ACR Appropriateness Criteria® Locoregional therapy for resectable oropharyngeal squamous cell carcinomas

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ABSTRACT: *Background.* There are no level I studies to guide treatment for resectable oropharyngeal squamous cell carcinoma (SCC). Treatment toxicities influence management recommendations. Ongoing investigations are examining deintensified treatments for human papillomavirus (HPV)-associated oropharyngeal SCC.

Methods. The Appropriateness Criteria panel, using modified Delphi methodology, produced a literature summary, an assessment of treatment recommendations, and cases to illustrate their use.

Results. A multidisciplinary team produces optimum results. Based on HPV status, smoking history, and staging, patients are divided into groups at low, intermediate, and high-risk of death. In the future, treatment recommendations may be influenced by HPV status, which has changed the epidemiology of oropharyngeal SCC.

Conclusion. T1 to T2N0M0 resectable oropharyngeal SCC can be treated with surgery or radiation without chemotherapy. Patients with T1-2N1-2aM0 disease can receive radiation, chemoradiation, or transoral surgery with neck dissection and appropriate adjuvant therapy. Patients with T1-2N2b-3M0 disease should receive chemoradiation or transoral surgery with neck dissection and appropriate adjuvant therapy. Concurrent chemoradiation is preferred for T3 to T4 disease. © 2016 American College of Radiology. *Head Neck* **38**: 1299–1309, 2016

KEY WORDS: oropharyngeal cancer, human papillomavirus (HPV), tonsillar cancer, base of tongue cancer, transoral robotic surgery (TORS)

INTRODUCTION

The treatment options for resectable oropharyngeal carcinomas are diverse and include surgery, with or without postoperative radiotherapy/chemoradiotherapy (based on pathologic findings and patient factors), or definitive radiotherapy/chemoradiotherapy with or without adjuvant surgery (based on posttreatment imaging or biopsy findings). There is no level 1 evidence comparing definitive surgery with definitive chemoradiation, so comparing survival, local regional control, function, or quality of life between surgical and nonsurgical therapies objectively has been difficult.

Before the initiation of treatment, all patients with oropharyngeal cancer should be evaluated by a multidisciplinary treatment team that includes a head and neck surgical oncologist. Only the surgeon can decide if the individual cancer can appropriately be treated by resection (by either transoral or transcervical techniques). Whether a particular oropharyngeal cancer can be removed with adequate postoperative form and function will depend upon the head and neck surgeon, the reconstructive team, adjunctive services (such as speech and swallowing therapy), the patient's ability to participate in the rehabilitation, and the need for adjuvant therapy.

Common indications of unresectability of oropharyngeal squamous cell carcinoma (SCC) include involvement of the pterygoid muscles with severe trismus, pterygopalatine fossa involvement with cranial neuropathy, gross extension of tumor to the skull base (including erosion of the pterygoid plates or sphenoid bone), deep extension to the eustachian tube and lateral nasopharyngeal wall, and direct invasion or encasement of the internal or common

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VARIANT 1. T1–2 N0 M0. A 45-year-old man with a 20 pack/year smoking history.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	8	
Altered fractionation radiotherapy alone	8	
Brachytherapy and conventionally fractionated EBRT	5	This procedure depends on size and location of primary.
Concurrent platinum-based chemoradiation	1	
Concurrent cetuximab and radiation	1	
Induction chemotherapy followed by conventionally fractionated EBRT	1	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	1	
Induction chemotherapy followed by concurrent cetuximab and radiation	1	
Transoral or conventional surgical resection and neck dissection (if resectable)	8	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	7	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy.

carotid artery with radiographic evaluation suggesting disease involving $\geq 270^{\circ}$ of the vessel circumference.[1] For purposes of this monograph, all other oropharyngeal SCCs (including those of the base of the tongue that can be removed without concomitant total laryngectomy) are considered "resectable."

When deciding on the optimal treatment for a given patient, the treating team must consider the relative oncologic efficacy of various nonsurgical and surgical techniques, as well as preservation of appearance, swallowing, and speech function. For nonsurgical approaches, various treatment-intensification strategies have demonstrated

VARIANT 2. T1–2 N1–2a M0. A 45-year-old man with no tobacco exposure history, HPV-positive.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	6	
Altered fractionation radiotherapy alone	8	
Brachytherapy and conventionally fractionated EBRT	5	
Concurrent platinum-based chemoradiation	8	
Concurrent cetuximab and radiation	6	
Induction chemotherapy followed by conventionally fractionated EBRT	2	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	2	
Induction chemotherapy followed by concurrent cetuximab and radiation	2	
Transoral or conventional surgical resection and neck dissection (if resectable)	8	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	7	
If concurrent chemotherapy is given		
Cisplatin (100 mg/m^2) × 2–3 cycles	8	
Cisplatin (75 mg/m^2) × 3 cycles	6	
Cisplatin weekly ($<$30 mg/m^2)	3	
Cisplatin weekly ($\geq$30 mg/m^2)	5	
Carboplatin/PF	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: HPV, human papillomavirus; EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin and 5-fluorouracil.

VARIANT 3. T1–2 N2b–3 M0. A 45-year-old man with no tobacco exposure history, HPV-positive.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiotherapy alone	5	
Brachytherapy and conventionally fractionated EBRT	2	
Concurrent platinum-based chemoradiation	8	
Concurrent cetuximab and radiation	6	
Induction chemotherapy followed by conventionally fractionated EBRT	2	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	5	
Induction chemotherapy followed by concurrent cetuximab and radiation	3	
Transoral or conventional surgical resection and neck dissection (if resectable)	7	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	7	
If concurrent chemotherapy is given		
Cisplatin (100 mg/m^2) × 2–3 cycles	8	
Cisplatin (75 mg/m^2) × 3 cycles	6	
Cisplatin weekly (<30 mg/m^2)	3	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/PF	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: HPV, human papillomavirus; EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin and 5-fluorouracil.

increased success in locoregional disease control rates but at the cost of an increased risk of late swallowing dysfunction[2–4] with quantifiable impact on quality of life measures[5] (see Variant 1).

Treatment selection is further influenced by the recent dominance of positive human papillomavirus (HPV)-related cancers within the oropharynx. HPV-related cancers are typically characterized by a younger patient population and a more favorable prognosis, as defined by superior locoregional control and survival rates.[6] It is clear that, among HPV-related oropharyngeal carcinomas, there is clinically significant heterogeneity, defined by clinical factors, such as tobacco exposure or TNM classification. Regardless, this changing epidemiologic profile, compared to the prior profile associated with tobacco and ethanol abuse, has led to a reevaluation of successful treatment strategies and has provided the impetus to evaluate various treatment deintensification strategies, including radiotherapy dose deescalation protocols, elimination of chemotherapy, and reintroduction of surgery in an effort to limit the toxicities of the other 2 modalities. The impact of the clinical factors remains the subject of investigations and represents important stratification considerations in optimizing future deintensification strategies.

Therapeutic implications of patients with human papillomavirus–positive oropharyngeal carcinomas

Population-based reports,[7] retrospective reports,[8–15] and clinical trials[16–21] analyzed with post hoc stratification based on the HPV status and at least 1 prospective trial,[22] confirm that patients with HPV-positive oropharyngeal carcinomas have significantly improved results after treatment. Most of these trials reported the results of patients treated with concurrent chemoradiotherapy. However, this does not guarantee that the favorable prognosis is due to increased radiation and chemotherapy sensitivity. Several studies have reported that patients who were HPV-positive and were treated with surgery with or without postoperative radiotherapy had significantly improved survival compared with HPV-negative patients with oropharyngeal carcinomas,[9,11,13] suggesting improved prognosis may be treatment-independent (see Variant 2).

Complicating how oropharyngeal carcinomas in patients who are HPV-positive should be treated is the recognition that a subgroup of these patients has an intermediate-level survival advantage compared to HPV-negative patients with oropharyngeal carcinomas.[13] It is clear that a significant history of tobacco exposure consistently and adversely affects survival.[15,19,23,24] Advanced clinical stage HPV-positive oropharyngeal carcinoma is associated with an inferior survival. This includes T4 tumors[25] and advanced nodal status, defined differently in many analyses. For example, the analysis of Radiotherapy Oncology Group (RTOG) 0129 used N2b to N3 nodal classification to "upstage" patients with HPV-positive disease into the intermediate-risk group,[26] and a retrospective subgroup analysis of RTOG 9003 and 0129 used N0 to N1 versus N2 to N3[19] to separate groups, although the Princess Margaret series suggested that N3 disease and patients with N2c disease not treated with chemotherapy are at higher risk for distant metastases.[25] Overall, when compared to the HPV status, the influence of N classification can have less prognostic influence and potentially less therapeutic

VARIANT 4. T1–2 N1–2a M0. A 65-year-old man with a 20 pack/year smoking history.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	3	
Altered fractionation radiotherapy alone	7	
Brachytherapy and conventionally fractionated EBRT	5	
Concurrent platinum-based chemoradiation	8	
Concurrent cetuximab and radiation	6	
Induction chemotherapy followed by conventionally fractionated EBRT	2	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	2	
Induction chemotherapy followed by concurrent cetuximab and radiation	2	
Transoral or conventional surgical resection and neck dissection (if resectable)	7	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	5	
If concurrent chemotherapy is given		
Cisplatin (100 mg/m^2) $\times$ 2–3 cycles	8	
Cisplatin (75 mg/m^2) $\times$ 3 cycles	6	
Cisplatin weekly ($<$30 mg/m^2)	3	
Cisplatin weekly ($\geq$30 mg/m^2)	5	
Carboplatin/PF	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin and 5-fluorouracil.

implications than what holds true for HPV-negative patients with oropharyngeal carcinomas.[9,11,14] However, the specific finding of extracapsular extension does seem to continue to affect survival,[11] although further investigation continues and the definition of extracapsular extension is also evolving. These risk classifications require further validation but are likely to be important in identifying patients who may be suitable for treatment deintensification strategies. Alterations to standard therapeutic recommendations cannot yet be recommended (see Variant 3).

Despite the continued debates, for the favorable HPV cohort in which mature 3-year disease-free survival rates on the order of $\geq$80% can be achieved,[26] there is increasing emphasis on reducing the risk of late treatment complications, especially the risk of swallowing dysfunction. How this can be achieved is unclear at this time, but emphasis on radiotherapy dose reduction and alternative concurrent targeted therapy, chemotherapy regimens, and schedules, or even elimination of chemotherapy are all under active consideration. Definitive transoral surgery may reduce or eliminate the need for radiation and/or chemotherapy for some patients. These efforts are based on the finding that the risk of late swallowing dysfunction and percutaneous endoscopic gastrostomy dependency have been shown to be independently affected by concurrent chemotherapy.[2,3] At this time, no level I evidence exists to favor any of these approaches.

For the intermediate-risk HPV cohort, disease-free survival rates on the order of 55% to 65% can be expected using current treatment strategies,[13,15,19,26] suggesting a need for further judicious treatment intensification balanced against the possibility of long-term treatment complications. For the HPV-negative cohort, for whom survival rates of $\leq$50% can be expected when treated with standard concurrent chemoradiation, further investigational approaches are warranted. These can include further nonsurgical treatment intensification or a reevaluation of new transoral surgical techniques that carry less risk of swallowing complications[27–29] (see Variant 4).

Optimal radiotherapy treatment intensification

Several strategies using radiotherapy intensification have yielded evidence demonstrating that improvements in locoregional disease control translate into survival gains. These include the incorporation of interstitial brachytherapy techniques, altered fractionated radiotherapy, and intensity-modulated radiotherapy (IMRT) with simultaneous in-field boost (SIB).

The study of brachytherapy techniques has been limited to institutional experiences,[30–34] and their relative oncologic efficacy compared to external-beam radiotherapy techniques is completely untested. The generalizability of the results of these techniques is limited by the high level of skill and experience required for administering this treatment properly. The attraction of brachytherapy lies in the dosimetric advantages it confers both to the tumor and to the swallowing organs considered at risk for radiation injury. There is some controversy as to whether brachytherapy does[31,32] or does not[34] reduce the risk of late swallowing complications.

Meta-analyses have demonstrated that altered fractionation schedules can translate into survival gains.[35,36]

VARIANT 5. T3–4 N0–2a M0. A 65-year-old man.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiotherapy alone	4	This procedure is used if chemotherapy cannot be given.
Brachytherapy and conventionally fractionated EBRT	2	
Concurrent platinum-based chemoradiation	9	
Concurrent cetuximab and radiation	6	
Induction chemotherapy followed by conventionally fractionated EBRT	2	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	5	
Induction chemotherapy followed by concurrent cetuximab and radiation	4	
Transoral or conventional surgical resection and neck dissection (if resectable)	6	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	4	
If concurrent chemotherapy is given		
Cisplatin (100 mg/m^2) × 2–3 cycles	8	
Cisplatin (75 mg/m^2) × 3 cycles	6	
Cisplatin weekly (<30 mg/m^2)	3	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/PF	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin and 5-fluorouracil.

RTOG study 9003 demonstrated that in patients with locoregionally advanced head and neck cancer censored at 5 years, hyperfractionation showed a statistically significant improvement in survival[37] when compared to conventionally fractionated radiotherapy. However, using all information, both hyperfractionation and the concomitant boost arms decreased locoregional failure, compared to standard fractionation alone, by 19% ($p = .08$ for both). Functionally, those treated with hyperfractionation had better outcomes, with only 4.8% of disease-free patients at 5 years having feeding tubes versus 13.0% of concomitant-boost patients.

These original fractionation studies predated the use of IMRT. It is reasonable to extrapolate a similar tumor control benefit for altered fractionation while using IMRT. However, any increased corresponding toxicity might theoretically be mitigated because the volume of normal tissue subjected to altered fractionation should be much smaller with IMRT than with conventional 3D techniques.

More recently, the use of IMRT has facilitated the ability to prescribe an SIB, offering the ability to achieve highly conformal dose intensification. It remains to be determined if this prescription technique is equivalent to the delayed concomitant boost-accelerated fractionation schedule.[38] The only phase I trial conducted for SIB-IMRT enrolled 20 patients and demonstrated that a maximum tolerated dose occurred at 2.36 Gy delivered over 30 fractions to a total dose of 70.8 Gy. The final conclusion, based on acute toxicity evaluation, was that 2.27 Gy over 30 daily fractions was deemed to be safe; however, 6 of 12 patients (11 of 12 oropharyngeal carcinomas) were reported to have late toxicities, with 4 of 6 patients experiencing swallowing dysfunction.[39] Despite the recent increase in the use of IMRT for reasons of dose escalation and dosimetrically based normal-tissue sparing,[40] with some exceptions,[41,42] the published experience for IMRT remains largely composed of retrospective institutional reports reflecting heterogeneous prescription and treatment-planning approaches.[43,44] Institutional retrospective reports[43,45] and comparative phase III studies[46–48] support the role of IMRT for parotid-sparing indications. Conventional 3D conformal radiotherapy delivered by opposed lateral ports remains an acceptable alternative, but the weight of the evidence indicates that it does not offer the quality of life advantages seen with IMRT. The optimal prescription dose remains undefined, although most regimens attempt to mimic dose-fractionation patterns prescribed with conventional techniques or follow established institutional experiences. Procedures for cross-sectional anatomically based target definition and dose prescription have become critically important in the era of highly conformal radiation techniques. Close monitoring of IMRT outcomes in routine practice or referral to centers with expertise has been recommended, given the significant learning curve associated with the application of highly conformal irradiation to the head and neck[49,50] and the significant impact that appropriate treatment-planning techniques can have on outcomes.[51]

Optimal concurrent chemotherapy

A meta-analysis[52] and multiple phase III trials[53,54] support the contention that platinum-based chemoradiation improves survival as compared to standard radiation

alone. These experiences largely reflect but are not limited to the use of bolus dose schedules of cisplatin dose schedules typically at 100 mg/m^2. It is unclear if doublet regimens, such as cisplatin or carboplatin in combination with 5-fluorouracil (5-FU), produce survival gains comparable or superior to cisplatin alone.[55] Alternative regimens have gained recent attention because efforts are underway to develop risk-adapted therapies for low-risk HPV-associated oropharyngeal carcinomas and for the elderly population, in which the risk of late swallowing toxicities is of increased concern. Meta-analysis has demonstrated that with increasing patient age, treatment intensification with concurrent chemotherapy[52] (and altered fractionation[36]) provides less survival benefit and no significant benefit for patients over the age of 70. In addition, RTOG analyses show that advancing age is an independent risk factor for late swallowing toxicity when patients are treated with chemoradiation[4] (see Variant 5).

Weekly dosing of cisplatin has been favored by some in the hope that the regimen is as effective but better tolerated than the traditional bolus cisplatin schedule of 100 mg/m^2 every 3 weeks. However, an intergroup randomized trial of 307 eligible patients comparing 20 mg/m^2 of cisplatin with radiation to the same radiotherapy alone demonstrated no improvement in overall survival or freedom from failure, suggesting that 20 mg/m^2 (weekly) was too low a dose. Unfortunately, low-dose cisplatin was still hazardous; the study revealed an increased risk of late laryngeal and esophageal toxicities with weekly cisplatin at 20 mg/m^2.[56] In the face of recognized toxicity, institutional practices favoring a weekly schedule have typically favored doses of $\geq$30 mg/m^2. This is supported by data from nasopharyngeal carcinoma, in which, in endemic areas, phase III studies of weekly cisplatin at 30 to 40 mg/m^2 demonstrated significantly improved survival rates compared to radiotherapy alone.[57,58] The ability to generalize findings from nasopharyngeal cancer to oropharyngeal carcinoma is unclear because of the different behaviors of carcinomas between these anatomic sites. A retrospective report of 50 patients, mostly with advanced laryngeal cancer, compared administration of bolus cisplatin at 100 mg/m^2 every 3 weeks in younger patients with more favorable performance status to a schedule of weekly cisplatin at 40 mg/m^2 given to older patients with less favorable performance status,[59] combined with conventionally fractionated radiotherapy to 70 Gy. At short-term follow-up, locoregional disease control rates were comparable, but the follow-up was too short to make this conclusion anything but a working hypothesis.

Several small retrospective comparative reports using a range of weekly cisplatin doses from 20 mg/m^2 (in combination with 5-FU) to 40 mg/m^2 versus bolus cisplatin at 80 to 100 mg/m^2 have demonstrated more chemotherapy omissions and delays with use of the bolus high-dose schedule, raising concerns about the ability to achieve adequate dose intensity.[60,61] Several other institutional reports have described their results with weekly cisplatin at 40 mg/m^2 and 30 mg/m^2.[62–64] Overall, these results suggest comparable efficacy at 30 to 40 mg/m^2, with a potentially more favorable acute toxicity profile with weekly cisplatin; but hematologic toxicities may still be limiting at a weekly dose of 40 mg/m^2.[63] Despite these investigations, it is important to note that the most widely accepted standard of care, supported by level I evidence, remains the bolus cisplatin schedule.

Concurrent chemotherapy and altered fractionation

For locally advanced cancers with poor prognosis, expert opinion has favored the use of concurrent chemotherapy with conventionally fractionated radiation over altered-fractionated radiation alone because of the consistent survival gains seen in individual phase III trials of chemoradiation. In Groupe d'Oncologie Radiothérapie Tête et Cou 99-02, concurrent chemotherapy with conventionally fractionated radiation showed improved 3-year progression-free survival (PFS) over accelerated radiation alone (hazard ratio = 0.82; p = .041).[65] Concurrent chemotherapy may also potentially decrease the risk of distant relapse in advanced N2b to N3 neck disease.[66] A large retrospective analysis further supports the potential impact of concurrent chemotherapy on the risk of distant metastases in patients with HPV-associated oropharyngeal carcinoma with advanced N2b to N2c neck disease.[25]

Altered fractionated radiotherapy schedules have also been studied in combination with concurrent chemotherapy[67] (see Variant 6). Updated results from a German multicenter trial demonstrated improved locoregional control rates and overall survival with the addition of concurrent carboplatin and 5-FU to an accelerated fractionation schedule (using a delayed concomitant boost) in the treatment of stage III/IV oropharyngeal and hypopharyngeal carcinomas.[68] In contrast, accelerating the radiotherapy while using concurrent chemotherapy does not seem to confer an additional survival benefit. RTOG 0129 demonstrated no significant improvement in 5-year overall survival (hazard ratio = 0.90; p = .18) with the use of a concomitant boost schedule and 2 cycles of concurrent bolus cisplatin when compared to a standard daily fractionated schedule with 3 cisplatin cycles. One conclusion generated by these results was that the beneficial effects of acceleration facilitated the omission of the third cycle of cisplatin. Similar findings were seen in Groupe d'Oncologie Radiothérapie Tête et Cou 99-02,[65] with no difference in PFS seen between accelerated radiation combined with 2 cycles of carboplatin and 5-FU versus conventional radiation and 3 cycles of chemotherapy, although acute mucosal toxicity seemed increased with the accelerated chemoradiation. It should be noted that these trials, similar to the radiation-alone trials, predated the use of IMRT.

The role of cetuximab

The use of weekly cetuximab, an epidermal growth factor receptor inhibitor, is another emerging radiosensitizing strategy. Mature results now confirm that superior locoregional disease control and survival rates are seen with the addition of concurrent cetuximab to radiation.[69] In the initial analysis, it was suggested that the greatest activity may occur for oropharyngeal carcinomas,[70] which represented the majority of cancers in the trial. In both arms, 75% of the patients were treated with either accelerated or hyperfractionation therapy. The hypothesis that the combination of cetuximab and conventional radiation would be equally efficacious as schedules that use altered

VARIANT 6. T1–2 N2b–3 M0. A 65-year-old man with a 20 pack/year smoking history.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiotherapy alone	4	This procedure is used if chemotherapy cannot be given.
Brachytherapy and conventionally fractionated EBRT	2	
Concurrent platinum-based chemoradiation	9	
Concurrent cetuximab and radiation	6	
Induction chemotherapy followed by conventionally fractionated EBRT	2	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	5	
Induction chemotherapy followed by concurrent cetuximab and radiation	4	
Transoral or conventional surgical resection and neck dissection (if resectable)	7	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	7	
If concurrent chemotherapy is given		
Cisplatin (100 mg/m^2) × 2–3 cycles	8	
Cisplatin (75 mg/m^2) × 3 cycles	6	
Cisplatin weekly (<30 mg/m^2)	3	
Cisplatin weekly (≥30 mg/m^2)	5	
Carboplatin/PF	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin and 5-fluorouracil.

fractionation has not been tested. In the initial analysis, the opposite was suggested, as the combination of cetuximab with an altered fractionation schedule seemed to produce higher efficacy than when adding it to a conventional schedule.[69]

How cetuximab directly compares to cisplatin as a radiosensitizer is currently unknown, but RTOG 1016 (which has completed accrual) addressed the issue in patients with HPV-positive disease with final results pending. RTOG 0522 evaluated the relative efficacy of accelerated fractionation radiotherapy in combination with either cisplatin or cisplatin and cetuximab.[71] Ang et al[71] reported that with a median follow-up of 3.8 years, both PFS and overall survival were not significantly improved with the addition of cetuximab, including a cohort of p16-positive tumors. However, increased acute toxicities, including mucositis, were observed (including increased radiotherapy interruptions) with the addition of concurrent cetuximab. Thus, use of concurrent cetuximab in combination with concurrent platinum chemoradiation cannot be recommended.

A randomized phase II trial of concurrent chemoradiation plus cetuximab in the postoperative setting has recently been reported.[72] Patients with high-risk SCC were randomized to concurrent external radiation plus cetuximab with either concurrent cisplatin (30 mg/m^2/wk) or docetaxel (15 mg/m^2/wk). The docetaxel arm had a 13% 2-year distant failure rate, compared to a 25% 2-year distant failure rate for cisplatin. This is being followed up with a phase III trial.

Role for induction chemotherapy

The addition of docetaxel[73–75] or paclitaxel[76] to the traditional cisplatin and 5-FU (PF) induction backbone in several phase III trials has improved survival. A significant motivation to use induction chemotherapy was the hope that it might have an impact on the distant relapse rate, which becomes more relevant as locoregional disease control rates improve. Meta-analysis confirms that the addition of a taxane to PF does significantly reduce the risk of distant metastasis ($p = .009$), PFS ($p < .001$), and overall survival ($p < .001$).[77] Locoregional failure was also significantly reduced ($p = .007$), although it is difficult to determine how much the induction chemotherapy is contributing to this endpoint, given the heterogeneity of the 5 randomized trials evaluated. In 2 phase III trials, 21% to 23% of patients who began with induction docetaxel + PF were not able to receive the subsequent planned chemoradiation.[73,74,78]

To date, 4 randomized trials comparing induction chemoradiation to concurrent chemoradiation alone have been reported. Two of the trials closed early because of poor accrual rates. No significant survival differences were identified.[79,80] In the Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity trial, unplanned subgroup analysis demonstrated a nonsignificant trend to superior PFS in patients with oropharyngeal carcinomas who were treated with concurrent chemoradiotherapy alone compared with the oropharyngeal carcinoma cohort receiving induction

VARIANT 7. T3–4 N2b–3 M0. A 45-year-old man.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiotherapy alone	3	Consider this procedure if chemotherapy cannot be given.
Brachytherapy and conventionally fractionated EBRT	2	
Concurrent platinum-based chemoradiation	9	
Concurrent cetuximab and radiation	5	
Induction chemotherapy followed by conventionally fractionated EBRT	2	
Induction chemotherapy followed by concurrent platinum-based chemoradiation	6	
Induction chemotherapy followed by concurrent cetuximab and radiation	5	
Transoral or conventional surgical resection and neck dissection (if resectable)	5	This procedure is used with appropriate adjuvant therapy based on pathologic findings.
Radiation technique		
IMRT	9	
3D multifield techniques	4	
If concurrent chemotherapy is given		
Cisplatin (100 mg/m^2) $\times$ 2–3 cycles	8	
Cisplatin (75 mg/m^2) $\times$ 3 cycles	6	
Cisplatin weekly ($<$30 mg/m^2)	3	
Cisplatin weekly ($\geq$30 mg/m^2)	5	
Carboplatin/PF	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	5	

Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate.

Abbreviations: EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin and 5-fluorouracil.

chemotherapy. HPV status was not evaluated in this trial. Thus, it is not clear to what extent the induction chemotherapy is contributing beyond the impact of concurrent chemoradiotherapy, although it is clear that toxicities are increased.[80] In the DeCIDE trial, enrollment was limited to patients with N2 to N3 disease with no significant improvement in distant failure-free survival, recurrence-free survival, or overall survival.[79] Hitt et al[81] reported the results of a 3-arm phase III trial of induction docetaxel + PF for 3 cycles followed by concurrent cisplatin (bolus scheduled) chemoradiotherapy, induction PF for 3 cycles followed by concurrent cisplatin chemoradiotherapy and concurrent cisplatin-chemoradiotherapy in 439 patients with unresectable head and neck SCC (43% with oropharyngeal carcinomas). With a median follow-up of 23.8 months (range, 0.4–86.3 months), no significant differences were seen in the primary endpoint of PFS and time to treatment failure. A randomized phase II trial of patients with unresectable stage III/IV head and neck SCC, including the oropharynx, conducted by Italian investigators demonstrated superior complete response rates (primary endpoint), with a nonsignificant trend of improved PFS and overall survival with the combination of induction chemotherapy followed by concurrent chemoradiotherapy (PF) compared to concurrent chemoradiotherapy alone.[82] Unfortunately, the concurrent chemotherapy was weak and nonstandard.[55]

Based on the evidence to date, the administration of induction chemotherapy combining a taxane with the PF doublet cannot be routinely recommended. Whether the activity seen with induction docetaxel + PF benefits high-risk cohorts of patients, such as those with a significant history of tobacco exposure, HPV-positive carcinoma, or HPV-negative carcinoma, is unclear, and is the subject of clinical trials.

From a technical perspective, the impact of induction chemotherapy on highly conformal radiotherapy treatment-planning can be significant. Major unsettled issues include the optimal number of chemotherapy cycles (as it impacts the time to start the radiotherapy); the optimal target volume definition, including whether or not the postchemotherapy volume can be treated and to what prescribed dose; and whether or not the treatment-planning CT imaging should be done before or after the induction chemotherapy, because of potential dosimetric effects in changes in the neck contour with response to therapy (see Variant 7).

In summary, induction chemotherapy in resectable oropharyngeal carcinomas remains investigational, and its use should be restricted to selected patients at this time, preferably those treated on a clinical trial. Further intensification of induction regimens and novel multiagent or targeted agent combinations for either the induction or concurrent phase are being explored. Trials have also been initiated using less demanding strategies after induction; in some cases, no concurrent systemic therapy is given, or a targeted therapy can be given concurrently after the induction program. These approaches are considered strictly investigational.

Role of organ-preserving surgery

Transoral techniques offer the potential for organ-preserving surgical therapy, with retrospective and

prospective reports showing less morbidity, with similar local control rates comparable to the experiences seen in radiotherapy series.[27–29,83–86] These techniques are preferred to traditional open surgical approaches because swallowing complication rates seem lower, with permanent gastrostomy tube rates ranging from 0% to 3.9%.[27–29] As with the radiotherapy-based approaches, these reports have not evaluated speech and swallowing functions prospectively, but they reflect less-invasive approaches to exposure of the primary tumor that would otherwise have contributed to swallowing complications in the past. These methods remain limited to institutions with expertise in the techniques, and, hence, their generalizability has not been established. Transoral results are under active investigation (HPV-positive: Eastern Cooperative Oncology Group 3311, NCT01898494) and the number of surgeons with demonstrated expertise is rising rapidly. There are no randomized trials directly comparing surgical and nonsurgical approaches. It has been hypothesized that, given the poor survival rates seen in HPV-negative patients with oropharyngeal carcinomas treated with radiotherapy as the primary modality, surgical resection might be of benefit[8]; but, once again, strong evidence to support this contention is lacking. Indications for postoperative adjuvant radiotherapy[87] or chemoradiotherapy[88,89] have not been differentiated by HPV status, and this is another area with a wealth of theories but no convincing data.

Role of nonsurgical deintensification therapy

There is a low-risk cohort of patients with HPV-associated oropharyngeal carcinomas that has a favorable prognosis with current treatment but is also at risk for significant late treatment-related toxicities, including swallowing dysfunction that can impair quality of life. Defining this low-risk cohort is an area of investigation, along with treatment strategies intending to ameliorate current concurrent chemoradiotherapy toxicity. These include: (1) the substitution of potentially more-selective radiosensitizers, such as cetuximab (the subject of the recently closed-to-accrual RTOG 1016, with no results available at this time); (2) deescalation trials, including several ongoing institutional studies that are reducing the total radiotherapy dose with or without concurrent chemotherapy, as well as the national study in this vein, NRG-HN002; or (3) radiotherapy deescalation based on responses observed after induction chemotherapy. One of the earliest trials to investigate the role of deintensification using induction chemotherapy to identify a favorable cohort of HPV-associated oropharyngeal carcinomas was E1308. Preliminary results of this phase II trial demonstrate that acute toxicities seem to be reduced, with no mature oncologic results available.[90] Treatment deintensification of HPV-associated oropharyngeal carcinomas cannot be recommended outside of a clinical trial.

Summary of recommendations

Despite a smoking history, T1 to T2 N0 M0 resectable lateral oropharyngeal cancer should be treated with either definitive surgery or definitive radiation, without any systemic agent.

A patient with T1 to T2 N1 to N2a M0 resectable oropharyngeal cancer who is HPV-positive and a nonsmoker can be treated with definitive radiation alone, concurrent chemoradiation, or transoral surgery with neck dissection and appropriate adjuvant therapy.

A patient with T1 to T2 N2b to N3 M0 resectable oropharyngeal cancer who is HPV-positive and a nonsmoker is best treated with concurrent external radiation and cisplatin, or transoral surgery, neck dissection, and appropriate adjuvant therapy.

A patient with T1 to T2 N1 to N2a M0 resectable oropharyngeal cancer, either HPV-positive or HPV-negative, with a significant smoking history can be treated with definitive radiation alone, concurrent chemoradiation, or transoral surgery with neck dissection and appropriate adjuvant therapy.

A patient with T1 to T2 N2b to N3 M0 resectable oropharyngeal cancer, either HPV-positive or HPV-negative, with a significant smoking history should receive concurrent chemoradiation or transoral surgery with neck dissection and appropriate adjuvant therapy.

Patients with resectable T3 to T4 N0 to N2a M0 oropharyngeal cancer should preferentially receive concurrent external radiation and cisplatin.

Patients with resectable T3 to T4 N2b to N3 M0 oropharyngeal cancer should preferentially receive concurrent external radiation and cisplatin.

Summary of evidence

Of the 90 references cited in the *ACR Appropriateness Criteria Locoregional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas* document, all of them are categorized as therapeutic references, including 42 well-designed studies, 29 good-quality studies, and 2 quality studies that may have design limitations. There are 17 references that may not be useful as primary evidence.

The 90 references cited in the *ACR Appropriateness Criteria Locoregional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas* document were published between 1993 and 2014.

Although there are references that report on studies with design limitations, 71 well-designed or good-quality studies provide good evidence.

Supporting documents

For additional information on the Appropriateness Criteria methodology and other supporting documents, go to www.acr.org/ac.

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