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LOCOREGIONAL THERAPY FOR RESECTABLE OROPHARYNGEAL SQUAMOUS CELL CARCINOMAS

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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 ≥270° 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 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 local regional control and survival rates [6]. It is clear that amongst HPV-related OP carcinomas there is clinically significant heterogeneity, defined by clinical

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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 ≥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 ≤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 locoregional 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 locoregional 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/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 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/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 radiation therapy 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 larynx 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 ≥30 mg/m^2. This is supported by data from nasopharyngeal carcinoma, where in endemic areas phase III studies of weekly cisplatin at 30–40 mg/m^2 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/m^2 every 3 weeks in younger patients with more favorable performance status (PS) to a schedule of weekly cisplatin at 40 mg/m^2 given to older patients with less favorable PS [59], combined with conventionally fractionated radiation therapy 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 80–100 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 [62,63] and 30 mg/m^2 [64]. Overall, these results suggest comparable efficacy at 30–40 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 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 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 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 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 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/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 employ 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 cisplatin and 5-FU does significantly reduce the risk of distant metastasis (P=0.009), PFS (P<.001), and overall survival (P<0.001) [77]. Locoregional 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® 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 from 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.

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Clinical Condition: **Locoregional 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: **Locoregional 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	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locoregional 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	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locoregional Therapy for Resectable Oropharyngeal Squamous Cell Carcinomas**

Variant 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) × 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	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locoregional 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) × 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	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Locoregional 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	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Locoregional 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) × 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	5	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		