review article

Evolving Treatment Paradigms for Oropharyngeal Squamous Cell Carcinoma

abstract

Oropharyngeal squamous cell carcinoma (OPSCC) is increasing in incidence in the United States and in many countries worldwide primarily as a result of increasing rates of human papillomavirus (HPV) infection. HPV-positive OPSCC represents a distinct disease entity from head and neck squamous cell carcinoma caused by traditional risk factors such as tobacco and alcohol, with different epidemiology, patterns of failure, and expected outcomes. Because patients with HPV-positive OPSCC have a younger median age and superior prognosis compared with their HPV-negative counterparts, they live longer with the morbidity of treatment, which can be severe. Therefore, efforts are under way to de-escalate therapy in favorable-risk patients while maintaining treatment efficacy. Additional work is being undertaken to discover new therapies that may benefit both HPV-positive and HPV-negative patient subsets. Herein, we will review the available data for the evolving treatment paradigms in OPSCC as well as discuss ongoing clinical trials.

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Authors' disclosures of potential conflicts of interest and contributions are found at the end of this article.

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INTRODUCTION

Human papillomavirus (HPV) is an increasingly important cause of oropharyngeal squamous cell carcinoma (OPSCC) worldwide as recognized by the WHO.[1] Compared with head and neck squamous cell carcinoma (HNSCC) caused by traditional risk factors, such as tobacco and alcohol, HPV-positive OPSCC behaves differently in terms of epidemiology, failure pattern, treatment response, and expected outcomes, leading to a paradigm shift in our management of these patients.[2,3] Specifically, the markedly improved prognosis of HPV-positive OPSCC coupled with its increased incidence in younger patient populations has spurred serious efforts at treatment deintensification to reduce the long-term toxicities associated with radiation and/or chemotherapy while still maintaining high cure rates.[3] The thrust to date has primarily involved reduction of radiation dose and/or volumes, implementation of less toxic chemotherapy regimens, or combinations thereof (Fig 1). Additional information is emerging regarding modifying salvage surgery in favor of surveillance after treatment and incorporation of novel therapies including immune modulators. A number of trials are planned or ongoing that endeavor to investigate these modifications.

EVOLVING TREATMENT STRATEGIES

Radiation De-Escalation

High-dose radiation is considered the most notorious cause of both acute and long-term toxicity for patients with locally advanced head and neck cancer. Mucositis and dermatitis are extremely common and can translate into late sequelae of taste alterations, problems with xerostomia and deglutition, and fibrosis and muscle atrophy (Fig 2). Cmelak et al[4] presented results from the Eastern Cooperative Oncology Group (ECOG) 1308 trial that aimed to identify candidates for radiation dose reduction on the basis of response to induction chemotherapy (IC). Ninety patients with resectable stage III, IVA, or IVB HPV-positive OPSCC were given IC with paclitaxel, cisplatin, and cetuximab. Patients who experienced a clinical complete response (cCR) at the primary site were treated with 54 Gy of radiation using intensity-modulated radiation therapy (IMRT), whereas any patient in whom less than cCR was observed received 69.3 Gy. Both arms received concurrent cetuximab with IMRT. With a median follow-up of 23 months, 71% of patients were noted to have a cCR to IC. The progression-free survival (PFS) rate at 23 months in this group was 84%, with a primary site local control rate of 94%, nodal control rate of

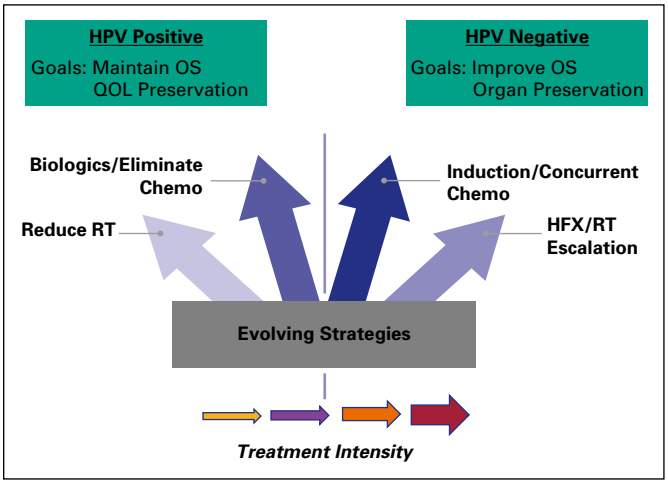

Fig 1 – Evolving strategies in human papillomavirus (HPV) –positive versus HPV-negative oropharyngeal squamous cell carcinoma. Chemo, chemotherapy; HFX, hyperfractionated; OS, overall survival; QOL, quality of life; RT, radiotherapy.

95%, and distant control rate of 92%. Only one late grade 3 toxicity (hypomagnesemia) occurred in a reduced-dose patient at 30 months, and a significant improvement in patient-reported difficulty swallowing solids, dry mouth, and alteration in taste and smell was noted at 12 months in the low-dose versus high-dose group (composite incidence, 67% *v* 100%, respectively; Table 1).

A phase II trial performed by Chera et al[5] included 43 patients with nonmetastatic HPV-positive T0-3N0-2c OPSCC or HNSCC of unknown primary with minimal or remote smoking history. Treatment was limited to 60 Gy using IMRT with concurrent weekly cisplatin. All patients underwent post-treatment biopsies of the primary site as well as selective dissection of pretreatment-positive lymph node (LN) regions. At a median follow-up of 14.6 months, all patients were alive without recurrence with an overall pathologic complete response (CR) rate of 86% (98% in the neck, 84% in the nodes). The incidence of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicity was as follows: mucositis, 34%; general pain, 5%; nausea, 18%; vomiting, 5%; dysphagia, 39%; and xerostomia, 2%. A temporary feeding tube was required in 39% of patients.

Villaflor et al[6] performed a phase I/II trial of 94 patients with stage IVA or IVB HNSCC investigating the addition of everolimus to IC. As part of the study, they incorporated a novel response-adapted volume de-escalation approach using response to IC to guide radiation treatment volumes. The IC regimen consisted of two cycles of cisplatin, paclitaxel, and cetuximab with or without everolimus. Of note, everolimus was discontinued after interim analysis revealed a lack of improvement of response to IC. Patients with a good response (GR) to IC (defined as a $\geq$ 50% reduction in the sum of tumor diameters) were treated with concurrent paclitaxel, fluorouracil, hydroxyurea, and radiation to 75 Gy using 1.5-Gy twice-daily fractionation given every other week to a single planning target volume (PTV1) encompassing only gross disease. Patients with a nonresponse (NR) to treatment ($<$ 50% response) were given

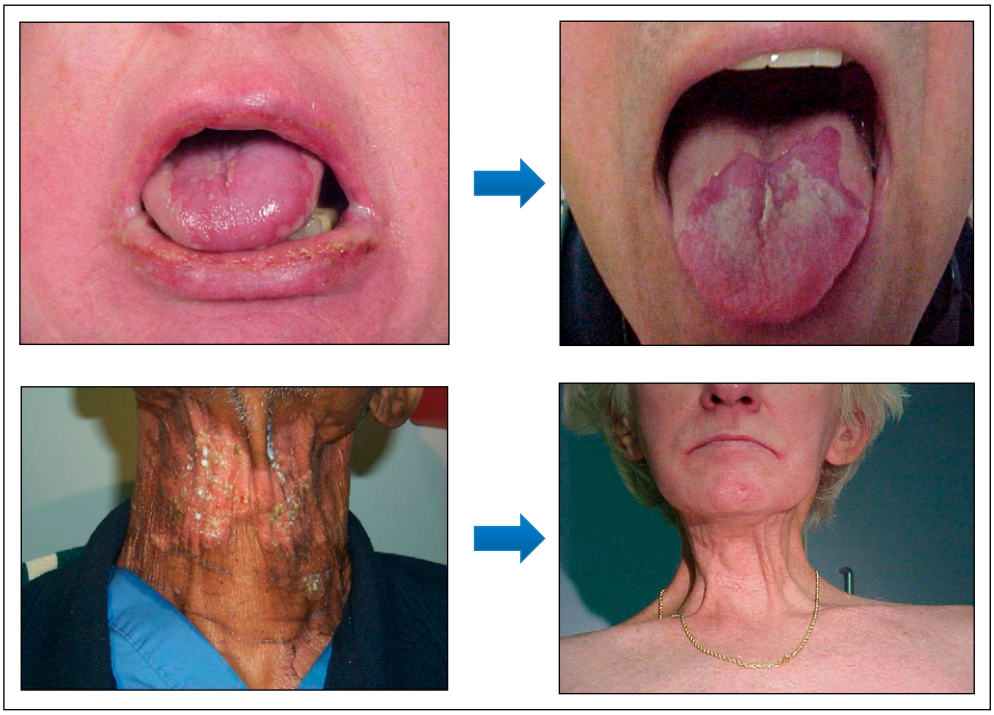

Fig 2 – Acute toxicities can translate into long-term sequelae from high-dose radiotherapy.

Table 1 – Eastern Cooperative Oncology Group 1308: Significant 12-Month Toxicity Clusters

Symptom Cluster Score ≥ 2 at 12 Months	No. of Questions in Cluster	Patients Scoring ≥ 2 (%)
Swallowing solids	8	49
Dry mouth	5	62
Taste/smell altered	5	39

NOTE. Composite incidence for the three symptom clusters in patients who were progression free at 12 months after treatment was 67% in patients who received reduced-dose radiation (54 Gy) compared with 100% in patients who received standard-dose radiation (69.3Gy; $P = .049$). Adapted from Cmelak, et al.[29]

paclitaxel, fluorouracil, hydroxyurea, and radiation with the same fractionation schedule as the GR group. However, an additional second planning target volume encompassing the next nodal station at risk was treated to a dose of 45 Gy followed by a sequential boost to PTV1 to 75 Gy. Sixty-three percent of patients had HPV-positive disease, of whom 81% (30 patients total) had a GR to IC compared with 13% of HPV-negative patients. Two-year PFS and overall survival (OS) were 93.1% and 92.1%, respectively, for HPV-positive patients with GR and 74% and 95%, respectively, for HPV-positive patients with NR. The majority of locoregional failures (12 of 13 locoregional failures; 92.3%) were in field, and all but one occurred in the highest risk PTV1. Reduced toxicity was seen in the GR arm because these patients were less likely to undergo gastrostomy tube placement (50% of GR arm *v* 73.5% of NR arm) during treatment and be gastrostomy tube dependent at 6-month follow-up (5.7% of GR arm *v* 32.6% of NR arm).

Chemotherapy Deintensification

Since the publication of the study by Bonner et al[7] showing improved survival for patients with HNSCC treated with radiation plus cetuximab versus radiation alone, interest has grown in determining whether cetuximab can replace traditional cytotoxic chemotherapy agents, such as cisplatin. A study from Memorial Sloan Kettering Cancer Center retrospectively compared 174 consecutive patients with HNSCC treated definitively between 2006 and 2008 with concurrent radiation and single-agent cisplatin or cetuximab. Although HPV status was not reported, 76% of patients had OPSCC. At a median follow-up of 22.5 months, patients treated with concurrent cisplatin, compared with those treated with cetuximab, had lower 2-year locoregional failure (5.7% *v* 39.9%, respectively) and improved failure-free survival (87.4% *v* 44.5%, respectively) and OS (92.8% *v* 66.6%, respectively). Treatment with cisplatin, as compared with cetuximab, was associated with improved locoregional control (LRC), failure-free survival, and OS on multivariable analysis. Late grade 3 or 4 toxicity or feeding tube dependence was similar between the groups.

A retrospective analysis of 168 HPV-positive patients with OPSCC treated both postoperatively (n = 23) and definitively (n = 145) at The Ohio State University Wexner Medical Center between 2010 and 2013 was performed.[8] Forty-two patients received concurrent cetuximab, whereas the remainder (n = 126) were given concurrent platinum-based therapy. For patients receiving cetuximab compared with platinum chemotherapy, multivariable analysis revealed inferior 2-year OS (80% *v* 96%, respectively), local relapse–free survival (74% *v* 91%, respectively), and distant metastasis–free survival (74% *v* 90%, respectively).

Magrini et al[9] recently published the first randomized trial directly comparing radiation with concurrent cisplatin versus cetuximab. Slow accrual resulted in early discontinuation of the trial after 70 of 130 planned patients were enrolled. Patients with stage III, IVA, or IVB HNSCC were randomly assigned to either radiation to 70 Gy with concurrent weekly cisplatin or weekly cetuximab. No HPV testing was performed, although almost half of the enrolled patients (n = 33) had OPSCC. No significant differences in OS, local control, or distant control were noted on analysis of the entire patient set. However, subset analysis of the patients with OPSCC revealed significantly improved local control, cause-specific survival, and OS in patients treated with cisplatin. Interestingly, radiation discontinuation for more than 10 days was more frequent in the cetuximab arm versus the cisplatin arm (13% *v* 0%, respectively), and severe adverse events related to treatment were more frequent with cetuximab than with cisplatin (19% *v* 3%, respectively). Additionally, three patients (9%) were noted to have cetuximab infusion reactions requiring removal from the trial. Toxicity profiles differed; more hematologic, GI, and renal toxicity was seen with cisplatin, whereas more cutaneous toxicity and nutritional support requirements were seen with cetuximab.

Surveillance Strategy

In line with the movement to deintensify treatment of HPV-positive OPSCC, efforts are being undertaken to determine the most effective and least invasive surveillance strategy for patients after treatment completion. The conventional treatment paradigm involved planned post-treatment neck dissection to assess for residual disease within the neck. Current practice has shifted toward an image-guided approach based primarily on retrospective

data regarding the effectiveness of cross-sectional imaging, including enhanced techniques such as positron emission tomography (PET) and computed tomography (CT).[10-12]

Investigators at the H. Lee Moffitt Cancer Center and Research Institute recently reported a retrospective review of 246 patients with HPV-positive OPSCC treated with definitive radiation or chemoradiation between 2006 and 2014.[13] All patients underwent a 3-month post-treatment PET/CT scan. Median follow-up for all patients was 36 months, with a 3-year local control rate of 97.8%. All local failures (n = 6) were detected by direct visualization or flexible laryngoscopy. Regional control was 95.3% at 3 years, and 89% of regional recurrences were found by symptoms or 3-month PET/CT. Combined 3-year LRC rate was 94%, with 92% of locoregional failures detected by examination or post-treatment PET/CT. Of the 9% of patients (n = 21) who experienced distant recurrence, the majority of recurrences (71%) were found as a result of symptoms or the 3-month post-treatment imaging. Factors predictive for distant failure included LN ⩾ 6 cm, bilateral lymphadenopathy, ⩾ 5 involved LNs, or LN involvement of level IV. Taken together, these data suggest that a 3-month post-treatment PET/CT scan and regular, thorough physical examination with direct visualization are sufficient to detect the majority of disease recurrences in HPV-positive OPSCC.

Mehanna et al[14] recently published results from the PET-NECK (PET-CT Surveillance Versus Neck Dissection in Advanced Head and Neck Cancer) noninferiority trial, which randomly assigned 564 patients with HNSCC (84% with OPSCC, 75% HPV positive) and N2 or N3 disease to PET/CT-guided surveillance performed 12 weeks after treatment versus a planned neck dissection approach. Patients in the PET/CT arm who experienced an equivocal or incomplete response underwent neck dissection within 4 weeks after imaging, whereas patients with a CR at the primary site and LNs underwent regular surveillance with imaging and examination. A CR was observed in 185 (69%) of 270 patients in the PET/CT arm. PET/CT-guided surveillance resulted in significantly fewer neck dissections than the planned dissection approach (54 *v* 221 dissections, respectively), and the rates of surgical complications were similar between the groups (42% *v* 38%, respectively) in patients who eventually underwent dissection. The 2-year OS rates were 84.9% in the surveillance group and 81.5% in the planned surgery group. Importantly, the hazard ratio (HR) for death in the surveillance group versus the planned surgery group slightly favored the surveillance group (0.92), meeting the definition for noninferiority for the trial. Additionally, the per-person cost saving for surveillance versus planned dissection was $2,190.

Novel surveillance techniques are currently being investigated to further guide post-treatment management of HPV-positive patients with OPSCC. HPV type 16 DNA can be detected in exfoliated cells from oral rinses in up to two thirds of patients with OPSCC before treatment.[15,16] The infection persists in a small subset of patients upon treatment completion and has been shown previously in retrospective studies to represent a potential early marker of disease recurrence.[17,18] Rettig et al[19] prospectively collected oral rinse samples from 124 HPV-positive patients with OPSCC treated between 2009 and 2013 to evaluate for HPV-16 DNA at diagnosis and after treatment. Oral HPV-16 DNA was found in 54% of patients (n = 67) upon initial diagnosis but was detected in only 5% of patients (n = 6) after treatment, including five patients in whom HPV-16 DNA was detected at baseline. All five patients with persistent oral HPV-16 DNA developed disease recurrence, including three patients with local recurrence, whereas only 8% of patients (nine of 119 patients) without persistent infection experienced disease recurrence. The median time from earliest post-treatment oral HPV-16 DNA detection to recurrence was 7 months. Persistent oral HPV-16 DNA was also associated with significantly worse disease-free survival (DFS; HR, 29.7) and OS (HR, 23.5).

Immune Modulation in HNSCC

Precedent exists for implementation of immune therapies in HNSCC because cetuximab, a monoclonal antibody (moAb) targeting epidermal growth factor receptor, has been shown to improve survival when added to radiation in the definitive treatment of HNSCC.[7] Current interests focus primarily on using immune checkpoint modulation of the programmed death-1 (PD-1) and cytotoxic T-cell lymphocyte-4 (CTLA-4) pathways to enhance the body's own immune response for treatment of HNSCC, as has previously been done for melanoma and lung cancer. A substantial percentage of patients with HNSCC have underlying immunophenotypic changes that would predict a response to immune checkpoint modulation,[20,21] and tumor immunophenotype has been shown to be prognostic in HPV-positive and HPV-negative patients.[20,22]

The majority of clinical data for immune checkpoint inhibition in HNSCC comes from the recurrent or metastatic setting. The initial cohort of the phase Ib Study of Pembrolizumab (MK-3475)

in Participants with Advanced Solid Tumors (KEYNOTE-012) trial included 60 patients with advanced HNSCC enriched for PD ligand-1 (PD-L1) expression who were administered fixed-dose biweekly pembrolizumab, an moAb targeting PD-1.[23] Tumor RNA expression levels for interferon-γ–related genes associated with clinical outcomes in the melanoma cohort of the KEYNOTE-001 study[24] were also collected to calculate a composite expression score. Of the 60 patients, 23 (38%) were HPV positive. Ten patients (17%) treated with pembrolizumab experienced grade 3 or 4 drug-related adverse events. No drug-related deaths were noted. The overall response rate (ORR) for the entire population was 18% per central imaging review compared with 21% per investigator review. HPV-positive patients had a 25% ORR, whereas the ORR was only 14% for HPV-negative patients. The median OS for the entire cohort was 13 months. Interestingly, analysis revealed that PD-L1 expression levels and presence of stromal staining were significant predictors for best overall response and PFS, as was interferon-γ–related gene composite expression score. Subsequently, an expansion cohort of 132 patients unselected for PD-L1 expression was accrued who receive pembrolizumab every 3 weeks for 24 months or until disease progression or intolerable toxicity. These patients were heavily pretreated (59% had received two or more previous therapies).[25,26] The ORR per Response Evaluation Criteria in Solid Tumors (RECIST) was 23.7%, with two CRs, 39 partial responses (PRs), and 25.4% of patients with stable disease. Improved ORR was seen in patients who received two or fewer prior therapies (31 of 97 patients; ORR, 32.0%; two CRs and 29 PRs) compared with patients who received more than two prior therapies (10 of 63 patients; ORR, 16%; 10 PRs). ORR was comparable between HPV-positive and HPV-negative patients (23.6% *v* 25.0%, respectively).

Preliminary results from the CheckMate-141 phase III trial recently reported at the American Association for Cancer Research and ASCO annual meetings also show significant promise for PD-1 pathway blockade in HNSCC.[27,28] A total of 361 patients with platinum-refractory recurrent or metastatic HNSCC were randomly assigned 2:1 to nivolumab, an moAb PD-1 inhibitor, versus investigator's choice (ICh) chemotherapy with docetaxel, methotrexate, or cetuximab. Planned interim analysis after 218 patient deaths revealed a 30% reduction in risk of death (HR, 0.70) with nivolumab versus ICh. Median OS for all patients was 7.5 months with nivolumab compared with 5.1 months with ICh. At 1 year, OS was 36% in the nivolumab arm compared with 17% in the ICh arm. Importantly, the survival benefit for nivolumab was seen in both HPV-positive and HPV-negative patients (Table 2). The ORR for nivolumab in patients with PD-L1 expression ⩾ 1%, ⩾ 5%, and ⩾ 10% was 18.2%, 25.9%, and 32.6%, respectively, compared with ORRs of 3.3%, 2.3%, and 2.9%, respectively, for ICh. Grade 3 or 4 treatment-related adverse effects occurred in 13.6% of patients in the nivolumab arm compared with 35.1% of patients receiving ICh.

ONGOING CLINICAL TRIALS

Intensive efforts are under way to further assess the feasibility of treatment deintensification involving more conventional treatment modalities for HPV-positive patients with OPSCC to minimize the long-term sequelae of treatment. Additional work is being done to discover less toxic, more effective therapies.

Radiation Trials

ECOG 3311 (ClinicalTrials.gov identifier: NCT01898494) is an ongoing phase II trial of 377 patients with planned transoral robotic surgery and neck dissection with stage III or IVB HPV-positive OPSCC followed by risk-adapted adjuvant therapy. The primary study end point is 2-year PFS. Low-risk patients (T1-2N0-1; negative margins) and high-risk patients (positive margins, > 1 mm extracapsular

Table 2 – Checkmate-141: OS Summary

	Nivolumab		Investigator's Choice Chemotherapy		Comparison of Nivolumab to Investigator's Choice: HR (95% CI)
Patient Group	No. of Patients	Median OS (months)	No. of Patients	Median OS (months)	
All patients	240	7.5	121	5.1	0.70 (0.51 to 0.96)*
PD-L1 ⩾ 1%	88	8.7	61	4.6	0.55 (0.36 to 0.83)
PD-L1 < 1%	73	5.7	38	5.8	0.89 (0.54 to 1.45)
p16 positive	63	9.1	29	4.4	0.56 (0.32 to 0.99)
p16 negative	50	7.5	36	5.8	0.73 (0.42 to 1.25)

NOTE. Adapted from Gillison et al.[27]

Abbreviations: HR, hazard ratio; OS, overall survival.

*HR and 97.73% CI.

extension [ECE], five or more positive LNs) will be administered standard of care therapy with observation and adjuvant concurrent cisplatin and radiation to 66 Gy, respectively. The primary study question will be addressed in the intermediate-risk patients (close margins, < 1 mm ECE, two to four positive LNs, perineural invasion, or lymphovascular space invasion) who will be randomly assigned to either 50 or 60 Gy of postoperative radiotherapy (PORT; Fig 3).

The Quarterback trial (NCT01706939) is an actively accruing phase III noninferiority trial with planned enrollment of 365 patients that aims to determine the feasibility of radiation dose de-escalation in responders to IC. Patients with nonmetastatic stage III or IV HPV-positive OPSCC, unknown primary, and nasopharyngeal carcinoma with a smoking history < 20 pack-years will be administered IC with a combination of docetaxel, cisplatin, and fluorouracil. Patients with a clinical or radiographic CR or PR will be randomly assigned 2:1 to reduced-dose (56 Gy) versus standard-dose (70 Gy) radiation with concurrent carboplatin, whereas the remaining patients will receive standard therapy. The primary study end point is LRC and PFS at 3 years.

EA3143 is a proposed ECOG/American College of Radiology Imaging Network nodal deintensification study proposed as a follow-up to E2399 and E1308. In this randomized, phase II study, 128 patients with stage III or IV nonmetastatic HPV-positive OPSCC and limited smoking history will undergo IC with cisplatin, paclitaxel, and cetuximab followed by evaluation of their clinical response to treatment. Patients who experience a clinical CR at the primary site will be treated to 54 Gy of IMRT with concurrent cetuximab to the primary site and initially involved LNs with random assignment to standard-field (bilateral prophylactic nodal irradiation to 45 Gy) versus reduced-field (36 Gy of prophylactic radiation to next echelon nodes only; no distant neck nodes) nodal irradiation. If stable disease or PR is noted at the primary site, patients will go on to receive standard IMRT to 69.3 Gy with concurrent cetuximab (Fig 4). The primary study end points are 12-month treatment toxicity as assessed by the Vanderbilt Head and Neck Symptoms Survey and 2-year PFS.

Chemotherapy Trials

Radiation Therapy Oncology Group (RTOG) 1016 (NCT01302834) is an ongoing phase III trial that has completed accrual. A total of 987 HPV-positive patients with stage III or IV nonmetastatic OPSCC were randomly assigned to concurrent cetuximab versus high-dose cisplatin with accelerated IMRT to 70 Gy in 6 weeks. The primary study end point is 5-year OS. Initial results from the trial are pending.

The Tasman Radiation Oncology Group 12.01 trial (NCT01855451) is a phase III trial with a similar aim as RTOG 1016 that is currently still accruing patients. This study plans to randomly assign 200 HPV-positive patients with stage III or IV OPSCC to definitive 70-Gy IMRT with concurrent weekly cisplatin versus cetuximab. Symptom severity at 20 weeks is the primary outcome measure.

De-ESCALaTE (Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in HPV-Positive OPSCC; NCT01874171) is another phase III trial that plans to assess a similar question as Tasman Radiation Oncology Group 12.01 and RTOG 1016. HPV-positive patients with locally advanced OPSCC (planned accrual of 304 patients) will be randomly assigned to concurrent cetuximab versus high-dose cisplatin with IMRT to 70 Gy. Severe acute and late toxicity as assessed by CTCAE (version 4.0) is the primary study outcome.

NRG-HN002 (NRG is a research protocol organization including the National Surgical Adjuvant

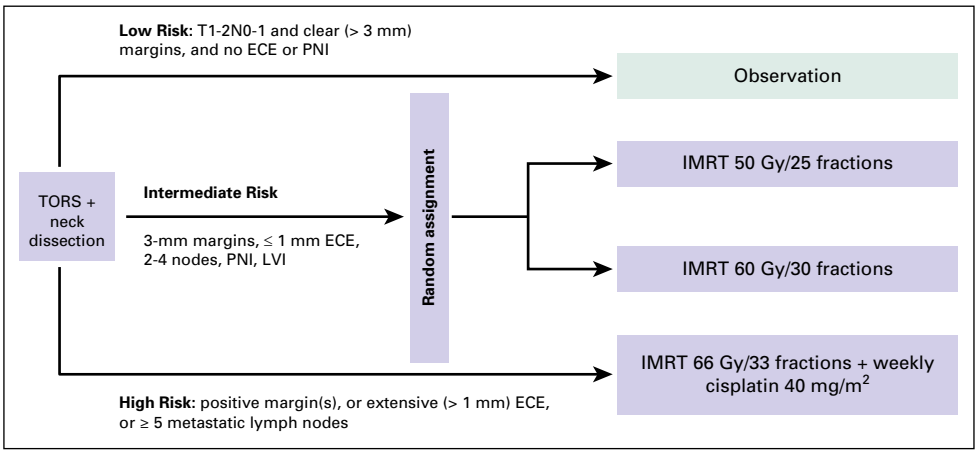

Fig 3 – Schema of Eastern Cooperative Oncology Group 3311 study, a phase II randomized trial of transoral surgical resection followed by low-dose or standard-dose intensity-modulated radiation therapy (IMRT) in resectable p16-positive locally advanced oropharyngeal squamous cell carcinoma. ECE, extracapsular extension; LVI, lymphovascular invasion; PNI, perineural invasion; TORS, transoral robotic surgery.

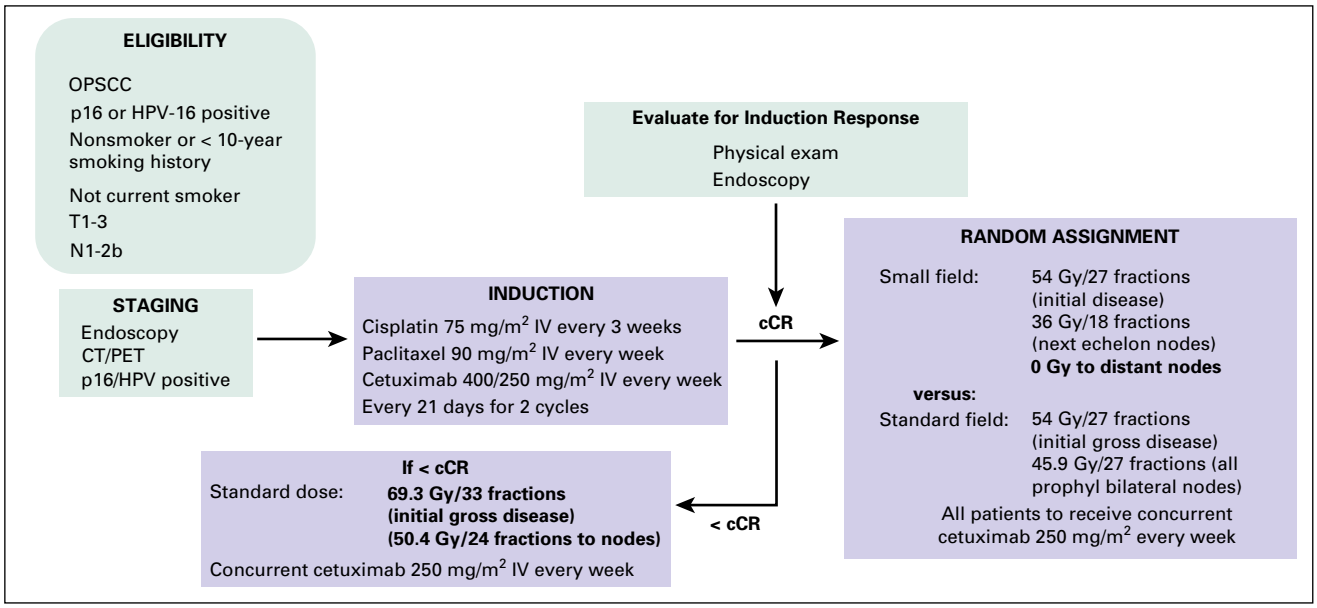

Fig 4 – EA3143: proposed follow-up to Eastern Cooperative Oncology Group (ECOG) 1308 testing nodal radiation deintensification. cCR, clinical complete response; CT, computed tomography; HPV, human papilloma virus; IV, intravenous; OPSCC, oropharyngeal squamous cell carcinoma; PET, positron emission tomography.

Breast and Bowel Project, RTOG, and Gynecologic Oncology Group; NCT02254278) is a randomized phase II trial that aims to eliminate chemotherapy for good-risk, HPV-positive patients with OPSCC. The study plans to accrue 296 clinical stage T1-2N1-2b or T3N0-2bM0 HPV-positive patients with a smoking history of ⩽ 10 pack-years and to randomly assign the patients to reduced-dose IMRT to 60 Gy in 6 weeks with weekly cisplatin versus accelerated fractionation IMRT (60 Gy in 5 weeks) alone. The primary objective of the study is to select the arm(s) achieving a 2-year PFS of ⩾ 85% without unacceptable swallowing toxicity at 1 year.

ADEPT (Postoperative Adjuvant Therapy Deintensification Trial for Human Papillomavirus–Related, p16-Positive Oropharynx Cancer; NCT01687413) is a currently accruing phase III trial of 500 patients with transoral robotic surgery–resected, T1-4, HPV-positive OPSCC with positive nodes and ECE. Patients will be randomly assigned to PORT to 60 Gy with or without concurrent weekly cisplatin. Two-year DFS and LRC are the primary outcomes.

RTOG 0920 (NCT00956007) is a phase III trial of PORT with or without cetuximab for locally advanced HNSCC. The study plans to accrue 700 patients with surgically resected T2-3N0-2M0 or T1N1-2M0 disease with at least one of the following intermediate-risk features: perineural invasion, lymphovascular space invasion, single LN greater than 3 cm or two or more LNs (all < 6 cm without ECE), close margins, T3 or microscopic T4a tumor, or T2 oral cavity lesion with a depth of invasion of greater than 5 mm. Random assignment will be to IMRT to 60 Gy with or without concurrent and adjuvant weekly cetuximab. Although non–HPV-related histologies are included in the trial, HPV testing is mandatory for all patients with OPSCC. Stratification will be made based on primary site and HPV status, allowing for assessment of applicability of the study results to the HPV-positive population.

Immunotherapy Trials

RTOG 0534 (NCT02764593) is a randomized, placebo-controlled, double-blind phase III trial of 185 patients that will determine the utility of concurrent and adjuvant nivolumab in addition to cisplatin-based definitive chemoradiotherapy for patients with stage III or IV HNSCC. A phase I safety lead-in trial assesses treatment of patients with concurrent and adjuvant nivolumab plus radiation and cisplatin- or cetuximab-based chemotherapy or plus radiation alone. The primary outcome of the initial phase of the trial is dose-limiting toxicity as it relates to the direct toxic effects of nivolumab or the ability to complete chemotherapy or radiotherapy. In the phase III portion of the trial, nivolumab, cisplatin, and IMRT will be compared with placebo, cisplatin, and IMRT. Notably, only intermediate-risk or high-risk HPV-positive patients with OPSCC based on tumor stage, nodal status, and smoking history will be entered onto the trial. This study is not yet open for accrual.

NCT02296684 is a currently accruing phase II trial of concurrent and adjuvant pembrolizumab for 46 planned patients with surgically resectable, stage III or IV HNSCC. HPV-positive patients are excluded from trial entry. All patients will undergo neoadjuvant treatment with pembrolizumab before surgery with

adjuvant standard-of-care therapy dictated by surgical pathology. Patients determined to have high-risk disease based on the presence of ECE or positive margins will receive adjuvant nivolumab after recovery from postoperative chemoradiation. Distant failure rate and LRC at 1 year are the primary outcome measures. NCT02641093 is another phase II trial involving pembrolizumab for patients with surgically resectable, locally advance HNSCC with similar inclusion criteria and treatment regimen as NCT02296684, but it also plans to assess 30-day treatment toxicity via CTCAE version 4.0 in addition to 1- and 3-year DFS as its primary outcomes.

Ipilimumab, an moAb targeting CTLA-4, is also currently being investigated in locally advanced HNSCC. NCT01860430 is a phase IB trial currently aiming to accrue 18 patients with stage III or IV intermediate- or high-risk HNSCC to identify the starting dose of ipilimumab in combination with standard cetuximab plus IMRT for further clinical trials. Low-risk HPV-positive patients (smoking history < 10 pack-years, N1 disease) are not eligible.

HPV-positive OPSCC is a distinct disease entity from HPV-negative HNSCC that disproportionately impacts younger, healthier patients, exhibits different patterns of disease evolution and recurrence, and has as its hallmark an improved prognosis. These factors result in more long-term survivors of HNSCC treatment, which presents an increasing challenge for oncologists to limit the chronic sequelae of surgery, chemotherapy, and/or radiation used to treat these patients. Major efforts are under way to identify low-risk patients in whom treatment can be deintensified while maintaining high cure rates. Additional work is being performed to discover novel treatments that will improve outcomes for all patients with HNSCC, especially those with high-risk disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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