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Head and Neck Cancer (CP Rodriguez, Section Editor)

Postoperative Treatment of Oropharyngeal Cancer in the Era of Human Papillomavirus

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Opinion statement

Despite an overall decline in the incidence of tobacco-related cancers, human papillomavirus (HPV)–related head and neck squamous cell carcinoma (HNSCC) of the oropharynx is on the rise. The prognosis of HPV-related oropharynx cancer (HPV-OPC) is generally favorable even in locoregionally advanced disease, and a variety of treatment options are available. Though the primary treatment modality of choice remains definitive radiation (RT), surgical resection followed by appropriate adjuvant therapy remains an option, especially in those patients who may not be favorable candidates for definitive radiotherapy, particularly when concurrent chemotherapy is warranted. Upfront resection may offer a chance to avoid the well-described acute toxicity and long-term morbidity associated with concurrent chemoradiotherapy (CRT) in select patients. Despite the overall favorable prognosis of HPV-OPC, indications for therapy remain unchanged from the recommendations for treatment in tobacco-related OPC and other anatomic sites of HNSCC. Ongoing studies assessing deintensification strategies in HPV-OPC are focused on maintaining high cure rates while improving treatment-related toxicities. Currently, no clear guidelines exist for the choice of primary therapy, surgical resection, or RT in patients with HPV-OPC, highlighting the need for multidisciplinary discussion and review of the individual patient before selecting the most appropriate curative modality. This review seeks to present the data for postoperative therapy in HPV-related oropharyngeal HNSCC.

Introduction

Pharyngeal squamous cell carcinoma accounts for an estimated 17,000 cases annually in the USA, representing just over 1% of new cancer cases per year [1]. As in other cancers located in the head and neck mucosa, the most common underlying etiology of pharyngeal cancer historically is tobacco and alcohol exposure. However, HPV infection is now known as a major oncologic driver of tumorigenesis in oropharyngeal squamous cell carcinoma, with the incidence of HPV-related disease steadily increasing over the past decade while the decline of tobacco-related HNSCC is largely congruent with a decrease in smoking trends [2–4]. The Centers for Disease Control and Prevention reported that oropharynx cancer (OPC) was one of only five cancer types increasing in incidence from 1975 to 2009 [5]. Today, nearly 70% of all OPC is associated with HPV infection, and the number is expected to continually rise in the coming years [6].

As differences are seen in incidence and prevalence patterns between HPV-related OPC (HPV-OPC) and tobacco-related disease, response to treatment and overall prognosis among the two etiologies also differ. HPV serves as a significant prognostic indicator in OPC with improved treatment response leading to improved survival rates in patients with HPV-OPC compared with HPV-negative disease irrespective of treatment modality [7]. Ang and colleagues reported the difference in 3-year progression-free survival (PFS) between HPV-OPC and HPV-negative disease of 75–82% and 45–57%, respectively [2]. Furthermore, HPV-related outcomes improve over time, and individuals with HPV-OPC have a reduced risk of death.

The favorable statistics of HPV-OPC led to the design and implementation of an updated staging system in HNSCC to reflect more appropriate disease severity and overall prognosis [8••]. Despite the updated system differentiating between HPV-related and unrelated OPC for staging and prognosis, it is important to note that HPV status does not influence treatment decision in the staging system. Thus, therapeutic paradigms for HPV-OPC remain unchanged from that of HPV-negative disease. However, the improved treatment responses (up to 80%) seen in HPV-OPC coupled with improvements in survival endpoints lend to the wide array of treatment options to consider. While the most frequently employed treatment strategy remains definitive radiotherapy (RT), a primary surgical approach is an important consideration for certain patients. The paucity of level I data comparing the two curative approaches in treating HPV-OPC further highlights the need to consider patient selection when determining an appropriate course of therapy.

Standard curative therapeutic modalities for all HNSCC, regardless of anatomic location and underlying etiology, come with significant short- and long-term toxicities. Given the more favorable outcomes associated with HPV-OPC, clinical trials are ongoing to test so-called deintensification strategies for this patient population, with the goal of preserving high cure rates and favorable overall survival (OS) outcomes while lessening the burden of treatment-related side effects and morbidities. Such trials are assessing variations in all modes of curative therapy, including alternative surgical interventions, radiation schema, and systemic therapies.

This review will focus on the management of HPV-OPC following a primary surgical resection and will include current standard treatment recommendations, important prognostic considerations in this disease, and the current landscape of clinical investigation in HPV-OPC.

Outcomes in HPV-related OPC

The improved overall prognosis of patients with HPV-OPC compared with HPV-negative OPC has been well-established by both retrospective and prospective reports [2, 9, 10]. In a subgroup analysis, Ang and colleagues demonstrated that tumor HPV status is an independent prognostic factor for OS (82% vs. 51% at 3 years) and progression-free survival (PFS) (73% vs. 43% at 3 years) in patients with oropharyngeal squamous cell carcinoma [2]. This report also proposed a risk stratification schema for HPV-OPC patients, separating patients

into low, intermediate, or high risk based on smoking history and tumor (T) and nodal (N) staging of disease. These risk groups are utilized to determine prognosis as well as define eligibility criteria for disease-specific clinical trials. Other studies also demonstrate that HPV-OPC is more responsive to treatment with a 60% lower risk for death than HPV-negative OPC [7, 9, 11–13]. Importantly, these trials encompassed different treatment paradigms and exhibited a survival benefit regardless of primary radiotherapy or surgical resection as the backbone of curative therapy in patients with HPV-OPC.

HPV-OPC also displays improved outcomes in the recurrent and metastatic settings over HPV-negative disease. Analysis of two large cooperative group studies (RTOG 0129 and RTOG 0522) reported on 181 OPC patients who progressed after receiving curative therapy and found tumor HPV status to be a strong and independent predictor for OS after disease progression [14]. While patterns of failure and median time to progression were similar among HPV-related and HPV-unrelated OPC patients, 2-year OS rates were significantly different (54.6% vs. 27.6%). Deeken and colleagues also reported more favorable outcomes in patients with HPV-related disease when treated with various modalities in the recurrent/metastatic setting, with median OS of 10.6 months in HPV-negative disease versus not reached in HPV-OPC after mean follow-up of 21 months, and 58% of HPV-OPC patients were still alive after 33 months—significantly longer than the median OS of the HPV-negative patients [15].

Current treatment approaches to postoperative HPV-OPC

Despite differing risk factors, disease biology, response to therapy, and prognosis and survival outcomes in HPV-related and unrelated OPC, current treatment guidelines do not distinguish between the two diseases. Presently, treatment recommendations for OPC are made without reference to HPV status. While the most frequently employed strategy for curative management of OPC remains primary RT, upfront surgical resection remains a reasonable treatment approach to patients with clinically low stage of disease, those in whom the extended treatment time of RT is infeasible, or those who are not ideal candidates for standard concurrent CRT.

Postoperative RT (PORT) is the mainstay of adjuvant therapy in advanced head and neck cancer as established by a multitude of retrospective analyses published several decades ago [16–18]. Common risk factors used to guide recommendation for adjuvant RT include pathologic tumor and nodal stage, with bulkier tumors and higher nodal staging leading to greater risk for occult microscopic disease remaining following resection. This is demonstrated by the higher risks of locoregional recurrences seen in advanced nodal presentations [19]. Close margins, perineural invasion (PNI), and lymphovascular invasion (LVI) of the tumor also suggest more aggressive disease with a higher risk of locoregional recurrence; thus, PORT may also be utilized for these isolated findings [20]. The standard recommended dosing of PORT is 2 Gy per fraction delivered to involved areas, including the nodal regions and tumor bed, for a total dose of 60–66 Gy, based on randomized data [21]. Accelerated PORT studies were found to have no OS benefit yet markedly increased mucosal toxicity and are not recommended [2, 22, 23].

Radiosensitizing cisplatin chemotherapy, dosed 100 mg/m^2 every 3 weeks for three doses, added to PORT was compared with PORT alone in two contemporaneous landmark studies, the Radiation Therapy Oncology Group (RTOG) 9501 and European Organisation for Research and Treatment of Cancer (EORTC) 22931, with the combined analysis indicating a benefit seen when concurrent systemic therapy was administered to patients with positive surgical margins and/or extracapsular nodal extension (ECE) [24–26]. Initial results from both studies demonstrated an improvement in locoregional control and PFS. OS was statistically better in the EORTC study with a trend toward statistical benefit in the RTOG study. Acute toxicity including mucositis, myelosuppression, and nausea and vomiting was increased in the chemotherapy arms of both studies, though no significant increase in grade 3–4 toxicity was seen.

The results of RTOG 9501 and EORTC 22931 established the standard of care treatment for advanced HNSCC following primary resection. It is important to note that HPV-OPC could not be assessed in these studies, and it is unclear whether low-risk, favorable prognosis HPV-OPC patients benefit from combined adjuvant therapy. Presently, any HPV-OPC patient with either positive surgical margins or ECE on pathology following oncologic resection warrants adjuvant therapy with concurrent CRT as per standard treatment guidelines. The use of concurrent CRT following primary surgical resection has great implications for treatment-related toxicities, both short and long terms, with many institutions favoring definitive chemoradiotherapy in the absence of resection in efforts to spare the patient trimodal therapy and the resulting adverse effects.

Alternative dosing schedules of cisplatin or substituting chemotherapy agents for cisplatin, such as carboplatin, mitomycin C, bleomycin, cetuximab, and taxanes, have been studied in efforts to reduce toxicity [27–33]. However, none of these strategies have been shown to have a survival benefit when added to RT. A recent phase III study comparing weekly cisplatin (30 mg/m^2) versus 3-weekly dosing with concurrent RT in locally advanced HNSCC demonstrated locoregional relapse of 42.2% versus 29.6% [34]. The authors concluded the 3-weekly dosing of cisplatin is superior to weekly cisplatin dosing, a conclusion that has long been accepted as the preferred radiosensitizing cisplatin dose for HNSCC. Important to note, however, is the patient population studied consisted of an overwhelming majority of oral cavity tumors, and it is unclear whether these results are applicable to oropharyngeal cancer patients. Weekly cisplatin (30 or 40 mg/m^2) is generally a clinically acceptable alternative when 3-weekly dosing is considered too toxic; however, it is important to note a paucity of evidence supporting use of weekly cisplatin. At present, there is no acceptable evidence to support the use of a systemic therapy other than 3-weekly cisplatin when combined with RT in the postoperative setting. Finding a better tolerated but equally efficacious agent is an area for further investigation, particularly in the low-risk HPV-OPC where treatment responses and survival outcomes are high, making the long-term morbidity of such treatment a glaring reminder of the cost of curative therapy.

Concept of deintensifying therapy

RT confers significant acute and chronic toxicities to even the most medically fit patients with such toxicities occurring in the adjuvant setting as well as definitive therapy. The addition of chemotherapy to RT demonstrates even worse grade 3–4 toxicities [35]. Acute treatment-related effects, occurring in an estimated 80% of patients, include mucositis, dysphagia, and odynophagia, which may lead to subsequent malnutrition and weight loss necessitating alternative means of enteral nutrition [2, 35–37]. While acute toxicities certainly affect quality of life, they may also impact treatment delivery and clinical outcomes. Increased pain from mucositis leading to dysphagia and odynophagia can compromise the patient's nutritional status and overall performance status, which may affect the treatment plan [38]. The subsequent treatment of these toxicities further contributes to the financial burden associated with cancer-directed therapy, with placement and management of feeding tubes and use of pain medications commonly required.

Some acute treatment-related adverse effects predict for late effects, including xerostomia and dysphagia [39]. RT dose and tissue volumes of treatment are well-established factors contributing to the development of chronic dysphagia [40–42]. Reducing RT dose and/or fractionation, adjusting anatomic targets of RT, reducing target volumes, and sparing critical structures like pharyngeal constrictors are some examples of deintensifying therapeutic approaches. Other strategies to decrease toxicity while preserving the survival outcomes seen in the HPV-OPC patient population involve risk stratification and selection of patients based on clinical characteristics.

Several clinical trials aimed at low-risk HPV-related OPC have recently completed accrual while others are ongoing. In one of the first large study publications of a prospective approach to deintensification in HPV-OPC patients, the Eastern Cooperative Oncology Group (ECOG) evaluated whether induction chemotherapy (IC) could be used as a biomarker to select patients for whom reduced-dose RT could be administered to maintain survival rates while improving late toxicities to treatment [43•]. Patients with HPV-OPC stages III–IV (AJCC 7th Edition) were treated with three cycles of cisplatin, paclitaxel, and cetuximab. Those who demonstrated a complete response after IC went on to receive definitive reduced-dose IMRT of 54 Gy with weekly cetuximab while patients with less than a complete response received standard 69.3 Gy with cetuximab. The results revealed 2-year PFS and OS rates of 96% for both parameters in patients with favorable-risk disease (<T4, <N2c, and ≤ 10 pack-year smoking history). The study also demonstrated a significant improvement in dysphagia and nutritional impairment in patients treated with dose-reduced RT compared with patients treated with standard dose.

A recently completed phase II study for HPV-related OPC evaluated a de-escalated course of RT administered twice daily for 2 weeks for a total dose of 30–36 Gy (a 50% reduction of standard dose) with concurrent docetaxel 15 mg/m^2 given on days 1 and 8 of adjuvant treatment [44]. Eighty patients were treated on study, and 2-year locoregional disease control rate (96.3%) and progression-free survival (91.3%) outcomes compared favorably with historical results with an improved toxicity profile (grade ≥ 2 toxicity 10% compared with

historical rates exceeding 50%). The results of these studies demonstrate the feasibility of a deintensified approach to curative treatment in this patient population and justify further phase III investigations.

Another deintensification study, cooperative group NRG HN002, compares a moderately reduced RT dose with concurrent weekly cisplatin to a modestly accelerated RT treatment without systemic therapy (NCT02254278); target accrual has been reached and results are forthcoming. Still, other studies are looking to add alternative systemic agents, including targeted agents and immunotherapy programmed death (PD)-1/PD-ligand-(L)1 inhibitors, as alternatives to cisplatin chemotherapy concurrently with RT in the definitive and postoperative settings (NCT01783587, NCT03196843, NCT03258554).

Though a promising idea and worthy of investigation, not all attempts at deintensification therapy have proven successful. The RTOG issued a landmark statement of initial results from the study RTOG 1016 comparing concurrent cetuximab and RT with standard cisplatin and RT in good-risk HPV-OPC, hypothesizing the former treatment paradigm would be less toxic yet just as efficacious with non-inferior survival endpoints. The results were disappointing: not only was the study arm of cetuximab-RT just as toxic (albeit the toxicity profile expectedly different), the survival outcomes were inferior to that of cisplatin and RT (National Cancer Institute Press Release, August 14, 2018). Overall survival on the cetuximab arm was significantly inferior to the standard cisplatin arm, while overall rates of grade 3–4 toxicities were similar for patients in both arms. A similar phase 3 study (De-ESCALaTE HPV) completed in Europe also demonstrated superiority of cisplatin and RT compared with cetuximab and RT in HPV-related OPC [45]. Thus, RT with cisplatin is reinforced as the standard of care in a non-operative approach to treatment in patients with HPV-OPC regardless of good-risk disease.

The results of RTOG 1016, though disheartening, represent deintensification efforts in the definitive RT-systemic therapy setting, leaving hope for a reduced toxicity treatment plan by a different approach. Ongoing attempts at reducing the toxicity of curative therapy in good-risk HPV-OPC patients by other means remain: focusing on alternative operative strategies, reduction in postoperative radiotherapy plans, and alternative systemic therapies.

Transoral surgery as a method of deintensification

Until recently, surgical approach to OPC using the traditional open transcervical and mandibulotomy approach resulted in severe functional and cosmetic morbidity [46]. Newer transoral surgical (TOS) approaches, such as the transoral robotic surgery (TORS) and the transoral laser microsurgery (TLS), have emerged as a functional organ preservation approach resulting in decreased postsurgical morbidity with the less invasive methods while achieving optimal oncologic resection with improved visualizations of the tumor-host interface [47]. Earlier studies have demonstrated lower complication rate and faster postoperative recovery without compromising oncologic outcomes [48, 49]. A multi-institutional retrospective study of 410 head and neck cancer patients undergoing TORS, 89% of which were OPC, found promising 2-year locoregional control rate of 91.8% (95% CI, 87.6–94.7%), disease-specific

survival of 94.5% (95% CI, 90.6–96.8%), and overall survival of 91% (95% CI, 86.5–94.0%) [50].

The debate between surgical and nonsurgical treatment strategies for early-stage HPV-OPC will be ongoing, as there is paucity of high-quality data directly comparing these two strategies. An observational study assessed outcomes of primary surgical approach or definitive CRT in patients with HPV-related OPC using the National Cancer Database [51]. Interestingly, while both treatment paradigms yielded comparable 3-year OS outcomes, the majority of patients who were treated with primary surgery (65.4%) received trimodal therapy with adjuvant CRT, demonstrating a clear need to consider surgical selection of patients. Perhaps this will be addressed in prospective fashion, as the ORATOR2 study is underway, which directly compares the clinical outcomes of a primary surgical approach with a primary RT approach for treatment of early-stage HPV-OPC as determined by PFS (NCT03210103). The study is also looking at quality of life profiles in order to inform a phase III trial. The patients are randomized in a 1:1 fashion to either undergo a transoral surgery (TOS) ± neck dissection or deintensified RT ± chemotherapy, and outcomes will be compared with historical controls. This study follows the ORATOR study, one of the first studies to compare upfront surgery versus radiation in this population. In addition to quality of life metrics and survival endpoints, this study also seeks to describe functional outcomes and toxicities associated with each primary modality of therapy, which is paramount to this disease. Given overall favorable prognostic outcomes in the treatment of HPV-OPC, such parameters outside of the standard survival metrics will likely guide therapy choice.

Strategies for adjuvant deintensification

Like any surgical approach, TOS approaches allow more appropriate use of adjuvant therapy based on accurate pathologic staging. While single modality treatment with surgery alone is one strategy for treatment deintensification, several ongoing prospective trials are exploring various strategies for deintensification in the adjuvant setting. Table 1 lists all known active studies in resected HPV-related OPC with deintensification of adjuvant therapy at the core of the objectives.

Reduction of adjuvant radiation dose

The largest of these studies, ECOG 3311, has recently completed accrual and results are forthcoming. This trial is a four-arm phase II study evaluating TORS of HPV-OPC in efforts for pathologic risk reduction in adjuvant radiotherapy (NCT01898494). Patients with resectable disease undergo TORS and subsequent postoperative management is based on pathologic findings and respective risk group allocation: low, intermediate, or high risk. Low-risk patients (T1-T2, N0-N1 by AJCC 7th Edition and > 3-mm margins without ECE or PNI/LVI) are observed following resection. High-risk patients (positive surgical margins, > 1-mm ECE, or ≥ 5 metastatic LN) receive standard postoperative RT 66 Gy with concurrent weekly cisplatin. Those patients who fall into the so-called intermediate-risk category, defined as near margins, minimal ECE, N2a/N2b disease, or PNI/LVI, are randomized to either 50 or 60 Gy of adjuvant RT alone.

Table 1. Current deintensification studies involving surgery/adjuvant therapy

Trial	Patient population (AJCC 7th Edition)	Treatment	Primary outcome measures	Deintensification trategy
ORATOR2 NCT03210103	T1-2, N0-2, p16-positive or HPV-positive	Deintensified primary RT ± chemotherapy vs. TOS and neck dissection (plus RT if required); randomized 1:1 ratio	2-year PFS	Upfront surgery
ECOG 3311 NCT01898494	Resectable stage III–IVB HPV-OPC	TORS then risk-adapted postoperative therapy (observation/50 vs. 60 Gy/66 Gy with weekly cisplatin)	2-year PFS, accrual rate, risk distribution, and surgical events (bleeding, positive margin rate)	Reduction of adjuvant RT
SIRS Trial NCT02072148	Resectable T1N0-2B, T2N0-2B, p16-positive	TORS then risk-adapted postoperative therapy (imaging surveillance/50 Gy/50 Gy with weekly cisplatin/56 Gy with weekly cisplatin)	DFS, LRC	Reduction of adjuvant RT
PATHOS NCT02215265	Resectable T1-3, N0-2b HPV-OPC	TOS then risk-adapted postoperative therapy (observation/50 vs. 60 Gy/60 Gy ± weekly cisplatin	Swallowing outcome, QOL, toxicity, OS, DFS	Reduction of adjuvant RT; omission of adjuvant chemotherapy
ADEPT NCT01687413	Resectable, p16-positive, stage III, IV, + ECE	TOS then 60 Gy ± weekly cisplatin	DFS, LRC	Omission of adjuvant chemotherapy
University of Pennsylvania NCT02159703	Resectable, p16-positive, T1-2, N2a-c	TORS then forgo adjuvant RT to primary bed if no PNI in primary and surgical margins ≥ 2 mm	LCR, QOL, toxicity	Omission of adjuvant RT to primary bed
Mayo Clinic NCT02736786	Resectable T1-2, N1-3 OPC	TOS then mucosal sparing PBT if negative margin and no PNI/LVI in primary	LCR, QOL, toxicity	Omission of adjuvant RT to primary bed and the use of PBT

SIRS, The Sinai Robotic Surgery Trial in HPV Positive Oropharyngeal Squamous Cell Carcinoma; *TORS*, transoral robotic surgery; *Gy*, gray; *DFS*, disease-free survival; *LRC*, locoregional control; *ORATOR2*, Primary Radiotherapy Versus Primary Surgery for HPV-Associated Oropharyngeal Cancer; *HPV*, human papillomavirus; *RT*, radiotherapy; *TOS*, transoral surgery; *PFS*, progression-free survival; *ECOG*, Eastern Cooperative Oncology Group; *HPV-OPC*, HPV-related oropharyngeal cancer; *ECE*, extracapsular nodal extension; *PBT*, proton bean therapy; *LCR*, local control rate; *QOL*, quality of life

Similar to ECOG 3311, the SIRS Trial involves patients with intermediate-risk HPV-OPC and risk-stratified adjuvant therapy following TORS based on histologic features (NCT02072148). Following resection, patients will receive postoperative therapy based on which risk group pathology indicates. The low-risk group, consisting of a complete resection, no ECE, or other poor features, will

proceed with interval oncologic surveillance imaging. The intermediate-risk group (complete resection though margins < 1 mm, LVI, PNI, minimal ECE) will receive adjuvant RT (50 Gy). There are two experimental high-risk groups based on margin status and extend of ECE, and those groups will receive concurrent CRT with weekly cisplatin and either 50 Gy or 56 Gy depending on pathology.

The PATHOS trial (NCT02215265), a phase II/III multi-institutional trial in the UK, also stratifies the patients postoperatively into low-, intermediate-, and high-risk groups. The intermediate-risk group (negative margin, at least pT3 disease or pT1-2 disease with pN2a/b, PNI, LVI, or close margin [1–5 mm]) will be randomized to 60 Gy in 30 fractions versus 50 Gy in 25 fractions. The primary outcome measures include patient-reported swallowing outcomes, measured using the MD Anderson Dysphagia Inventory (MDADI). Secondary outcome measures include qualitative and quantitative swallowing assessments, quality of life questionnaires (EORTC QLQ C30 and HN35), acute and late toxicity, OS, and DFS.

Omission of adjuvant chemotherapy

Given the favorable outcomes of HPV-related OPC, several studies have questioned the prognostic implications of ECE, raising concern for the broad application of RTOG 9501 and EORTC 22931 to this specific patient population. In the Washington University experience of 152 HPV-OPC patients after TLS, the rate of disease-free survival (DFS) was not significantly different among patients with ECE versus those without ECE (3-year DFS 89% [95% CI 84–95%] vs. 94% [95% CI 83–100%], respectively) [52]. The authors also compared DFS in patients with ECE who received either RT alone versus CRT and did not find any benefit of adding chemotherapy (3-year DFS 94.6% vs. 91.8%, respectively). A retrospective study out of the University of Pittsburgh, which examined 76 patients with HPV-OPC, 45 of which had ECE, corroborates these findings. The authors found no difference in the rates of disease-specific survival (DSS) among patients with or without ECE ($p = 0.936$) [53].

The prognostic value of ECE and the benefit of adding chemotherapy to radiation in HPV-OPC patients with ECE remain an unanswered question. Furthermore, there are studies that bring forth the issues of significant intra- and inter-observer variability in assessing ECE as well as the oversimplification of assessing ECE in the historic dichotomization of ECE (positive vs. negative) [52, 54]. There are several prospective trials investigating this pivotal question. The UK PATHOS trial includes postoperative stratification of HPV-OPC patients into high-risk group (positive margins [< 1 mm] or + ECE), and these patients are randomized to 60 Gy with or without concurrent cisplatin. Similar to the PATHOS high-risk group, the ADEPT phase III trial (NCT01687413), which is now closed to accrual, also included postsurgical patients with ECE but negative surgical margins randomized to 60 Gy with or without concurrent cisplatin therapy.

Omission of adjuvant radiation

Another potential deintensification strategy is to omit adjuvant radiation to the primary tumor bed in early T stage disease. The rationale is that given adequate margin control with transoral surgery and low rates of tumor bed recurrences in patients with early T stage HPV-OPC, adjuvant radiation to the primary site may

not be necessary. In majority of these early T stage disease, the indications for adjuvant therapy are largely driven by the pathologic nodal staging. This deintensification of adjuvant radiation to the oropharynx can translate to reduced radiation volume, especially of the critical anatomic structures, and potentially less morbidity. A recent publication of 92 HPV-OPC patients with T1-2 disease treated with transoral surgery alone without adjuvant radiation to the primary tumor bed found a local recurrence rate of only 3% [55]. Half of these patients did receive adjuvant radiation to the neck only. Those spared adjuvant RT to the primary tumor bed also had lower gastrostomy tube rates (10% vs. 2% at 1 year). Although there is theoretical benefit to eliminating adjuvant radiation targeting the primary tumor bed, dosimetric studies comparing primary plus neck irradiation with neck-only irradiation have only found a modest potential benefit with this strategy. One study in patients with tonsillar OPC found that primary site still received a mean dose of 53.9 Gy with a slight benefit in dose reduction specifically to the oral cavity (34.0 Gy vs. 29.8 Gy; $p = 0.002$) and superior pharyngeal constrictors (46.1 Gy vs. 42.9 Gy; $p = 0.01$) [56]. A separate study looking at base of tongue OPC patients found a mean dose of 40.2 Gy in the primary tumor bed with a benefit in dose reduction to the oral cavity only (47.4 Gy vs. 22.3 Gy) [57]. The lack of significant dose reduction in the primary tumor bed may be due to the fact that the level II lymph nodes, which represent the first echelon nodal basin for OPC and, thus, are always in the neck radiation volume, are located directly adjacent to the primary oropharyngeal tumor bed.

Currently, there are several clinical trials assessing the omission of primary bed radiation. A University of Pennsylvania phase II trial (NCT02159703) is a single-arm phase II trial of HPV-OPC patients with pT1-2, N2a-c patients after TORS, resected with negative margins (> 2 mm) who will receive adjuvant radiation to the neck only. Another single-institution observational study (NCT02736786) at the Mayo Clinic is evaluating the clinical and functional outcomes of mucosal sparing proton bean therapy in patients with resected T1-2 HPV-OPC with negative margin and no PNI or LVI in the primary site. Both studies will be investigating the local control rate, acute and late toxicity, and quality of life data.

While the favorable survival outcomes of HPV-OPC are well-established, it is important to note that these outcomes have been determined through current treatment guidelines and recommendations. Though the focus of many studies on treatment deintensification in HPV-OPC patients is reasonable and warranted, until randomized trials data and subsequent evidence-based guidelines implicate such treatments as standard of care, deintensifying therapy of any type should only be considered within the context of clinical study. The initial results of RTOG 1016 further confirm the need to await additional results for such clinical decision-making.

Summary

Despite the distinct biologies of disease, staging paradigms, and prognostic differences separating HPV-related and HPV-unrelated disease, current standard treatment guidelines do not make such distinctions. As such, treatment recommendations for oropharyngeal cancer remain the same regardless of

underlying etiology. This further highlights the need for ongoing investigation into specific treatment paradigms using patient-specific eligibility criteria. Such trials are ongoing to assess the possibility of deintensifying curative therapy for the more favorably prognostic HPV-related OPC, maintaining the high response rates and survival endpoints while reducing the treatment-related toxicities and morbidity. While results from initial deintensification trials, such as RTOG 1016, have been disappointing, they continue to demonstrate the excellent disease control and overall survival of established treatment with the backbone of primary radiotherapy and cisplatin. It is yet unknown if a primary surgical approach followed by a deintensified adjuvant course is non-inferior to standard postoperative chemoradiotherapy with cisplatin though studies such as ECOG 3311 are ongoing. Until large studies prove deintensification of therapy is safe from a survival standpoint, current standard approaches to therapy should be implemented irrespective of HPV status in OPC.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
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