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Special Article

Radiation therapy for oropharyngeal squamous cell carcinoma: Executive summary of an ASTRO Evidence-Based Clinical Practice Guideline

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Abstract

Purpose: To present evidence-based guidelines for the treatment of oropharyngeal squamous cell carcinoma (OPSCC) with definitive or adjuvant radiation therapy (RT).

Methods and materials: The American Society for Radiation Oncology convened the OPSCC Guideline Panel to perform a systematic literature review investigating the following key questions: (1) When is it appropriate to add systemic therapy to definitive RT in the treatment of OPSCC? (2) When is it appropriate to deliver postoperative RT with and without systemic therapy following primary surgery for OPSCC? (3) When is it appropriate to use induction chemotherapy in the treatment of OPSCC? (4) What are the appropriate dose, fractionation, and volume regimens with and without systemic therapy in the treatment of OPSCC?

Results: Patients with stage IV and stage T3 N0-1 OPSCC treated with definitive RT should receive concurrent high-dose intermittent cisplatin. Patients receiving adjuvant RT following surgical resection for positive surgical margins or extracapsular extension should be treated with concurrent high-dose intermittent cisplatin, and individuals with these risk factors who are intolerant of cisplatin should not routinely receive adjuvant concurrent systemic therapy. Induction chemotherapy should not be routinely delivered to patients with OPSCC. For patients with stage IV and stage T3 N0-1 OPSCC ineligible for concurrent chemoradiation therapy, altered fractionation RT should be used.

Conclusion: The successful management of OPSCC requires the collaboration of radiation, medical, and surgical oncologists. When high-level data are absent for clinical decision-making, treatment recommendations should incorporate patient values and preferences to arrive at the optimal therapeutic approach.

Introduction

The epidemiology and prognosis of oropharyngeal squamous cell carcinoma (OPSCC) has changed dramatically over the past 30 years, such that its treatment and expected outcomes are vastly improved from a generation ago. The intended focus of these guidelines is the curative management of OPSCC with primary radiation therapy (RT) with or without concurrent systemic therapy. These guidelines also address the use of adjuvant RT and chemoradiation therapy (CRT) for those patients selected for primary surgical management. Specific recommendations as to the selection of the primary treatment modality (surgical vs nonsurgical approaches) are beyond the scope of these guidelines. Although it is clear that human papillomavirus (HPV) status and smoking history strongly influence the prognosis of patients with oropharyngeal cancer,[1] such outcomes have been achieved with standard therapies; because of the absence of convincing data confirming similarly favorable outcomes with deintensified therapy, the panel has made treatment recommendations independent of HPV and smoking status. Studies assessing deintensified therapy for non-heavy smokers with HPV-related OPSCC are ongoing, and their results may, or may not, alter future guidelines for these patients. This guideline is endorsed by the American Society of Clinical Oncology and the European Society for Radiotherapy & Oncology.

Methods and materials

American Society for Radiation Oncology Evidence-Based Practice Guideline panels generate recommendation statements using strict criteria and processes approved by the American Society for Radiation Oncology Guidelines Subcommittee, Clinical Affairs and Quality Committee, and Board of Directors. These processes are based on the Institute of Medicine and Grading of Recommendations Assessment, Development, and Evaluation standards that were developed to ensure unbiased, evidence-based guideline products. This methodology strongly prioritizes high-level data whenever available.

The Key Question (KQ) writing groups generally only considered studies in which OPSCC comprised at least 50% of the study population, although questions involving postoperative RT (PORT) considered more data sources, owing to the smaller OPSCC composition of these studies. All Tumor-Node-Metastasis stages are derived from the American Joint Commission on Cancer, version 7, staging system,[2] because the data driving these recommendations are based on the older, HPV-agnostic staging system.

For more information on the literature review, the grading of the recommendations and evidence, and the consensus methodology, please see the full guideline. (http://dx.doi.org/10.1016/j.prro.2017.02.002)

Results

KQ 1. When is it appropriate to add systemic therapy to definitive RT in the treatment of OPSCC?

1. *In the scenario of stage IVA-B disease?*
   A. Concurrent high-dose intermittent cisplatin should be delivered to patients with stage IVA-B OPSCC receiving definitive RT. *(Strong recommendation [Strong], high-quality evidence [HQE], percent consensus 100%)*

B. Concurrent cetuximab or carboplatin-fluorouracil should be delivered to patients with stage IVA-B OPSCC receiving definitive RT who are not medically fit for high-dose cisplatin. *(Strong, HQE, 88%)*
C. Concurrent weekly cisplatin may be delivered to patients with stage IVA-B OPSCC receiving definitive RT who are not medically fit for high-dose cisplatin, after a careful discussion of patient preferences and the limited prospective data supporting this regimen. *(Conditional recommendation [Conditional], low-quality evidence [LQE], 94%)*
D. Concurrent cetuximab should not be delivered in combination with chemotherapy to patients with stage IVA-B OPSCC receiving definitive RT. *(Strong, HQE, 100%)*
E. Intra-arterial chemotherapy should not be delivered to patients with stage IVA-B OPSCC receiving definitive RT. *(Strong, HQE, 100%)*

Data from multiple randomized trials are consistent that concurrent chemotherapy improves locoregional control (LRC) and typically overall survival (OS) for patients with locally advanced OPSCC, regardless of fractionation approach.[3] Although chemotherapy significantly increased acute toxicities, these trials did not confirm that physician-assessed late effects were worse than those after treatment with RT alone, recognizing that late complications may be challenging to study. The single randomized trial using cetuximab also confirmed LRC and OS advantages with concurrent systemic therapy.[4] Because the majority of the patients in these trials presented with stage IV disease, concurrent systemic therapy should be delivered in this population of patients, with bolus cisplatin favored because of its long track record in successful large multi-institutional trials and well-known and predictable toxicity profile.

Although weekly cisplatin may be an acceptable alternative to high-dose administration, the evidence suggesting a survival benefit with its use is significantly weaker and based on extrapolation rather than high-level evidence. The Ghosh-Laskar randomized trial using weekly cisplatin (30 mg/m^2) showed an LRC but no OS benefit to CRT, although the trial was underpowered.[5] The Eastern Cooperative Oncology Group 2382 study randomized patients to RT with or without weekly cisplatin (20 mg/m^2). This dose is now understood to be too low for adequate radiosensitization, but weekly cisplatin nevertheless did not improve failure-free survival or OS.[6] The prime rationale for weekly delivery is to improve tolerability without compromising tumor control, but retrospective studies are mixed on the relative risks and benefits of the 2 schedules. Existing data do not consistently support the contentions that weekly cisplatin is better tolerated and/or allows for a similar or higher chemotherapy dose intensity, which has never been convincingly shown to impact outcomes in the weekly setting. For example, although some of these studies showed increased renal toxicity and hospitalization risk from high-dose intermittent cisplatin (HDIC),[7,8] weekly administration was associated with more mucositis and less total cisplatin delivery.[8] Weekly cisplatin may be given if the patient is not a candidate for bolus delivery, but the lack of data guiding its use should be discussed with the patient, especially considering high-level data supporting OS gains with competing regimens.

2. *In the scenario of stage III disease?*
F. Concurrent systemic therapy should be delivered to patients with T3 N0-1 OPSCC receiving definitive RT. *(Strong, Moderate-quality evidence [MQE], 100%)*
G. After a careful discussion of patient preferences and the limited evidence supporting its use, concurrent systemic therapy may be delivered to patients with T1-T2 N1 OPSCC receiving definitive RT who are considered at particularly significant risk for locoregional recurrence. *(Conditional, LQE, 100%)*

The stage III subgroup typically comprised a minority of the total population in the randomized studies of concurrent systemic therapy; these trials were therefore underpowered to address the benefit of CRT in this cohort. However, because concurrent systemic therapy is consistently associated with survival benefits in the randomized trials, the panel strongly recommends that patients with T3 N0-1 OPSCC, a population with bulkier and presumably more radioresistant primary disease, receive concurrent systemic therapy. For most patients with T1-2 N1 OPSCC, RT alone should be sufficient to obtain LRC. That the new 8th edition of the American Joint Commission on Cancer staging system recategorizes patients with p16-positive, T1-2 N1 OPSCC as stage I speaks to these patients' expected excellent prognosis. However, certain patients with T1-2 N1 OPSCC who are considered at particularly significant risk for locoregional recurrence may receive concurrent systemic therapy, because the absolute benefit of combined modality therapy may justify its toxicities in this population.

3. *In the scenario of stage I-II disease?*
H. Concurrent systemic therapy should not be delivered to patients with stage I-II OPSCC receiving definitive RT. *(Strong, LQE, 100%)*

No evidence was found supporting the use of systemic therapy in this generally favorable population.

KQ 2: When is it appropriate to deliver postoperative RT with and without systemic therapy following primary surgery of OPSCC?

1. *In the scenario of positive margins and/or extracapsular nodal extension (ECE)?*

A. Concurrent high-dose intermittent cisplatin should be delivered with postoperative RT to patients with positive surgical margins (PSMs) and/or extracapsular nodal extension; this high-risk population includes patients independent of HPV status or the extent of extranodal tumor. *(Strong, MQE, 100%)*
B. Concurrent weekly cisplatin may be delivered with postoperative RT to patients who are considered inappropriate for standard high-dose intermittent cisplatin after a careful discussion of patient preferences and the limited evidence supporting this treatment schedule. *(Conditional, LQE, 94%)*
C. For the high-risk postoperative patient unable to receive cisplatin-based concurrent chemoradiation therapy, RT alone should be routinely delivered without concurrent systemic therapy; given the limited evidence supporting alternative regimens, treatment with non-cisplatin systemic therapy should be accompanied by a careful discussion of the risks and unknown benefits of the combination. *(Strong, MQE, 94%)*
D. Patients treated with postoperative RT should not receive concurrent weekly carboplatin. *(Strong, MQE, 88%)*
E. Patients treated with postoperative RT should not receive cetuximab, either alone or in combination with chemotherapy, although such regimens are currently under investigation. *(Strong, LQE, 94%)*
F. Patients treated with postoperative RT should not routinely receive concurrent weekly docetaxel given the limited evidence supporting its use, although such regimens are currently under investigation. *(Strong, LQE, 88%)*
G. Patients treated with postoperative RT should not receive concurrent mitomycin-C, alone or with bleomycin, given the limited evidence and experience supporting its use. *(Strong, MQE, 100%)*
H. Postoperative chemotherapy should not be delivered alone or sequentially with postoperative RT. *(Strong, HQE, 94%)*

The results of 2 landmark trials of adjuvant chemoradiation therapy, European Organisation for Research and Treatment of Cancer 22931[9] and Radiation Therapy Oncology Group (RTOG) 9501,[10] were published simultaneously in 2004. Both studies compared PORT with postoperative CRT, using concurrent HDIC in patients deemed at high risk for recurrence. OS was statistically better in the European Organisation for Research and Treatment of Cancer study,[9] but only trended toward improvement in the first RTOG report. Long-term follow-up from the RTOG trial[10] no longer demonstrated any statistical benefit from the chemotherapy in the primary comparisons. Using retrospective, unplanned subgroup analysis, improved LRC and disease-free survival outcomes (with a strong trend toward improved OS) were identified in the CRT-treated patients with PSMs or ECE.[11] These observations have led to the strong recommendations for the addition of concurrent HDIC to adjuvant RT in these 2 high-risk populations. Although the implications of ECE in OPSCC have been questioned,[12] prospective studies that replicate these provocative retrospective results are needed before PORT alone can be recommended for HPV-positive OPSCC with ECE, even with microscopic extent.

In recent years, there has been considerable interest in lower dose, weekly drug administration schedules (30-40 mg/m^2/week) based on the assumption of less toxicity with comparable treatment efficacy. Despite the recognition that weekly dosing was adopted in RTOG 1216,[13] the panel does not feel the evidence is currently sufficient to strongly recommend its delivery in lieu of HDIC, because the high-dose regimen was evaluated in 2 large prospective phase 3 randomized trials with positive results.

Although cetuximab and docetaxel are promising agents in combination with RT,[7,14] no prospective or even retrospective studies have suggested efficacy when used alone in combination with PORT. Pending the results of active RTOG trials using these agents, the panel strongly recommends against using cetuximab and against routinely using docetaxel with PORT. In patients with a contraindication to cisplatin, RT alone provides an LRC benefit and is the recommended treatment choice, even when the risk of disease recurrence is high.

2. *In the scenario of intermediate-risk pathologic factors such as lymphovascular invasion (LVI), perineural invasion (PNI), T3-4 disease, or positive lymph nodes?*
I. Patients with intermediate-risk factors should not routinely receive concurrent systemic therapy with PORT. *(Strong, MQE, 88%)*
J. Patients with intermediate-risk factors whose surgical procedure and/or pathologic findings imply a particularly significant risk of locoregional recurrence may receive concurrent cisplatin-based chemotherapy after a careful discussion of patient preferences and the limited evidence supporting its use in this scenario; alternative systemic treatment regimens should only be used in the context of a clinical trial. *(Conditional, LQE, 88%)*
K. PORT should be delivered to patients with pathologic T3 or T4 disease. *(Strong, LQE, 94%)*
L. PORT should be delivered to patients with pathologic N2 or N3 disease. *(Strong, LQE, 100%)*
M. PORT may be delivered to patients with pathologic N1 disease after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario. *(Conditional, LQE, 88%)*
N. PORT may be delivered to patients with LVI and/or PNI as the only risk factor(s), after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario. *(Conditional, LQE, 100%)*

Because of the paucity of prospective randomized trials of adjuvant RT alone versus observation following surgery, the majority of data implicating intermediate-risk factors with locoregional recurrence are retrospective. Retrospective studies suggest that the risk of regional recurrence is sufficiently high with pathologic N2 disease to strongly recommend adjuvant RT in this population,[15] but the data on recurrence after observation for pN1 disease are much more variable, ranging from approximately 5%[16] to more than 20%[17]; therefore, the panel made a conditional recommendation that this latter population may receive adjuvant RT. It is particularly difficult to estimate the risk of locoregional recurrence in patients for whom PNI or LVI is the only adverse pathologic factor. These characteristics are often found in patients with other known risk factors for recurrence; this confounding can be difficult to resolve. Retrospective data are generally mixed on the relationship between locoregional failure and LVI and PNI, but there is certainly the suggestion that they reflect more aggressive locoregional disease.[14] Given the morbidity and mortality risk of local recurrence, PORT may be used for patients with either pathologic factor as the only adverse characteristic.

3. *In the scenario of no pathologic risk factors?*
   O. PORT may be delivered to patients without conventional adverse pathologic risk factors only if the clinical and surgical findings imply a particularly significant risk of locoregional recurrence, after a careful discussion of patient preferences and the potential harms and benefits of RT. *(Conditional, LQE, 100%)*

Narrative

There are limited prospective data on outcomes following primary surgery alone for oropharyngeal cancer. Although patients with pathologic stage I-II disease with wide margins, a pathologically negative neck, and no other adverse pathologic factors can typically be observed, patients whose surgical procedure or margin width are more concerning for local recurrence may be considered for adjuvant therapy. Careful discussion and collaboration among the members of the multidisciplinary team is necessary to optimize locoregional therapy.

KQ 3: When is it appropriate to use induction chemotherapy (IC) in the treatment of OPSCC?

A. IC should not be routinely delivered to patients with OPSCC. *(Strong, HQE, 100%)*
   The panel considered the potential indications for IC at length, and as expected, there was robust discussion. Ultimately, the panel considered the 3 published randomized trials (Combination Chemotherapy and Radiation in Treating Patients With Stage III or IV Head and Neck Cancer [PARADIGM]; A Phase III Randomized Trial Of Docetaxel (D), Cisplatin (P), 5-Fluorouracil (F) (TPF) Induction Chemotherapy (IC) in Patients With N2/N3 Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN) [DeCIDE]; and Spanish Cooperative Group) and found no progression-free or OS benefit with IC followed by CRT, yet all 3 studies confirmed higher rates of serious adverse events.[18-20] Thus, IC should not be routinely implemented in patients with OPSCC.

KQ 4: What are the appropriate dose, fractionation, and volume regimens with and without systemic therapy in the treatment of OPSCC?

In the scenario of definitive nonsurgical therapy?

A. A dose of 70 Gy over 7 weeks should be delivered to gross primary and nodal disease in patients with stage III-IV OPSCC selected to receive standard, once-daily definitive RT. *(Strong, MQE, 100%)*
B. The biologically equivalent dose of approximately 50 Gy in 2-Gy fractions or slightly higher should be delivered electively to clinically and radiographically negative regions at-risk for microscopic spread of tumor. *(Strong, LQE, 100%)*
C. Altered fractionation should be used in patients with stage IVA-B OPSCC treated with definitive RT who are not receiving concurrent systemic therapy. *(Strong, HQE, 94%)*
D. Either accelerated RT or hyperfractionated RT may be used in patients with OPSCC treated with altered fractionation definitive RT after a careful discussion of patient preferences and the limited evidence supporting 1 regimen over the other. *(Conditional, HQE, 100%)*
E. Either standard, once-daily RT or accelerated fractionation may be used when treating OPSCC with concurrent systemic therapy, after a careful discussion of patient preferences and the risks and benefits of both approaches. *(Conditional, HQE, 88%)*
F. Altered fractionation should be used in patients with T3 N0-1 OPSCC treated with definitive RT who do not receive concurrent systemic therapy. *(Strong, MQE, 94%)*
G. Altered fractionation may be used in patients with T1-2 N1 or T2 N0 OPSCC treated with definitive RT alone who are considered at particularly significant risk of locoregional recurrence, after a careful discussion of patient preferences and the limited evidence supporting its use in this scenario. *(Conditional, LQE, 100%)*

Narrative

The concept of altered fractionation (AltFX) refers to fractionation regimens that differ from standard, once-daily treatment. The majority of studies have demonstrated consistent and meaningful improvements in LRC and trends

toward reductions in overall mortality with AltFX, although individual trials were unable to confirm an OS advantage. Given the adverse clinical consequences of locoregional failure and the potential for a survival gain with its use, the panel strongly recommends AltFX RT for patients with stage IVA-B OPSCC managed with primary radiation alone. The panel concludes that the available evidence does not clearly support the use of 1 AltFX regimen over another, and either accelerated or hyperfractionated RT may be delivered. Although certain trends within the literature may support hyperfractionated RT, we refer the reader to the full guideline for a robust discussion of the data driving the recommendations statements on fractionation regimens.

Deriving recommendations for patients with stage III OPSCC is more challenging, because the proportion of patients with this stage was typically less than 30% in the defining clinical trials. However, because the preponderance of data strongly suggests that patients with larger volume disease need intensification beyond conventional RT alone, patients with T3 N0-1 disease who are not candidates for concomitant systemic therapy should receive AltFX alone.

The data guiding RT fractionation recommendations for stage II and III (T1-2 N1) disease are far less compelling, and there is significant volume heterogeneity even in this cohort. For individuals with T2 N0 and T1-2 N1 stage III disease considered at particularly significant risk for primary and/or nodal recurrence, AltFX may be used, but the clinician must weigh the patient's estimated risk of locoregional failure with conventional treatment against the recognized toxicities of AltFX.

The therapeutic alternative to AltFX for locally advanced head and neck cancer is concurrent chemoradiation therapy, the benefits of which were discussed in a prior narrative (KQ1). Because 2 large randomized trials[21,22] have shown no significant difference in oncologic outcomes or toxicities between conventional and accelerated fractionation with 3 and 2 cycles of bolus cisplatin or carboplatin/fluorouracil, respectively, the panel concludes either fractionation approach may be considered for patients with stage IVA-B oropharyngeal cancer treated with concurrent systemic therapy.

Intensity modulated RT (IMRT) has become the most commonly used modality in the United States,[23] because randomized trials have shown that IMRT leads to fewer cases of moderate to severe xerostomia, commonly known as dry mouth, than other radiation techniques.[24] Although there are various IMRT treatment strategies (eg, sequential IMRT, simultaneous integrated boost), the guideline does not recommend 1 approach over another.

In the scenario of adjuvant PORT?

A. Adjuvant PORT should be delivered to regions of microscopically positive primary site surgical margins and extracapsular nodal extension at 2 Gy/fraction once daily to a total dose between 60 and 66 Gy. *(Strong, MQE, 100%)*

B. Adjuvant PORT delivered without concurrent systemic therapy should treat regions of microscopically positive primary site surgical margins and extracapsular nodal extension at 2 Gy/fraction once daily to a total dose of 66 Gy, although there are limited data guiding this recommendation. *(Conditional, WQE, 100%)*

C. Adjuvant PORT should be delivered to the tumor bed, and involved, dissected lymph node regions at 2 Gy/fraction once daily to a total dose of at least 60 Gy in the absence of primary site positive margins and extracapsular nodal extension. *(Strong, MQE, 100%)*

The small volume of randomized data suggests improved LRC with treatment doses beyond 57.6 Gy for patients with positive margins and/or ECE.[25] The 3 randomized trials of accelerated PORT provided mixed results on LRC, but they were consistent in showing no OS benefit and markedly increased mucosal toxicity with intensified treatment[1,26,27]; therefore, the panel strongly recommends that patients receiving adjuvant PORT for PSMs and/or ECE are treated using daily fraction sizes of 2 Gy to a total dose between 60 and 66 Gy. This dose (60 Gy) is comparable to the 63 Gy in 7 weeks from Peters et al, while reducing the total package time.[25]

There are insufficient data to properly answer whether dose escalation beyond 60 Gy provides additional clinical benefit in patients with high-risk pathology, although high-risk regions received 60 to 66 Gy in the landmark postoperative trials. The panel conditionally recommends that patients with PSMs and/or ECE receiving PORT alone receive a total dose to these regions of 66 Gy in 2-Gy fractions, although the lack of high-quality data guiding this statement must be acknowledged.

The evidence guiding dose and fractionation regimens in the setting of negative margins and no ECE is similarly scant. The Peters study showed no advantage with 63 Gy versus 57.6 Gy in this population, but grade 3-4 toxicity was higher with the higher dose.[25] The panel considers that the dose of 57.6 Gy in 1.8-Gy fractions is approximately equivalent to 56 Gy in 2-Gy fractions. Because few data show successful long-term control outcomes with 56 Gy, however, and the delivered dose to involved stations using opposed lateral fields was presumably higher than the nominal dose, the panel chose a more conservative level and strongly recommends delivering 60 Gy to the tumor bed and involved lymph node stations in the absence of PSMs and ECE.

In the scenario of early T-stage tonsillar carcinoma?

K. Unilateral RT should be delivered to patients with well-lateralized (confined to tonsillar fossa) T1-T2 tonsillar cancer and N0-N1 nodal category. *(Strong, MQE, 88%)*

L. Unilateral RT may be delivered to patients with lateralized (<1 cm of soft palate extension but without base of tongue involvement) T1-T2 N0-N2a tonsillar cancer without clinical or radiographic evidence of

extracapsular extension, after careful discussion of patient preferences and the relative benefits of unilateral treatment versus the potential for contralateral nodal recurrence and subsequent salvage treatment. *(Conditional, LQE, 100%)*

Narrative

A significant volume of almost entirely retrospective data support the use of ipsilateral-only RT for tonsillar cancer with limited nodal metastases and no soft palate or tongue involvement as effective therapy with very rare contralateral recurrences.[28-30] Given the reduction in acute and late toxicities, the panel therefore strongly recommends ipsilateral treatment in this cohort. There is limited clinical experience that can confirm low contralateral recurrence rates with T1/T2 disease with minimal soft palate involvement and/or N2a category. The existent data are sufficiently encouraging to conditionally recommend ipsilateral RT in this population, provided patient preferences should be fully engaged on the expected quality-of-life benefits versus the uncertain risk of contralateral recurrence. Because of the paucity of data showing a low contralateral recurrence risk in small-volume N2b disease, they are not included in the conditional recommendation for the use of ipsilateral RT.

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