical bed is recommended
when postoperative RT is delivered.39,40,44,70 The dose to the dissected, uninvolved neck (EQD2 5000 cGy) is
higher than that for the clinically-negative undissected neck because of the combination of conventional and
theoretical concerns about hypoxia in the postoperative setting.

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 GTV to high-risk clinical target volume (CTV) (7000 cGy, “CTV7000”) margin did not increase
recurrence when compared to irradiating the whole oropharynx to full dose. A retrospective study showed
improved toxicity without increased recurrence when reducing the GTV to CTV7000 margin from 10 mm to 6
mm. There is substantial data in other RCTs and studies using ≤5 mm margins from GTV to CTV7000. 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. However, there is still a need to treat microscopic disease beyond the radiologically
visible primary tumor using a CTV (Table 8).

There is limited prospective data supporting the oncologic safety of sparing elective nodal levels in
HPV-positive OPSCC. 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. 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 failure 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, given a lack of
prospective data and the potential for selection bias in the published data, Table 8 and the task force
recommendations are a conservative, rather than exhaustive, list of scenarios in which omission of nodal levels
may be appropriate.

There is also a lack of randomized data to define the criteria for omission of RT to the contralateral
neck in 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). A retrospective series demonstrate 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. 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 original 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. Furthermore, only 1 other retrospective series included patients with tonsillar
cancer and describes the extent of tongue base involvement. 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. Patients with primary base of tongue cancer are not included in recommendations to avoid the contralateral neck because of bilateral lymphatic drainage of the tongue base and the few published series quantifying base of tongue involvement.

Unilateral treatment for AJCC-7 stage N2a and N2b disease is one of the most controversial topics in tonsillar RT. Although multiple series report lower rates of failure among patients with this nodal burden, 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 (e.g., nodal size cutoffs, number of nodes, level of nodal involvement). Indeed, the data reflect this variability, as 1 series shows that the median and maximum number of nodes involved is nearly identical for patients treated unilaterally versus bilaterally. The data therefore suggest there is a subset of N2a and N2b patients for whom unilateral treatment is acceptable, but unfortunately that subset is not defined further. Given this uncertainty, bilateral treatment in select cases 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/retrostyloid nodes, which allows for aggressive sparing of the contralateral parotid and submandibular glands.

### Table 7 Fractionation Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Daily fraction size</th>
<th>Total dose</th>
<th>Total time</th>
<th>Fraction number</th>
<th>Fraction per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>200 cGy</td>
<td>6600–7000 cGy</td>
<td>7 weeks</td>
<td>33-35</td>
<td>5</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>120 cGy</td>
<td>7440–8160 cGy</td>
<td>7 weeks</td>
<td>62-68</td>
<td>10</td>
</tr>
<tr>
<td>Accelerated</td>
<td>150-200 cGy</td>
<td>6800–7200 cGy</td>
<td>6 weeks</td>
<td>34-42</td>
<td>Varies (5-10)*</td>
</tr>
<tr>
<td>Hypofractionation</td>
<td>210-220 cGy</td>
<td>6600–7000 cGy</td>
<td>6-6.5 weeks</td>
<td>30-33</td>
<td>5</td>
</tr>
</tbody>
</table>

*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.*

### Table 8 Target Volume Margins

<table>
<thead>
<tr>
<th>Margin Type (Refs)</th>
<th>Value</th>
<th>Requirements/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV to high-risk CTV OR highest dose level CTV</td>
<td>≤5 mm</td>
<td>The high-risk CTV expansion does not eliminate the need to treat microscopic disease beyond the visible GTV.</td>
</tr>
<tr>
<td>CTV to PTV</td>
<td>≤3-5 mm</td>
<td>Daily CBCT</td>
</tr>
<tr>
<td>Nodal level that typically can be omitted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Contralateral retrostyloid and retropharyngeal\(^6,71,72\) N/A • 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\(^66,88\) N/A • Clinically negative neck AND
• No oral cavity involvement (includes anterior tonsillar pillar)

Level V*\(^89\) N/A • Clinically negative neck AND
• No involvement of nasopharynx and/or hypopharynx

Abbreviations: CBCT = cone-beam computed tomography; CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.
*Each side of the neck is considered separately.

3.4. 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?

Table 9 Preferred techniques and appropriate normal tissue considerations

<table>
<thead>
<tr>
<th>KQ4 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with HPV+ OPSCC receiving definitive or postoperative RT, IMRT is recommended over 3-D CRT.</td>
<td>Strong</td>
<td>High 62,92</td>
</tr>
<tr>
<td>2. For patients with HPV+ OPSCC receiving definitive or postoperative RT, reducing dose to xerostomia OARs is recommended, as target coverage permits.</td>
<td>Strong</td>
<td>High 92-94</td>
</tr>
<tr>
<td>Implementation remark: Xerostomia OARs include parotid glands, submandibular glands, and oral cavity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. For patients with HPV+ OPSCC receiving definitive or postoperative RT, reducing dose to dysphagia/swallowing OARs is recommended, as target coverage permits.</td>
<td>Strong</td>
<td>Moderate 95-100</td>
</tr>
<tr>
<td>Implementation remark: Swallowing OARs include pharyngeal constrictors, larynx, and oral cavity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. For patients with HPV+ OPSCC receiving definitive or postoperative RT, reducing dose to the mandible is recommended to minimize risk of osteoradionecrosis, as target coverage permits.</td>
<td>Strong</td>
<td>Moderate 101-103</td>
</tr>
<tr>
<td>5. For patients with HPV+ OPSCC receiving definitive or postoperative RT, optimizing prescription dose homogeneity in target volumes is recommended.</td>
<td>Strong</td>
<td>Expert Opinion</td>
</tr>
</tbody>
</table>

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.
Delivery of RT in the definitive or postoperative setting can be accomplished using a variety of techniques including 3-dimensional conformal radiation therapy (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.\textsuperscript{62,92,104,105} One trial\textsuperscript{62} 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.\textsuperscript{92,104,105} 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 is no prospective data comparing outcomes of IMRT with proton therapy, although studies are in progress (NCT02923570, NCT01893307).

When planning IMRT for oropharyngeal cancer, the physician and dosimetrist must balance the need to provide sufficient dose coverage to the target and minimize dose to the organs at risk (OARs). In general, coverage of the PTV is prioritized, though this may necessitate a balance when gross disease approaches the spinal cord or brainstem. Dose homogeneity of the target volume should be optimized, moderating the maximum dose, and constraining it to within the target volume. Effort should be made to limit the dose to <107 to 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.\textsuperscript{106} As 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. As 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 neurological function is an important goal. A detailed discussion of dose and volume limits to the spinal cord and brainstem is found in QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic), as prospective data are sparse.\textsuperscript{107} Prospective randomized trials demonstrate reducing mean dose to the (contralateral) parotid gland decreases the risk of late xerostomia.\textsuperscript{62,92,104,105} 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
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 a RCT and multiple retrospective studies. Swallowing OARs include the oral cavity, pharyngeal constrictors, and larynx. Endpoints in studies examining dysphagia following IMRT for HNSCC include patient-reported swallow function, observer-reported dysphagia, aspiration, or gastrostomy tube dependence.

Moderate-to-high doses of RT to the mandible contribute to the risk of osteonecrosis. When possible, minimizing the volume of mandible receiving doses ≥5000 cGy and avoiding a point dose >105% prescription may reduce risk of any grade osteoradionecrosis, including grade 4 osteoradionecrosis which requires major surgery. Reduction in dose to the mandible is also associated with a lower rate of tooth loss and higher success of implant-based prosthetic rehabilitation and higher success of implant-based prosthetic rehabilitation.

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. 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. For most patients with oropharyngeal cancer, a mean ipsilateral dose <2000 cGy and contralateral dose <500 cGy can often be achieved.

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 post-treatment and is associated primarily with the mean dose to the thyroid, though this may be modified by the thyroid volume. Of note, a pooled analysis of 2 RCTs of 3-D CRT compared with IMRT demonstrates an increase in subclinical hypothyroidism with IMRT. 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 increase the risk of brachial plexopathy. RT to the neck is associated with carotid artery stenosis and stroke. 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 increase the risk of brachial plexopathy.\textsuperscript{119} RT to the neck is associated with carotid artery stenosis and stroke.\textsuperscript{120,121} In a large retrospective study, there was no clear dose-response between carotid dose and risk of carotid artery stenosis as evaluated by ultrasound.\textsuperscript{120} 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.

\textbf{Table 10} Guidance on dose constraints for xerostomia, swallowing, mandible, and neurologic OARs$^\ast,\dagger$

<table>
<thead>
<tr>
<th>OARs (Refs)</th>
<th>Dose Constraints\textsuperscript{‡}</th>
<th>Contour Considerations</th>
<th>Clinical Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xerostomia OARs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid gland\textsuperscript{93,122-124}</td>
<td>Contralateral mean 1800-2600 cGy</td>
<td>Contralateral mean ≤700 cGy</td>
<td>• Prioritize sparing of the gland in the node-negative neck&lt;br&gt;• Entire gland</td>
</tr>
<tr>
<td>Submandibular gland\textsuperscript{93}</td>
<td>Contralateral mean 3000-3900 cGy</td>
<td>Contralateral mean ≤1000 cGy</td>
<td>• Prioritize sparing of the gland in the node-negative neck&lt;br&gt;• Entire gland</td>
</tr>
<tr>
<td>Oral cavity\textsuperscript{93,94}</td>
<td>Mean ≤2000-3000 cGy</td>
<td>Mean ≤2000 cGy</td>
<td>• Includes lips, buccal mucosa, oral tongue, floor of mouth and hard palate&lt;br&gt;• If evaluation metric excludes PTV</td>
</tr>
<tr>
<td></td>
<td>Mean ≤3000-5000 cGy</td>
<td>Mean ≤3000 cGy</td>
<td>• If evaluation metric includes PTV</td>
</tr>
<tr>
<td><strong>Swallowing OARs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngeal constrictors (superior &amp; middle)\textsuperscript{95,97,99}</td>
<td>Mean 3500-5000 cGy</td>
<td>Mean 2500-4000 cGy</td>
<td>• If evaluation metric excludes PTV</td>
</tr>
<tr>
<td></td>
<td>Mean 4500-6000 cGy</td>
<td>Mean 3500-4500 cGy</td>
<td>• If evaluation metric includes PTV</td>
</tr>
<tr>
<td>Pharyngeal constrictors (inferior)\textsuperscript{99}</td>
<td>Mean 2000-3500 cGy</td>
<td>Mean 1500-2500 cGy</td>
<td>• Evaluation metric includes PTV</td>
</tr>
<tr>
<td>Larynx\textsuperscript{95,96}</td>
<td>Mean 2500-4000 cGy</td>
<td>Mean 1500-2500 cGy</td>
<td>• Include supraglottic and glottic larynx&lt;br&gt;• Evaluation metric includes PTV</td>
</tr>
<tr>
<td>Mandible\textsuperscript{101-103}</td>
<td>• Max point dose ≤100% highest prescription dose outside PTV, ≤105% prescription inside PTV (avoid hotspots)</td>
<td>• Max point dose ≤100% highest prescription dose outside PTV, ≤105% highest prescription inside</td>
<td>• Whole mandible should be included in the structure</td>
</tr>
</tbody>
</table>
PTV (avoid hotspots)
- Minimize V50 and V60 (volume of mandible receiving ≥5000 cGy)
- Minimize V50 and V60 (volume of mandible receiving ≥5000 cGy)
- Point dose defined to 0.03 cc volume

### Neurologic OARs

<table>
<thead>
<tr>
<th>OAR</th>
<th>Max point dose 3500-5400 cGy</th>
<th>Max point dose 3500-4500 cGy</th>
<th>Point dose defined to 0.03 cc volume</th>
<th>Myelopathy, nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem §</td>
<td>Max point dose 3500-5400 cGy</td>
<td>Max point dose 3500-4500 cGy</td>
<td>Point dose defined to 0.03 cc volume</td>
<td>Myelopathy</td>
</tr>
<tr>
<td>Spinal cord †</td>
<td>Max point dose 3500-4500 cGy</td>
<td>Max point dose 3500-4500 cGy</td>
<td>Point dose defined to 0.03 cc volume</td>
<td>Myelopathy</td>
</tr>
<tr>
<td>Cochlea</td>
<td>Mean ≤2000 cGy</td>
<td>Contralateral ≤500 cGy</td>
<td></td>
<td>Hearing loss</td>
</tr>
</tbody>
</table>

**Abbreviations:** Max = maximum; 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; dose constraints are for the most common fractionations.

† Assuming postoperative or definitive radiation therapy over 30 to 35 fractions.

‡ 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 ≤5000 cGy for the spinal cord, and ≤5400 for the brainstem.

### 3.5. KQ5: Preferred approaches for initial post-treatment 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 post-treatment restaging and management of the neck?

**Table 11** Preferred approaches for initial post-treatment restaging and management of the neck

<table>
<thead>
<tr>
<th>KQ5 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with HPV+ OPSCC receiving definitive RT with or without concurrent systemic therapy for node-positive disease, reassessment with PET-CT is recommended approximately 3 months after completing treatment.</td>
<td>Strong</td>
<td>Moderate 125-131</td>
</tr>
<tr>
<td>2. For patients with HPV+ OPSCC and node-negative disease receiving definitive RT with or without concurrent systemic therapy, reassessment with cross-sectional imaging is</td>
<td>Strong</td>
<td>Low 126,127,129,130,132,133</td>
</tr>
</tbody>
</table>
3. For patients with HPV+ OPSCC who undergo surgery with or without postoperative RT, reassessment with cross-sectional imaging is recommended approximately 3-6 months after completing treatment.

**Implementation remark:** Imaging modalities include PET-CT and/or contrast-enhanced anatomic imaging.

4. For patients with HPV+ OPSCC and node-positive disease receiving definitive RT with or without systemic therapy, neck dissection is recommended when a post-treatment PET-CT reports persistent isolated regional disease.

**Strong**

**Expert Opinion**

5. For patients with HPV+ OPSCC and node-positive disease receiving definitive RT with or without systemic therapy, neck dissection is conditionally recommended when post-treatment PET-CT reports an equivocal response in regional disease.

**Conditional**

**Moderate**

125,131,134-137

**Abnormalities:** HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma; KQ = key question; PET-CT = positron emission tomography-computed tomography; RT = radiation therapy.

After completion of definitive chemoradiation, imaging is recommended to assess treatment response at the primary site and neck. Historically, patients with node-positive OPSCC received a planned neck dissection, which is 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. 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. The PET-NECK RCT showed PET-CT could be used to select patients who do not require a neck dissection after definitive chemoradiation. 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 local-regional control, lower rates of surgery and was more cost effective.

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%, like that of the negative predictive value for...
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. These data support the role of PET-CT as a useful imaging modality for response-assessment. 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. However, a meta-analysis did not find superiority of PET over MRI. Cross-sectional imaging with PET-CT and/or contrast-enhanced anatomic imaging 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.

The timing of PET-CT influences the frequency of a reported inconclusive or equivocal response CT. The diagnostic accuracy and proportion of inconclusive results declined from 26% to 8.4% when PET was done 0 to 3 months versus 3 to 6 months post-treatment. 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. Therefore, post-treatment 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).

The optimal method of defining an equivocal radiologic response to treatment is not yet standardized. 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. Use of standardized PET-CT reporting criteria, such as the Hopkins criteria, reduces the number of equivocal reports and improves inter-reader agreement. 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. 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. Obtaining baseline imaging is important, and the consensus expert opinion on the use of cross-sectional imaging includes PET-CT and/or contrast enhanced CT neck or MRI 3 to 6 months after completion of all local therapy. This time frame provides baseline post-treatment imaging, and it may minimize the risk of false-positive findings because of acute post-treatment changes.

Neck dissection is recommended when patients with initially positive nodes have clear evidence of residual neck disease on restaging imaging. However, an equivocal response to treatment based on PET-CT requires more nuance in clinical decision-making and therefore the taskforce made a conditional
recommendation for a neck dissection in this scenario.\textsuperscript{125,131,134-137} Management options include neck dissection or close follow-up imaging. 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 conditionally recommended when faced with equivocal findings.\textsuperscript{125,131,134-137} 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.\textsuperscript{149} 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.\textsuperscript{150}

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.\textsuperscript{136,144,151} 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.\textsuperscript{152}

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\textsuperscript{153} or HPV sequencing.\textsuperscript{154} Approximately 90\% of patients with HPV-positive OPSCC have detectable plasma ctHPVDNA for the 5 most common HPV strains (16, 18, 31, 33, 35) at diagnosis.\textsuperscript{155,156} 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.\textsuperscript{155} 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 to imaging-based response assessment in prospective data. Therefore, post-treatment imaging alone remains the recommended method of response-assessment after curative-intent treatment.\textsuperscript{126,127,129,130,132,133}
4. 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. Even now, there is debate over which patients with early-stage HPV-positive OPSCC treated with definitive RT benefit from systemic therapy, and in the absence of pending clinical trials, such decisions will likely remain highly individualized. In the postoperative setting, ECOG 3311 opened the door to reducing the need for postoperative concurrent chemoradiation, but confirmatory data are needed before establishing a new standard of care. 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.

Ongoing work to determine the lowest acceptable definitive and postoperative RT doses, especially in the context of published data from de-escalation studies, has the potential for significant impact in this patient population. The proverbial stakes are high with dose reduction, as the potential improvement in acute and late toxicity may not offset an increased risk of locoregional failure 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 2).

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. Although biomarkers may play a role in future management of HPV-positive OPSCC, the existing data is 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, as 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 males. Patients in RTOG 1016 and HN002 were comprised of 90% male, 93% white and 84% male, 92% white, respectively. Based on these data, it is unclear how and to what extent these prospective data can be extrapolated to other racial, gender, and socioeconomic settings. Additional work is clearly needed to understand the impact of and optimal treatments for HPV-positive OPSCC in diverse populations.
5. Acknowledgments

We are grateful to XXX for collaborating on creation of the search strategy and methodologic support. The task force thanks XXX for literature review assistance.

The task force also thanks the peer reviewers for their comments and time spent reviewing the guideline. See Appendix E1 in the Supplementary Materials for their names and disclosures.

Figure 3 PRISMA 2020 Study Selection Flow Diagram
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This document contains confidential information, so it is not to be copied, disseminated, or referenced until publication.


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**Appendix E1. Peer Reviewers and Disclosures (Comprehensive)**

- Table is added prior to publication

**Appendix E2. Abbreviations**

3-D CRT = 3-dimensional conformal radiation therapy
5-FU = fluorouracil
AJCC = American Joint Committee on Cancer
CBCT = cone-beam computed tomography
cGy = centigray
tHPV DNA = cell-free plasma circulating tumor HPV DNA
CT = computed tomography
CTV = clinical target volume
ECOG = Eastern Cooperative Oncology Group
ENE = extranodal extension
EORTC = European Organisation for Research and Treatment of Cancer
EQD2 = equivalent dose in 200 cGY fractions
FDG = fluorodeoxyglucose
fx = fraction
GTV = gross tumor volume
HNSCC = head and neck squamous cell carcinoma
HPV+ OPSCC = HPV-positive oropharyngeal squamous cell carcinoma
IMRT = intensity modulated radiation therapy
JCOG = Japanese Clinical Oncology Group
KQ = key question
MRI = magnetic resonance imaging
OARs = organs at risk
OPSCC = oropharyngeal squamous cell carcinoma
P16+ = Cyclin-dependent kinase inhibitor 2A-positive
PET-CT = positron emission tomography-computed tomography
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
PTV = planning target volume
QoL = quality of life
## Appendix E3. PICOTS Questions / Literature Search Strategy

### Appendix A. PICOTs

**Search Limits:**

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**Universal Exclusion Criteria:**

1. Preclinical/nonhuman studies
2. Health economics/cost analysis studies
3. Studies available in abstract only
4. Comment or editorial
5. Guidelines or review articles
6. Pediatric patients
7. Otherwise not relevant or out of scope
8. Cervical esophageal cancer/carcinoma
9. HPV-negative oropharynx/oropharyngeal cancer/carcinoma [exclusively] – **NOTE:** papers that are HPV status agnostic should not be excluded from the initial search, only exclude exclusively HPV-negative
10. p16-negative oropharynx/oropharyngeal cancer/carcinoma [exclusively]
11. SEER, SEER-Medicare, and National Cancer Database (NCDB) studies
12. Recurrent, secondary primary, or distant metastatic cancer
13. Patients with unknown primary (tumor)
14. Treatment with noncurative or palliative intent

**Additional Universal Criteria:**

1. Removed RCTs and prospective nonrandomized studies with <50 pts
2. Removed retrospective studies with <100 pts for all KQs
3. Removed all retrospective studies for KQ1
4. Removed studies on intra-arterial cisplatin
5. Removed meta-analyses that did not include individual patient data
6. Removed all retrospective comparisons of technique (e.g., IMRT vs proton vs 3-D vs conventional)
7. Removed phase II or meta-analyses published before 2010 (all KQ1; KQ2B [not KQ2A], KQ3A,B, [not for KQ3C]; not for KQ4)
8. Induction chemotherapy trials: KQ1: only phase III. KQ2-4: phase III and phase II if 2010 onward and relevant.
<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Question and PICO(TSS) Framework</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Key clinical question(s)</strong></td>
<td><strong>Key Question 1:</strong> For patients receiving definitive RT for HPV+ OPSCC, what are the indications for systemic therapy?</td>
</tr>
<tr>
<td><strong>Definitions</strong></td>
<td>Since most early data incorporate both p16+ and p16- disease, the term “oropharyngeal squamous cell carcinoma” should include studies that do not differentiate between them.</td>
</tr>
<tr>
<td><strong>Participants/ population</strong></td>
<td>Patients with HPV+ and/or p16+ OPSCC receiving definitive RT</td>
</tr>
<tr>
<td><strong>Intervention(s)/ exposure(s)</strong></td>
<td>Systemic therapy, chemotherapy, biological therapy, immunotherapy</td>
</tr>
</tbody>
</table>
| **Comparator(s)/ control** | - RT alone  
- RT+ other concurrent regimens |
| **Outcomes: primary/critical** | - Overall survival  
- Progression-free survival  
- Locoregional control  
- Distant metastasis  
- Quality-of-life  
- Disparities in oncologic and quality-of-life outcomes |
| **Timing** | Neoadjuvant, concurrent, adjuvant |
| **Setting/context** | Any |
| **Study design** | Prospective studies ONLY |
| **Key search inclusion/exclusion criteria** | **Inclusion criteria:**  
- Adults age ≥18 years with OPSCC or head and neck SCC  
- Primary/definitive RT or chemoradiation  
- At least 30% of the cohort is OPSCC  
**Exclusion criteria:**  
- Universal exclusion criteria above  
- Treatment with primary surgery  
- Phase II induction chemotherapy trials or phase III induction chemotherapy trials in which RT/chemoradiation is not a comparator |

**Validation Set**  
29220295 or 30449625 or 30449623 or 12506176 or 16467544 or 25154822 or 22261362 or 1326 or 14657228 or 33862002 or 12506176 or 23414589 or 22261362 |

<table>
<thead>
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<th>Details</th>
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<tr>
<td><strong>Key Question and PICO(TSS) Framework</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Key clinical question(s)</strong></td>
<td><strong>Key Question 2:</strong> Following curative-intent surgery for patients with HPV+ OPSCC, what are the indications for postoperative RT with or without systemic therapy?</td>
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<tr>
<td><strong>Definitions</strong></td>
<td>Since most early data incorporate both p16+ and p16- disease, the term “oropharyngeal squamous cell carcinoma” should include studies that do not differentiate between them.</td>
</tr>
<tr>
<td><strong>Participants/ population</strong></td>
<td>Patients with HPV+ and/or p16+ OPSCC who received curative-intent surgery</td>
</tr>
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</table>
| **Intervention(s)/ exposure(s)** | (A) Adjuvant RT  
(B) Adjuvant chemoradiation (or biological therapy) plus RT |
| **Comparator(s)/ control** | (A) Surgery alone  
(B) Adjuvant RT alone |
| **Outcomes: primary/critical** | - Overall survival  
- Progression-free survival  
- Locoregional control  
- Distant metastasis  
- Quality-of-life  
- Disparities in oncologic and quality-of-life outcomes |
<p>| <strong>Timing</strong> | Postoperative |
| <strong>Setting/context</strong> | Any |
| <strong>Study design</strong> | See universal inclusion criteria |</p>
<table>
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<tr>
<th>Item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Question and PICO(TSS) Framework</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Key clinical question(s)</strong></td>
<td><strong>Key Question 3:</strong> 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?</td>
</tr>
<tr>
<td><strong>Definitions</strong></td>
<td>Since most early data incorporate both p16+ and p16- disease, the term “oropharyngeal squamous cell carcinoma” should include studies that do not differentiate between them</td>
</tr>
<tr>
<td><strong>Participants/ population</strong></td>
<td>Patients with HPV+ and/or p16+ OPSCC receiving definitive or postoperative RT with or without systemic therapy</td>
</tr>
<tr>
<td><strong>Intervention(s)/ exposure(s)</strong></td>
<td>(A) Altered fractionation (B) Dose de-intensification (C) Definitions of primary tumor and neck volumes</td>
</tr>
<tr>
<td><strong>Comparator(s)/ control</strong></td>
<td>(A) Standard fractionation (B) Standard dose (66-72 Gy for primary RT, 60-66 Gy for adjuvant RT) (C) Conventional fields</td>
</tr>
<tr>
<td><strong>Outcomes: primary/critical</strong></td>
<td>• Overall survival • Progression-free survival • Locoregional control • Distant metastasis • Quality-of-life • Disparities in oncologic and quality-of-life outcomes</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>Definitive and postoperative</td>
</tr>
<tr>
<td><strong>Setting/context</strong></td>
<td>Any</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>See universal inclusion criteria (A + B) Prospective only (C) Retrospective &amp; prospective</td>
</tr>
<tr>
<td><strong>Summary of the key selection criteria</strong></td>
<td><strong>Inclusion criteria:</strong>  • Adults age ≥18 years with OPSCC or head and neck SCC  • Treatment with definitive or adjuvant RT or chemoradiation  • At least 30% of the cohort is OPSCC  <strong>Exclusion criteria:</strong>  • Universal exclusion criteria above</td>
</tr>
<tr>
<td><strong>Validation Set</strong></td>
<td>(A) 115977795 or 25366680 or 24613816 or 22261362 or 14511925 or 20530316 (of note 20630316 is observational study; retrospective analysis of prospectively gathered trial data, whereas the rest are prospective interventional therapeutic trials)  (B) 34699271 or 33507809 or 33127491 or 32044165 or 28029303 (C) 35050342 or 33127491 or 31785337 or 28258895 or 22975604 or 11567806</td>
</tr>
</tbody>
</table>
### Key Question and PICO(TSS) Framework

#### Key clinical question(s)

**Key Question 4:** For patients receiving definitive and postoperative RT with or without systemic therapy for HPV+ OPSCC, what are the preferred RT techniques and appropriate normal tissue considerations?

#### Participants/ population

Patients with HPV+ and/or p16+ OPSCC receiving definitive or postoperative RT with or without systemic therapy

#### Intervention(s)/ exposure(s)

- IMRT
- Proton beam therapy
- Alternative thresholds for organs-at-risk

#### Comparator(s)/ control

Differential organ sparing across techniques (IMRT, proton therapy, 3-D)

#### Outcomes: primary/critical

- Quality-of-life (e.g., xerostomia, dysphagia, osteoradionecrosis)
- Locoregional control
- Patient-reported outcomes
- Disparities in oncologic and quality-of-life outcomes

#### Timing

Definitive and postoperative

#### Setting/context

Any

#### Study design

All types – See universal inclusion criteria

#### Summary of the key selection criteria

**Inclusion criteria:**

- Adults age ≥18 years with OPSCC or head and neck SCC
- Treatment with definitive or adjuvant RT or chemoradiation
- At least 30% of the cohort is OPSCC

**Exclusion criteria:**

- Universal exclusion criteria above
- Dosimetric-only comparisons

#### Validation Set

21236730 or 22296746 or 19540060 or 22056067 or 11395238 or 17848291 or 35000532 or 34754954 or 20421546

### Key Question and PICO(TSS) Framework

#### Key clinical question(s)

**Key Question 5:** Following definitive or postoperative RT with or without systemic therapy for patients with HPV+ OPSCC, what are the preferred approaches for initial post-treatment restaging and management of the neck?

#### Participants/ population

Patients with HPV+ and/or p16+ OPSCC receiving definitive or postoperative RT with or without systemic therapy

#### Intervention(s)/ exposure(s)

- Imaging,
- Biopsy
- Circulating HPV tumor DNA
- Neck dissection

#### Comparator(s)/ control

Clinical follow-up

#### Outcomes: primary/critical

- Overall survival
- Progression-free survival
- Regional/neck control
- Distant metastasis
- Quality-of-life
- Disparities in oncologic and quality-of-life outcomes

#### Timing

Post curative-intent treatment

#### Setting/context

Any

#### Study design

All types – See universal inclusion criteria
Summary of the key selection criteria

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults age ≥ 18 years with OPSCC or head and neck SCC</td>
</tr>
<tr>
<td>• Treatment with definitive or adjuvant RT or chemoradiation</td>
</tr>
<tr>
<td>• At least 30% of the cohort is OPSCC</td>
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</table>

<table>
<thead>
<tr>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Universal exclusion criteria above</td>
</tr>
</tbody>
</table>

Validation Set

28854069 or 27007578 or 16549836 or 21310545 or 9323143 or 22284033 or 24898672 or 28854069 or 24947059 or 35157995 or 34702772 or 32017652 or 31088830

Abbreviations: IMRT = intensity modulated radiation therapy; OPSCC = oropharyngeal squamous cell carcinoma, RT = radiation therapy; SCC = squamous cell carcinoma.

Appendix B. Database: Ovid MEDLINE(R) Search Strategy

All* or (tonsil* or oropharyn*)

1 ("30449625" or "30449623" or "12506176" or "16467544" or "25154822" or "22261362" or "14657228" or "33862002" or "34098030" or "12506176" or "23414589" or "22261362").ui. (10)

2 ("34850994" or "33325579" or "27688115").ui. (3)

3 ("35230884" or "34699271" or "22749632" or "15128894" or "15128893" or "29220295" or "16161069").ui. (7)

4 ("11597795" or "25366680" or "24613816" or "22261362" or "14511925" or "20530316" or "34699271" or "33507809" or "33127491" or "32044165" or "28029303").ui. (11)

5* (*25052236* or "35050342" or "33127491" or "31785337" or "28258895" or "22975604" or "11567806").ui. (7)

6 ("21236730" or "22296746" or "19540060" or "22056067" or "11395238" or "17848291" or "35000532" or "34754954" or "20421546").ui. (9)

7 ("28854069" or "27007578" or "16549836" or "21310545" or "9323143" or "22284033" or "24898672" or "28854069" or "24947059" or "35157995" or "34702772" or "32017652" or "31088830").ui. (12)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (56)

9 (tonsil* or oropharyn*).ti,ab,kf. (61039)

10 (head adj3 neck).ti. (49793)

11 (soft adj3 palate).ti,ab,kf. (5368)

12 (base adj3 tongue).ti,ab,kf. (3900)

13* Oropharynx/ (2255)

14* Palate, Soft/ (2264)

15* Palatine Tonsil/ (6243)

16 or/9-15 (114894)

17* Carcinoma, Squamous Cell/ (109023)

18 (cancer* or carcinoma* or squamous*).ti,ab,kf. (2680117)

19 17 or 18 (2688220)

20 16 and 19 (50232)

21 8 not 20 (0)

22 (radiotherap* or radiat* or irradiat* or chemoradi* or brachytherap* or IMRT or "intensity modulated radiation therapy" or VMAT or "volumetric modulated arc therapy").ti,ab,kf. (822236)

23* Radiotherapy/ or *radiotherapy, conformal/ or *radiotherapy, intensity-modulated/ or *radiotherapy dosage/ (46678)
24 or 23 (827860)

25 (altered* or accelerat* or week*) adj3 (radiat* or radiotherap* or chemoradiat* or chemoradiotherap* or fraction*).ti,ab,kf. (10764)

26 (hypofract* or hyperfract*).ti,ab,kf. (6998)

27 (de-intensif* or reduc* or de-escalat* or decreas* or shrink* or low*).ti,ab,kf. (246861)

28 (reduced-dose or low-dose).ti,ab,kf. (117542)

29 or/25-28 (261289)

30 (Target coverage or PTV coverage or PTV margin or target margin* or (planning adj3 margin) or (volume* or target* or GTV or CTV or PTV) adj6 (de-intensif* or reduc* or de-escalat* or decreas* or shrink* or low*)) or (PTV adj3 margin) or ((ipsilateral* or unilateral) adj3 (radiotherap* or radiat* or irradiat* or chemoradiat* or chemoradiotherap* or brachytherap* or IMRT or "intensity modulated radiation therapy" or VMAT or "volumetric modulated arc therapy") or (contralateral* adj3 (recur* or failure* or node* or nodal*)) or ((node* or nodal or I or II or III or IV or V) adj5 level*) or (retropharyngeal* adj3 (node* or nodal*)).ti,ab,kf. or *Radiotherapy, Conformal/mt or Radiotherapy, Intensity-Modulated/mt or radiotherapy/mt (387159)

31 (pharyngeal constrictor* or toxicit* or parotid* or submandibular* or saliv*).ti,ab,kf. (639645)

32 (chemotherap* or cisplatin* or carboplatin* or fluorouracil* or cetuximab* or "epidermal growth factor receptor inhibitor*" or "EGFR inhibitor*" or immunotherap* or pembrolizumab* or nivolumab* or avelumab* or checkpoint inhibitor*).ti,ab,kf. (685509)

33 induction*.ti,ab,kf. (555081)

34 *antineoplastic agents/ or *Antineoplastic Combined Chemotherapy Protocols/ or *carboplatin/ or *cetuximab/ or *fluorouracil/ or *Combined Modality Therapy/ or *Immunotherapy/ or *Antibodies, Monoclonal or *Antibodies, Monoclonal, Humanized or *Antineoplastic Agents, Immunological/ or *Programmed Cell Death 1 Receptor/ or Molecular Targeted Therapy/ (517693)

35 or/32-34 (1494850)

36 32 or 34 (993812)

37 "Head and Neck Neoplasms"/th [Therapy] (8950)

38 (resect* or dissect* or surg* or opera* or adjuvant* or neo,adjuvant*).ti,ab,kf. or (postoperative adj5 squamous cell).ti,ab. (3620246)

39 ("local**" or "locoregional**" or surviv* or progression-free or progression free or disparit*).ti,ab,kf. or *Survival Rate/ or *Disease-Free Survival/ or *Survival/ or *Progression-Free Survival/ or *Survival Analysis/ (2911568)

40 (swallow* or toxicit* or Late Effects of Normal Tissue or LENT SOMA or CTCAE or adverse event* or xerostomia* or dysphagia* or mucositis* or osteoradionecros* or "quality of life" or "quality-of-life" or "patient-reported-outcome**" or "patient reported outcome**").ti,ab,kf. or *xerostomia/ or *radiation injuries/ or *Patient Reported Outcome Measures/ or Radiotherapy/ae or Radiotherapy, Intensity-Modulated/ae or Radiotherapy, Conformal/ae or osteoradionecrosis/ (1171923)

41 (sensitivity or specificity or negative predictive value or positive predictive value).ti,ab,kf. (1258475)

42 "Sensitivity and Specificity"/ (368470)

43 39 or 40 (3872973)

44 or/39-42 (5151603)

45 (ctHPVDNA or ctHPV16DNA or ctDNA).ti,ab,kf. or circulating tumor DNA/ (4935)

46 ("cell-free**" or "cell free" or "circulating tumor**") adj3 DNA).ti,ab,kf. (11375)

47 ("positron emssion tomography" or "PET" or "PET/CT" or ultrasound).ti,ab,kf. (433956)
exp Positron-Emission Tomography/ or exp Tomography, X-Ray Computed/ or Positron Emission Tomography Computed Tomography/ (531481)

((persisten* or residual$) adj3 disease*).ti,ab,kf. (30532)

((incomplete* or complete*) adj3 response).ti,ab,kf. (56237)

or/45-50 (978531)

(trial* or phase II* or phase 2* or phase III* or phase 3* or meta-analys* or metaanalys* or randomi* or phase IV* or phase 4*).ti,ab,kf. (1760173)

clinical trial, phase II/ or clinical trial, phase III/ or clinical trial, phase IV/ or Meta-Analysis/ or controlled clinical trial/ or clinical trial/ or randomized clinical trial/ (791078)

52 or 53 (2135477)

54 52 or 53 (2135477)

55 54 not (1 or 3 or 4) (2135451)

56 20 and 24 and 36 and 43 and 54 (2356)

57 1 not 56 (0)

58 (20 and 24 and 38 and 43) not 35 (2978)

59 2 not 58 (0)

60 20 and 24 and 35 and 38 and 43 and 54 (1077)

61 3 not 60 (0)

62 20 and 24 and 29 and 43 and 54 (1086)

63 4 not 62 (0)

64 20 and 24 and 30 and 43 (1304)

65 5 not 64 (0)

66 20 and 24 and 31 and 40 (4017)

67 6 not 66 (0)

68 20 and (24 or 37) and 44 and 51 (2282)

69 7 not 68 (0)

70 56 or 58 or 60 or 62 or 64 or 66 or 68 (9210)

71 8 not 70 (0)

72 limit 70 to english language (8676)

73 limit 72 to "review articles" (1254)

74 meta-analys*.ti,ab,kf. (266169)

75 73 and 74 (125)

76 (72 not 73) or 75 (7547)

77 limit 76 to case reports (232)

78 limit 76 to letter (37)

79 ("case report" or "case-report" or "narrative review").ti,ab,kf. (424238)

80 76 not (77 or 78 or 79) (7270)

81 limit 80 to editorial (11)

82 (editorial* or "response to comment*").ti,ab,kf. (80877)

83 80 not (81 or 82) (7259)

84 ("Surveillance, Epidemiology, and End Results*" or SEER* or "National Cancer Database*" or NCDB).ti,ab,kf. (21160)

85 83 not 84 (7107)

86 exp Palliative Care/ or exp Palliative Medicine/ (63025)

87 palliati*.mp. (113181)
Line(s) | Purpose | Relevant (KQs)
---|---|---
1 | Validation Set | KQ1
2 | Validation Set | KQ2A
3 | Validation Set | KQ2B
4 | Validation Set | KQ3A&B
5 | Validation Set | KQ3C
6 | Validation Set | KQ4
7 | Validation Set | KQ5
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<tr>
<td>8</td>
<td>P</td>
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<tr>
<td>9-24*</td>
<td>I&amp;C: General Inclusive RT Topics</td>
<td>ALL KQ5</td>
</tr>
<tr>
<td>25-29*</td>
<td>I&amp;C: RT Altered Fractionation &amp; De-Intensification</td>
<td>KQ3A&amp;B</td>
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<tr>
<td>30</td>
<td>I&amp;C: RT Treatment Planning</td>
<td>KQ3C</td>
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<td>31</td>
<td>I&amp;C: RT OAR Sparing</td>
<td>KQ4</td>
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<td>32-34*</td>
<td>I&amp;C: Systemic Therapy (without induction keyword)</td>
<td>KQ1, 2B, 3-5</td>
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<td>35</td>
<td>I&amp;C: Induction Systemic Therapy</td>
<td>KQ2B, KQ3-5</td>
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<td>36</td>
<td>I&amp;C: All systemic therapy terms</td>
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<td>I&amp;C: Surgery (title only)</td>
<td>KQ2A&amp;B</td>
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<td>I&amp;C: Surgery (title, abstract, keywords)</td>
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<td>I&amp;C: Definitive RT (to exclude)</td>
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<td>40</td>
<td>O: Oncologic outcomes</td>
<td>All KQs</td>
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<tr>
<td>41</td>
<td>O: QoL Outcomes</td>
<td>All KQs</td>
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<td>42</td>
<td>O: Test sensitivity/specificity outcomes</td>
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<td>O: Oncologic &amp; QoL Outcomes Combined</td>
<td>KQ1-4</td>
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<tr>
<td>44</td>
<td>O: All outcomes combined</td>
<td>KQ5</td>
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<td>45-52*</td>
<td>I&amp;C: Post-treatment neck restaging/monitoring interventions</td>
<td>KQ5</td>
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<tr>
<td>53-55*</td>
<td>S: Prospective Phase II-IV Trials</td>
<td>KQ1, KQ2B, KQ3A&amp;B</td>
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<td>21 [P] and 24 [I&amp;C: General RT] and 34 [I&amp;C: Systemic Therapy] and 43 [O: Oncologic &amp; QoL Outcomes Combined] and 55 [S: Prospective Phase II-IV Trials]</td>
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<td>58</td>
<td>21 [P] and 24 [I&amp;C: General RT] and 36 [I&amp;C: Surgery] and 43 [O: Oncologic &amp; QoL Outcomes Combined] NOT 36 [I&amp;C: Systemic Therapy]</td>
<td>KQ2A</td>
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<td>59</td>
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<td>KQ2A</td>
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<td>21 [P] and 24 [I&amp;C: General RT] and 36 [I&amp;C: Systemic Therapy] and 37 [I&amp;C: Surgery] and 43 [O: Oncologic &amp; QoL Outcomes Combined] and 55 [S: Prospective Phase II-IV Trials]</td>
<td>KQ2B</td>
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<td>61</td>
<td>Confirmation no articles are missed by KQ2B output that are within KQ2B validation set</td>
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<tr>
<td>62</td>
<td>21 [P] and 24 [I&amp;C: General RT] and 29 [I&amp;C: RT Altered Fractionation &amp; De-Intensification] and 43 [O: Oncologic &amp; QoL Outcomes Combined] and 55 [S: Prospective Phase II-IV Trials]</td>
<td>KQ3A&amp;B</td>
</tr>
<tr>
<td>63</td>
<td>Confirmation no articles are missed by KQ3A&amp;B output that are within KQ3A&amp;B validation set</td>
<td>KQ3A&amp;B</td>
</tr>
<tr>
<td>64</td>
<td>21 [P] and 24 [I&amp;C: General RT] and 30 [I&amp;C: RT Treatment Planning] and 43 [O: Oncologic &amp; QoL Outcomes Combined]</td>
<td>KQ3C</td>
</tr>
<tr>
<td>65</td>
<td>Confirmation no articles are missed by KQ3C output that are within KQ3C validation set</td>
<td>KQ3C</td>
</tr>
<tr>
<td>66</td>
<td>21 [P] and 24 [I&amp;C: General RT] and 31 [I&amp;C: RT OAR Sparing] and 41 [O: QoL Outcomes]</td>
<td>KQ4</td>
</tr>
<tr>
<td>67</td>
<td>Confirmation no articles are missed by KQ4 output that are within KQ4 validation set</td>
<td>KQ4</td>
</tr>
<tr>
<td>68</td>
<td>21 [P] and 24 [I&amp;C: General RT] and 52 [I&amp;C: Post-treatment neck restaging/monitoring interventions] and 44 [O: All outcomes combined]</td>
<td>KQ5</td>
</tr>
<tr>
<td>69</td>
<td>Confirmation no articles are missed by KQ5 output that are within KQ5 validation set</td>
<td>KQ5</td>
</tr>
<tr>
<td>70</td>
<td>Output of all KQs combined to eliminate duplicates</td>
<td>All KQs</td>
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<tr>
<td>71</td>
<td>Final confirmation no articles are missed by KQ1-5 output that are within KQ1-5 validation set</td>
<td>All KQs</td>
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<tr>
<td>72</td>
<td>English Language Filter</td>
<td>All KQs</td>
</tr>
<tr>
<td>73-83</td>
<td>Filter to eliminate Review Articles without an associated meta-analysis, narrative reviews, case reports, editorials, and letters</td>
<td>All KQs</td>
</tr>
<tr>
<td>84-94</td>
<td>Filter to eliminate articles based on palliative care and cost assessments</td>
<td>All KQs</td>
</tr>
<tr>
<td>95</td>
<td>Eliminate nonadult studies</td>
<td>All KQs</td>
</tr>
<tr>
<td>96</td>
<td>Eliminate nonhuman studies</td>
<td>All KQs</td>
</tr>
<tr>
<td>99-102</td>
<td>Eliminate irrelevant histologies/tumor sites/topics</td>
<td>All KQs</td>
</tr>
<tr>
<td>103</td>
<td>Final confirmation no articles are missed by KQ1-5 output that are within KQ1-5 validation set</td>
<td>All KQs</td>
</tr>
<tr>
<td>104</td>
<td>Limit years of search from 2000-2022</td>
<td>All KQs</td>
</tr>
</tbody>
</table>

Abbreviations: KQ = key question; PICOTS framework: P = Population; I = Intervention; C = Comparative; T = Timing; S = Study Design; RT = Radiation Therapy; OAR = organ-at-risk; QoL = quality of life outcomes.

When there is a range of numbers, the last number contains all the previous sets.

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**Appendix D: PRISMA 2020 Checklist**

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Item #</th>
<th>Checklist item</th>
<th>Location where item is reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review.</td>
<td>Radiation Therapy for HPV-Positive Oropharyngeal Squamous Cell Carcinoma: An ASTRO Clinical Practice Guideline</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
<td>See the PRISMA 2020 for Abstracts checklist.</td>
<td>Abstract</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of existing knowledge.</td>
<td>Section 1, ¶1</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of the objective(s) or question(s) the review addresses.</td>
<td>Section 1, ¶2; Table 2 &amp; Appendix E3; also section 2.2</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>5</td>
<td>Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.</td>
<td>Section 2.3: ¶1</td>
</tr>
<tr>
<td>Information sources</td>
<td>6</td>
<td>Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.</td>
<td>Section 2.3: ¶1</td>
</tr>
<tr>
<td>Search strategy</td>
<td>7</td>
<td>Present the full search strategies for all databases, registers,</td>
<td>Appendix E4: Search Strategy</td>
</tr>
<tr>
<td>Section and Topic</td>
<td>Item #</td>
<td>Checklist item</td>
<td>Location where item is reported</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Selection process</strong></td>
<td>8</td>
<td>Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.</td>
<td>Section 2.3: ¶1</td>
</tr>
<tr>
<td><strong>Data collection process</strong></td>
<td>9</td>
<td>Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.</td>
<td>Section 2.3: ¶1</td>
</tr>
<tr>
<td><strong>Data items</strong></td>
<td>10a</td>
<td>List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.</td>
<td>Appendix E3</td>
</tr>
<tr>
<td><strong>Data items</strong></td>
<td>10b</td>
<td>List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.</td>
<td>Appendix E3</td>
</tr>
<tr>
<td><strong>Study risk of bias assessment</strong></td>
<td>11</td>
<td>Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.</td>
<td>Table 1</td>
</tr>
<tr>
<td><strong>Effect measures</strong></td>
<td>12</td>
<td>Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Synthesis methods</strong></td>
<td>13a</td>
<td>Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Synthesis methods</strong></td>
<td>13b</td>
<td>Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Synthesis methods</strong></td>
<td>13c</td>
<td>Describe any methods used to tabulate or visually display results of individual studies and syntheses.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Synthesis methods</strong></td>
<td>13d</td>
<td>Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Synthesis methods</strong></td>
<td>13e</td>
<td>Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Synthesis methods</strong></td>
<td>13f</td>
<td>Describe any sensitivity analyses conducted to assess robustness of the synthesized results.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Reporting bias assessment</strong></td>
<td>14</td>
<td>Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Certainty assessment</strong></td>
<td>15</td>
<td>Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.</td>
<td>Key Questions 1-5 via Strength of Evidence (SOE)</td>
</tr>
<tr>
<td>Section and Topic</td>
<td>Item #</td>
<td>Checklist item</td>
<td>Location where item is reported</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study selection</td>
<td>16a</td>
<td>Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.</td>
<td>Section 2.3 &amp; Appendix E6: Flow Diagram</td>
</tr>
<tr>
<td></td>
<td>16b</td>
<td>Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.</td>
<td>N/S</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>17</td>
<td>Cite each included study and present its characteristics.</td>
<td>Appendix E7: Evidence Table</td>
</tr>
<tr>
<td>Risk of bias in studies</td>
<td>18</td>
<td>Present assessments of risk of bias for each included study.</td>
<td>N/S</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>19</td>
<td>For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.</td>
<td>N/A</td>
</tr>
<tr>
<td>Results of syntheses</td>
<td>20a</td>
<td>For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>20b</td>
<td>Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>20c</td>
<td>Present results of all investigations of possible causes of heterogeneity among study results.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>20d</td>
<td>Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.</td>
<td>N/A</td>
</tr>
<tr>
<td>Reporting biases</td>
<td>21</td>
<td>Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.</td>
<td>N/A</td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>22</td>
<td>Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.</td>
<td>Tables 3, 5, 6, 9 &amp; 11 via Quality of Evidence and Strength of Recommendation</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>23a</td>
<td>Provide a general interpretation of the results in the context of other evidence.</td>
<td>Section 3: Key Questions and Recommendations</td>
</tr>
<tr>
<td></td>
<td>23b</td>
<td>Discuss any limitations of the evidence included in the review.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>23c</td>
<td>Discuss any limitations of the review processes used.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>23d</td>
<td>Discuss implications of the results for practice, policy, and future research.</td>
<td>Section 3: Key Questions and Recommendations &amp; Section 4: Conclusions and Future Directions</td>
</tr>
<tr>
<td>OTHER INFORMATION</td>
<td>24a</td>
<td>Provide registration information for the review, including register name and registration number, or state that the review was not registered.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>24b</td>
<td>Indicate where the review protocol can be accessed, or state that a protocol was not prepared.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>24c</td>
<td>Describe and explain any amendments to information provided at registration or in the protocol.</td>
<td>N/A</td>
</tr>
<tr>
<td>Support</td>
<td>25</td>
<td>Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.</td>
<td>Title Page</td>
</tr>
<tr>
<td>Section and Topic</td>
<td>Item #</td>
<td>Checklist item</td>
<td>Location where item is reported</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Competing interests</td>
<td>26</td>
<td>Declare any competing interests of review authors.</td>
<td>Title Page</td>
</tr>
<tr>
<td>Availability of data, code and</td>
<td>27</td>
<td>Report which of the following are publicly available and where they can be</td>
<td>N/S</td>
</tr>
<tr>
<td>other materials</td>
<td></td>
<td>found: template data collection forms; data extracted from included studies;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>data used for all analyses; analytic code; any other materials used in the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>review.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N/A = not applicable; N/S = not specified.


For more information, visit: http://www.prisma-statement.org/