

Manuscript: ACR Appropriateness Criteria® Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Expert Panel on Radiation Oncology–Head & Neck:

Jonathan J. Beitler, MD, MBA¹

Harry Quon, MD, MS²

Christopher U. Jones, MD³

Joseph K. Salama, MD⁴

Paul M. Busse, MD, PhD⁵

Jay S. Cooper, MD⁶

Shlomo A. Koyfman, MD⁷

John A. Ridge, MD, PhD⁸

Nabil F. Saba, MD⁹

Farzan Siddiqui, MD, PhD¹⁰

Richard V. Smith, MD¹¹

Francis Worden, MD¹²

Min Yao, MD, PhD¹³

Sue S. Yom, MD, PhD¹⁴

¹Principal Author, Emory University School of Medicine, Atlanta, Georgia.

²Co-author, Johns Hopkins University, Baltimore, Maryland.

³Co-author, Radiological Associates of Sacramento, Sacramento, California.

⁴Panel Vice-chair, Duke University Medical Center, Durham, North Carolina.

⁵Massachusetts General Hospital, Boston, Massachusetts.

⁶Maimonides Cancer Center, Brooklyn, New York.

⁷Cleveland Clinic Foundation, Cleveland, Ohio.

⁸Fox Chase Cancer Center, Philadelphia, Pennsylvania, American College of Surgeons.

⁹Emory University, Atlanta, Georgia, American Society of Clinical Oncology.

¹⁰Henry Ford Hospital, Detroit, Michigan.

¹¹Montefiore Medical Center, Bronx, New York, American College of Surgeons.

¹²University of Michigan, Ann Arbor, Michigan, American Society of Clinical Oncology.

¹³University Hospital Case Medical Center, Cleveland, Ohio.

¹⁴Panel Chair, University of California San Francisco, San Francisco, California.

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

Conflict of Interest:

Sue S. Yom, MD, PhD- “Genentech, Inc. - Research support (Dr. Yom is Principal Investigator of a supported clinical trial)”

Christopher U. Jones, MD- “Bristol Myers Squibb - Role: Speaking and Teaching.”

Corresponding Author:

Jonathan J. Beitler, MD, MBA

Attn: Department of Radiation Oncology

Emory University School of Medicine

550 Peachtree Street, NE

Atlanta, GA 30308

Email: jjbeitl@emory.edu

Reprint requests:

publications@acr.org

Abstract

Background: There are no level I studies to guide treatment for resectable oropharyngeal squamous cell carcinoma (OPSCC). Treatment toxicities influence management recommendations. Ongoing investigations are examining de-intensified treatments for HPV-associated OPSCC.

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 OPSCC.

Conclusions: T1-T2N0M0 resectable OPSCC can be treated with surgery or radiation without chemotherapy. T1-2N1-2aM0 patients can receive radiation, chemoradiation, or transoral surgery with neck dissection (TORS-ND) and appropriate adjuvant therapy. T1-2N2b-3M0 patients should receive chemoradiation or TORS-ND and appropriate adjuvant therapy. Concurrent chemoradiation is preferred for T3-4 disease.

Keywords –TBC

Oropharyngeal Cancer, HPV, Tonsil Cancer, Base of Tongue Cancer, TORS

Summary of Literature Review

Introduction/Background

The treatment options for resectable oropharyngeal (OP) carcinomas are diverse and include surgery, with or without postoperative radiation therapy (PORT)/chemoradiotherapy (based on pathologic findings and patient factors), or definitive radiation therapy/chemoradiotherapy with or without adjuvant surgery (based on post-treatment 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.

Prior to the initiation of treatment, all patients with oropharynx 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 oropharynx 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 rehabilitation, and the need for adjuvant therapy.

Common indications of unresectability of OP squamous cell carcinoma 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 carotid artery with radiographic evaluation suggesting disease involving $\geq 270^\circ$ of the vessel circumference [1]. For purposes of this monograph, all other OP squamous cell carcinomas (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 increased success in local-regional 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 local regional control and survival rates [6]. It is clear that amongst HPV-related OP carcinomas there is clinically significant

heterogeneity, defined by clinical factors such as tobacco exposure or tumor-node-metastasis stage. 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 radiation therapy dose de-escalation 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 Oropharyngeal Carcinomas in Human Papillomavirus–Positive Patients

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 OP 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 HPV-positive patients treated with surgery with or without PORT had significantly improved survival compared to HPV-negative patients with OP carcinomas [9,11,13], suggesting improved prognosis may be treatment independent (see [Variant 2](#)).

Complicating how OP carcinomas in HPV-positive patients should be treated is the recognition that a subgroup of these patients has an intermediate-level survival advantage compared to HPV-negative patients with OP 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 OP 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 Radiation Therapy Oncology Group[®] (RTOG[®]) 0129 used N2b-N3 nodal classification to “upstage” HPV-positive patients into the intermediate risk group [26], and a retrospective subgroup analysis of RTOG 9003 and 0129 used N0-1

versus N2-3 [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-stage can have less prognostic influence and potentially less therapeutic implications than what holds true for HPV-negative patients with OP carcinomas [9,11,14]. However, the specific finding of extracapsular extension (ECE) does appear to continue to affect survival [11], although further investigation continues and the definition of ECE 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 radiation therapy 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 1 evidence exists to favor any of these approaches.

For the intermediate-risk HPV cohort, disease-free survival rates on the order of 55%–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 Radiation Therapy Treatment Intensification

Several strategies using radiation therapy intensification have yielded evidence demonstrating that improvements in local-regional disease control translate into survival gains. These include the incorporation of interstitial brachytherapy techniques, altered fractionated radiation therapy, and intensity-modulated radiation therapy (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 radiation therapy 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]. 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 radiation therapy. However, using all information, both hyperfractionation and the concomitant boost arms decreased local-regional failure, compared to standard fractionation alone, by 19% ($P=0.08$ 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 3-D techniques.

More recently, the use of IMRT has facilitated the ability to prescribe a 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 (11 of 12 OP carcinomas) were reported to have late toxicities, with 4 of 6 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 3-D conformal radiation therapy 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/m². 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 OP carcinomas and for the elderly population, where 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/m² every 3 weeks. However, an Intergroup randomized trial of 307 eligible patients comparing 20 mg/m² of cisplatin with radiation to the same radiation therapy alone demonstrated no improvement in overall survival or freedom from failure, suggesting that 20 mg/m² (weekly) was too low a dose. Unfortunately, low-dose cisplatin was still hazardous; the study revealed an increased risk of late larynx and esophageal toxicities with weekly cisplatin at 20 mg/m² [56]. In the face of recognized toxicity, institutional practices favoring a weekly schedule have typically favored doses of ≥ 30 mg/m². This is supported by data from nasopharyngeal carcinoma, where in endemic areas phase III studies of weekly cisplatin at 30–40 mg/m² demonstrated significantly improved survival rates compared to radiation therapy alone [57,58]. The ability to generalize findings from nasopharyngeal cancer to OP carcinoma is unclear due to 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/m² every 3 weeks in younger patients with more favorable performance status (PS) to a schedule of weekly cisplatin at 40 mg/m² given to older patients with less favorable PS [59], combined with conventionally fractionated radiation therapy to 70 Gy. At short-term follow-up, local-regional 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/m² (in combination with 5-FU) to 40 mg/m² versus bolus cisplatin at 80–100 mg/m² 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/m² [62,63] and 30 mg/m² [64]. Overall, these results suggest comparable efficacy at 30–40 mg/m², 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/m² [63]. Despite these investigations, it is important to note that the most widely accepted standard of care, supported by level 1 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 due to the consistent survival gains seen in individual phase III trials of chemoradiation. In GORTEC 99-02, concurrent chemotherapy with conventionally fractionated radiation showed improved 3-year progression-free survival (PFS) over accelerated radiation alone (hazard ratio [HR], 0.82; *P*=0.041) [65]. Concurrent chemotherapy may also potentially decrease the risk of distant relapse in advanced N2b-3 neck disease [66]. A large retrospective analysis further supports the potential impact of concurrent chemotherapy on the risk of distant metastases in HPV-associated OP carcinoma patients with advanced N2b-N2c neck disease [25].

Altered fractionated radiation therapy schedules have also been studied in combination with concurrent chemotherapy [67] (see [Variant 6](#)). Updated results from a German multicenter trial demonstrated improved local-regional 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 OP and hypopharyngeal carcinomas [68]. In contrast, accelerating the radiation therapy while using concurrent chemotherapy does not seem to confer an additional survival benefit. RTOG 0129 demonstrated no significant improvement in 5-year overall survival (HR, 0.90; *P*=0.18) 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 GORTEC 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 appeared 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 local-regional 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 OP 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. The hypothesis that the combination of cetuximab and conventional radiation would be equally efficacious as schedules that use altered fractionation has not been tested. In the initial analysis, the opposite was suggested, as the combination of cetuximab with an altered fractionation schedule appeared 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 HPV-positive patients with final results pending. RTOG 0522 evaluated the relative efficacy of accelerated fractionation radiation therapy 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 radiation therapy 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 squamous cell cancer were randomized to concurrent external radiation plus cetuximab with either concurrent cisplatin (30 mg/m²/wk) or docetaxel (15 mg/m²/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 employ induction chemotherapy was the hope that it might have an impact on the distant relapse rate, which becomes more relevant as local-regional disease control rates improve. Meta-analysis confirms that the addition of a taxane to cisplatin and 5-FU does significantly reduce the risk of distant metastasis ($P=0.009$), PFS ($P<0.001$), and overall survival ($P<0.001$) [77]. Local-regional failure was also significantly reduced ($P=0.007$), though 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%–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 closed early due to poor accrual rates. No significant survival differences were identified [79,80]. In the PARADIGM trial, unplanned subgroup analysis demonstrated a nonsignificant trend to superior PFS in patients with OP carcinomas who were treated with concurrent chemoradiotherapy alone compared to the OP carcinoma cohort receiving induction 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 though it is clear that toxicities are increased [80]. In the DeCIDE trial, enrollment was limited to patients with N2-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 squamous cell carcinoma (HNSCC) (43% with OP carcinomas). With a median follow-up of 23.8 (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 HNSCC including the oropharynx conducted by Italian investigators demonstrated superior complete response rates (primary endpoint), with a nonsignificant trend of improved progression-free and overall survival with the combination of induction chemotherapy followed by concurrent chemoradiotherapy (cisplatin and 5-FU), 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 the subject of clinical trials.

From a technical perspective, the impact of induction chemotherapy on highly conformal radiation therapy treatment planning can be significant. Major unsettled issues include the optimal number of chemotherapy cycles (as it impacts the time to start the radiation therapy); 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 computed tomography imaging should be done before or after the induction chemotherapy, due to potential dosimetric effects in changes in the neck contour with response to therapy (see [Variant 7](#)).

In summary, induction chemotherapy in resectable OP 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 following 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 radiation therapy series [27-29,83-86]. These techniques are preferred to traditional open surgical approaches because swallowing complication rates appear lower, with permanent gastrostomy tube rates ranging from 0%–3.9% [27-29]. As with the radiation therapy-based approaches, these reports have not evaluated speech and swallowing function 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: ECOG 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 OP carcinomas treated with radiation therapy 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 radiation therapy [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 OP 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) de-escalation trials, including several ongoing institutional studies that are reducing the total radiation therapy dose with or without concurrent chemotherapy, as well as the national study in this vein, NRG-HN002; or 3) radiation therapy de-escalation based on responses observed following induction chemotherapy. One of the earliest trials to investigate the role of deintensification employing induction chemotherapy to identify a favorable cohort of HPV-associated OP carcinomas was E1308. Preliminary results of this phase II trial demonstrate that acute toxicities appear to be reduced, with no mature oncologic results available [90]. Treatment deintensification of HPV-associated OP carcinomas cannot be recommended outside of a clinical trial.

Summary of Recommendations

- Despite a smoking history, T1-2 N0 M0 resectable lateral OP cancer should be treated with either definitive surgery or definitive radiation, without any systemic agent.
- A patient with T1-2 N1-2a M0 resectable OP cancer who is HPV-positive and a nonsmoker can be treated with definitive radiation alone, concurrent chemoradiation, or transoral surgery/neck dissection and appropriate adjuvant therapy.
- A patient with T1-2 N2b-3 M0 resectable OP 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 T1-2 N1-2a M0 resectable OP cancer, either HPV-positive or HPV-negative, with a significant smoking history can be treated with definitive radiation alone, concurrent chemoradiation, or transoral surgery/neck dissection and appropriate adjuvant therapy.

- A patient with T1-2 N2b-3 M0 resectable OP cancer, either HPV-positive or HPV-negative, with a significant smoking history should receive concurrent chemoradiation or transoral surgery/neck dissection and appropriate adjuvant therapy.
- Patients with resectable T3-4 N0-2a M0 OP cancer should preferentially receive concurrent external radiation and cisplatin.
- Patients with resectable T3-4 N2b-3 M0 OP cancer should preferentially receive concurrent external radiation and cisplatin.

Summary of Evidence

Of the 90 references cited in the *ACR Appropriateness Criteria® Local-Regional 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 reference/references that may not be useful as primary evidence.

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

While 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.

References

1. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers. Version 2.2014.
Available at: http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed March 26, 2015.
2. Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2009;73(2):410-415.
3. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiother Oncol*. 2009;90(2):189-195.
4. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26(21):3582-3589.
5. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol*. 2008;26(22):3770-3776.
6. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol*. 2004;31(6):744-754.
7. Ernster JA, Sciotto CG, O'Brien MM, et al. Rising incidence of oropharyngeal cancer and the role of oncogenic human papilloma virus. *Laryngoscope*. 2007;117(12):2115-2128.
8. Chien CY, Su CY, Fang FM, et al. Lower prevalence but favorable survival for human papillomavirus-related squamous cell carcinoma of tonsil in Taiwan. *Oral Oncol*. 2008;44(2):174-179.
9. Fischer CA, Zlobec I, Green E, et al. Is the improved prognosis of p16 positive oropharyngeal squamous cell carcinoma dependent of the treatment modality? *Int J Cancer*. 2010;126(5):1256-1262.

0. Hannisdal K, Schjolberg A, De Angelis PM, Boysen M, Clausen OP. Human papillomavirus (HPV)-positive tonsillar carcinomas are frequent and have a favourable prognosis in males in Norway. *Acta Otolaryngol.* 2010;130(2):293-299.
1. Klozar J, Kratochvil V, Salakova M, et al. HPV status and regional metastasis in the prognosis of oral and oropharyngeal cancer. *Eur Arch Otorhinolaryngol.* 2008;265 Suppl 1:S75-82.
2. Klussmann JP, Mooren JJ, Lehnen M, et al. Genetic signatures of HPV-related and unrelated oropharyngeal carcinoma and their prognostic implications. *Clin Cancer Res.* 2009;15(5):1779-1786.
3. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol.* 2006;24(36):5630-5636.
4. Straetmans JM, Olthof N, Mooren JJ, de Jong J, Speel EJ, Kremer B. Human papillomavirus reduces the prognostic value of nodal involvement in tonsillar squamous cell carcinomas. *Laryngoscope.* 2009;119(10):1951-1957.
5. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol.* 2006;24(5):736-747.
6. Settle K, Posner MR, Schumaker LM, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. *Cancer Prev Res (Phila).* 2009;2(9):776-781.
7. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol.* 2008;26(19):3138-3146.
8. Kies MS, Holsinger FC, Lee JJ, et al. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. *J Clin Oncol.* 2010;28(1):8-14.

9. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. *J Clin Oncol*. 2012;30(17):2102-2111.
0. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol*. 2010;28(27):4142-4148.
1. Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J. HPV-associated p16-expression and response to hypoxic modification of radiotherapy in head and neck cancer. *Radiother Oncol*. 2010;94(1):30-35.
2. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008;100(4):261-269.
3. Hafkamp HC, Manni JJ, Haesevoets A, et al. Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. *Int J Cancer*. 2008;122(12):2656-2664.
4. Maxwell JH, Kumar B, Feng FY, et al. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. *Clin Cancer Res*. 2010;16(4):1226-1235.
5. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol*. 2013;31(5):543-550.
6. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.
7. Holsinger FC, McWhorter AJ, Menard M, Garcia D, Laccourreye O. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: I. Technique, complications, and functional results. *Arch Otolaryngol Head Neck Surg*. 2005;131(7):583-591.

8. Moore EJ, Henstrom DK, Olsen KD, Kasperbauer JL, McGree ME. Transoral resection of tonsillar squamous cell carcinoma. *Laryngoscope*. 2009;119(3):508-515.
9. Weinstein GS, Quon H, Newman HJ, et al. Transoral robotic surgery alone for oropharyngeal cancer: an analysis of local control. *Arch Otolaryngol Head Neck Surg*. 2012;138(7):628-634.
10. Harrison LB, Zelefsky MJ, Pfister DG, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue. *Head Neck*. 1997;19(3):169-175.
1. Horwitz EM, Frazier AJ, Martinez AA, et al. Excellent functional outcome in patients with squamous cell carcinoma of the base of tongue treated with external irradiation and interstitial iodine 125 boost. *Cancer*. 1996;78(5):948-957.
2. Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiother Oncol*. 2007;85(1):64-73.
3. Pernot M, Hoffstetter S, Peiffert D, et al. Role of interstitial brachytherapy in oral and oropharyngeal carcinoma: reflection of a series of 1344 patients treated at the time of initial presentation. *Otolaryngol Head Neck Surg*. 1996;115(6):519-526.
4. Petruson K, Mercke C, Lundberg LM, Silander E, Hammerlid E. Longitudinal evaluation of patients with cancer in the oral tongue, tonsils, or base of tongue--does interstitial radiation dose affect quality of life? *Brachytherapy*. 2005;4(4):271-277.
5. Budach W, Hehr T, Budach V, Belka C, Dietz K. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. *BMC Cancer*. 2006;6:28.
6. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368(9538):843-854.

7. Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2014;89(1):13-20.
8. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys*. 2000;48(1):7-16.
9. Lauve A, Morris M, Schmidt-Ullrich R, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II--clinical results. *Int J Radiat Oncol Biol Phys*. 2004;60(2):374-387.
0. Mell LK, Mehrotra AK, Mundt AJ. Intensity-modulated radiation therapy use in the U.S., 2004. *Cancer*. 2005;104(6):1296-1303.
1. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys*. 2010;76(5):1333-1338.
2. Toledano I, Graff P, Serre A, et al. Intensity-modulated radiotherapy in head and neck cancer: results of the prospective study GORTEC 2004-03. *Radiother Oncol*. 2012;103(1):57-62.
3. Eisbruch A, Ship JA, Dawson LA, et al. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. *World J Surg*. 2003;27(7):832-837.
4. Lee N, Xia P, Fischbein NJ, Akazawa P, Akazawa C, Quivey JM. Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. *Int J Radiat Oncol Biol Phys*. 2003;57(1):49-60.
5. Saarilahti K, Kouri M, Collan J, et al. Intensity modulated radiotherapy for head and neck cancer: evidence for preserved salivary gland function. *Radiother Oncol*. 2005;74(3):251-258.

- . Chao KS, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. *Int J Radiat Oncol Biol Phys*. 2001;49(4):907-916.
- . Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys*. 2006;66(4):981-991.
- . Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. 2011;12(2):127-136.
- . Gregoire V, De Neve W, Eisbruch A, Lee N, Van den Weyngaert D, Van Gestel D. Intensity-modulated radiation therapy for head and neck carcinoma. *Oncologist*. 2007;12(5):555-564.
- . Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. *J Clin Oncol*. 2006;24(17):2618-2623.
- . Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol*. 2010;28(18):2996-3001.
- . Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92(1):4-14.
- . Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21(1):92-98.
- . Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*. 2004;22(1):69-76.

5. Rodriguez CP, Adelstein DJ, Rybicki LA, et al. Randomized phase III study of 2 cisplatin-based chemoradiation regimens in locally advanced head and neck squamous cell carcinoma: Impact of changing disease epidemiology on contemporary trial design. *Head Neck*. 2014:[E-pub ahead of print].
6. Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *Int J Radiat Oncol Biol Phys*. 2011;81(3):719-725.
7. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol*. 2002;20(8):2038-2044.
8. Chen Y, Liu MZ, Liang SB, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1356-1364.
9. Uygun K, Bilici A, Karagol H, et al. The comparison of weekly and three-weekly cisplatin chemotherapy concurrent with radiotherapy in patients with previously untreated inoperable non-metastatic squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol*. 2009;64(3):601-605.
0. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. *Acta Oncol*. 2008;47(8):1513-1518.
1. Rades D, Fehlauer F, Sheikh-Sarraf M, et al. Toxicity of two cisplatin-based radiochemotherapy regimens for the treatment of patients with stage III/IV head and neck cancer. *Head Neck*. 2008;30(2):235-241.

2. Beckmann GK, Hoppe F, Pfreundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. *Head Neck*. 2005;27(1):36-43.
3. Steinmann D, Cerny B, Karstens JH, Bremer M. Chemoradiotherapy with weekly cisplatin 40 mg/m² in 103 head-and-neck cancer patients: a cumulative dose-effect analysis. *Strahlenther Onkol*. 2009;185(10):682-688.
4. Traynor AM, Richards GM, Hartig GK, et al. Comprehensive IMRT plus weekly cisplatin for advanced head and neck cancer: the University of Wisconsin experience. *Head Neck*. 2010;32(5):599-606.
5. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol*. 2012;13(2):145-153.
6. Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: altered fractionation regimens. *Lancet Oncol*. 2002;3(11):693-701.
7. Moreno-Jimenez M, Valero J, Lopez-Picazo JM, et al. Concomitant cisplatin, paclitaxel, and hyperfractionated radiotherapy in locally advanced head and neck cancer: comparison of two different schedules. *Am J Clin Oncol*. 2010;33(2):137-143.
8. Semrau R, Mueller RP, Stuetzer H, et al. Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: updated results of a randomized multicentric trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1308-1316.
9. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. 2010;11(1):21-28.
0. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354(6):567-578.

1. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522. *J Clin Oncol*. 2014:[E-pub ahead of print].
2. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. 2014;32(23):2486-2495.
3. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357(17):1705-1715.
4. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. 2007;357(17):1695-1704.
5. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst*. 2009;101(7):498-506.
6. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol*. 2005;23(34):8636-8645.
7. Blanchard P, Bourhis J, Lacas B, et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. *J Clin Oncol*. 2013;31(23):2854-2860.
8. Beitler JJ, Cooper JS. Seduction by induction? *J Clin Oncol*. 2009;27(1):9-10.
9. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol*. 2014;32(25):2735-2743.
0. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in

locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(3):257-264.

1. Hitt R, Grau JJ, Lopez-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol.* 2014;25(1):216-225.
2. Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. *Ann Oncol.* 2010;21(7):1515-1522.
3. Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC. Carcinoma of the tongue base treated by transoral laser microsurgery, part one: Untreated tumors, a prospective analysis of oncologic and functional outcomes. *Laryngoscope.* 2006;116(12):2150-2155.
4. Laccourreye O, Hans S, Menard M, Garcia D, Brasnu D, Holsinger FC. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. *Arch Otolaryngol Head Neck Surg.* 2005;131(7):592-599.
5. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg.* 2003;129(1):36-43.
6. Weinstein GS, O'Malley BW, Jr., Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. *Arch Otolaryngol Head Neck Surg.* 2007;133(12):1220-1226.
7. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys.* 1993;26(1):3-11.
8. Bernier J, Dommenege C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.

89. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350(19):1937-1944.
90. Marur S, Li S, Cmelak A, et al. E 1308: A phase II trial of induction chemotherapy (IC) followed by cetuximab with low dose versus standard dose IMRT in patients with human papilloma virus (HPV)-associated resectable squamous cell carcinoma of the oropharynx (OPSCC). *J Clin Oncol*. 2013;31:(suppl; abstr 6005).

Accepted Article

Tables: ACR Appropriateness Criteria® Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variant 1: T1-2 N0 M0. 45-year-old man with a 20 pack/year smoking history.

Treatment	Rating	Comments
Conventional fractionated external beam radiation therapy (EBRT) alone	8	
Altered fractionation radiation therapy 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	
3-D multifield techniques	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variant 2: T1-2 N1-2a M0. 45-year-old man with no tobacco exposure history, HPV-positive.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	6	
Altered fractionation radiation therapy 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	
3-D multifield techniques	7	
If Concurrent Chemotherapy Is Given		
Cisplatin (100 mg/m ²) × 2 to 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/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variant 3: T1-2 N2b-3 M0. 45-year-old man with no tobacco exposure history, HPV-positive.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiation therapy 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	
3-D multifield techniques	7	
If Concurrent Chemotherapy Is Given		
Cisplatin (100 mg/m ²) × 2 to 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/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variante 4: T1-2 N1-2a M0. 65-year-old man with a 20 pack/year smoking history.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	3	
Altered fractionation radiation therapy 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	
3-D multifield techniques	5	
If Concurrent Chemotherapy is given		
Cisplatin (100 mg/m^2) \times 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) \times 3 cycles	6	
Cisplatin weekly ($<30 \text{ mg/m}^2$)	3	
Cisplatin weekly ($\geq 30 \text{ mg/m}^2$)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variant 5: T3-4 N0-2a M0. 65-year-old man.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiation therapy 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	
3-D multifield techniques	4	
If Concurrent Chemotherapy Is Given		
Cisplatin (100 mg/m^2) \times 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) \times 3 cycles	6	
Cisplatin weekly ($<30 \text{ mg/m}^2$)	3	
Cisplatin weekly ($\geq 30 \text{ mg/m}^2$)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variant 6: T1-2 N2b-3 M0. 65-year-old man with a 20 pack/year smoking history.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiation therapy 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	
3-D multifield techniques	7	
If Concurrent Chemotherapy Is Given		
Cisplatin (100 mg/m ²) × 2 to 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/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	6	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Local-Regional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas

Variant 7: T3-4 N2b-3 M0. 45-year-old man.

Treatment	Rating	Comments
Conventional fractionated EBRT alone	2	
Altered fractionation radiation therapy 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	
3-D multifield techniques	4	
If Concurrent Chemotherapy Is Given		
Cisplatin (100 mg/m^2) \times 2 to 3 cycles	8	
Cisplatin (75 mg/m^2) \times 3 cycles	6	
Cisplatin weekly ($<30 \text{ mg/m}^2$)	3	
Cisplatin weekly ($\geq 30 \text{ mg/m}^2$)	5	
Carboplatin/cisplatin and 5-FU	5	
Carboplatin and paclitaxel	5	
Cetuximab weekly	5	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		