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Current Status and Future Directions of Treatment Deintensification in Human Papilloma Virus-associated Oropharyngeal Squamous Cell Carcinoma

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The prevalence of patients with human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is rapidly increasing, and it is now well known that these patients have a significantly better prognosis than patients with HPV-negative OPSCC. Though standard treatments result in excellent cancer control, they are also associated with substantial long-term toxicity. There is now great interest in evaluating less intensive (ie, deintensified) treatment regimens to improve the therapeutic ratio (maintain excellent cancer control and decrease toxicity). There are many different approaches that are being studied, and each have their own caveats, with varying degrees of actual deintensification. In this article, we critically review the current landscape of emerging deintensified treatment paradigms and future direction of the treatment of HPV-associated OPSCC.
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Introduction

The prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has been rapidly increasing over the past 20-30 years and is thought to be directly related to the corresponding increasing incidence of high-risk human papilloma virus (HPV) infection of the oropharynx.[1-3] Retrospective analyses of several clinical trials have shown that patients with HPV-associated OPSCC have a better response rate to chemotherapy and radiation and a significantly better local-regional control and overall survival (OS) with standard treatments as compared to patients with HPV-negative tumors.[4-7] Risk stratification based on HPV status, tobacco smoking history, and nodal stage is now standardly used in clinical practice when counseling patients on their prognosis. Patients with the most favorable prognosis are those with HPV-associated OPSCC, $\leq$ 10 pack years, and $<$N2c/N3 stage.[6,8]

There are 3 standard definitive treatment paradigms for OPSCC: (1) transoral surgery followed by pathological risk-adapted radiotherapy (RT) and chemotherapy, (2) concurrent RT and chemotherapy (ie, chemoradiotherapy [CRT]), and (3) neoadjuvant chemotherapy followed by CRT. The "preferred" standard treatment depends on institutional biases; however, overall the most used organ preservation approach is concurrent CRT (without surgery and neoadjuvant chemo).

These standard treatments result in excellent cancer control and survival in patients with HPV-associated OPSCC; however, they are associated with substantial toxicity.[9-13] Thus, we may be "over treating" many patients with HPV-associated OPSCC. There is now great interest in reducing the intensity of treatment with the goal of decreasing toxicity while maintaining cancer control (ie, improving the therapeutic ratio). There are many ways to deintensify treatment each with their own "pros" and "cons," and often the reduction in treatment intensity is small or reduction in 1 treatment modality is offset with an increase in another.[14] We here-in review and discuss the various ongoing deintensification approaches and

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forecast the future direction of deintensification for HPV-associated OPSCC.

Transoral Surgery Paradigm

Performing surgery first provides pathological information that can be used to tailor the use of adjuvant treatment, with the goal of reducing or omitting radiation and chemotherapy. Proponents of the definitive surgery approach believe that the toxicities of surgery ± radiation and chemotherapy are fewer than definitive CRT. Conventional surgery for OPSCC has been open en bloc resection with free flap reconstruction which, when compared with CRT, has similar outcomes but higher severe or fatal complications.[13]

Newer transoral surgical approaches (ie, transoral laser microsurgery [TLM] and transoral robotic surgery [TORS]) are garnering much interest for the treatment of HPV-associated OPSCC because these techniques are less invasive and thus have less toxicity. In fact, the toxicity of TLM and TORS ± CRT or RT has been suggested to be less than definitive CRT.[15,16] Because of the use of magnification and the transection of the tumor during surgery (TORS allows for en bloc resection), the "host-tumor" interface is better visualized, allowing for more precise negative margin resections, maximizing tumor removal, and limiting removal of normal healthy tissue, resulting in "surgically targeted therapy.[16,17]" Furthermore, similar to CRT, HPV-associated OPSCC is also associated with a better prognosis when treated with primary surgery.[7] The major potential benefits of primary TLM and TORS are reduction in surgical morbidity and reduction in the intensity of CRT without compromising oncologic outcomes. Primary surgery provides pathologic information that influences adjuvant treatment recommendations. RT and chemotherapy may be omitted or at least the RT dose may be reduced. The deintensification of RT and chemotherapy after TLM or TORS has been arbitrary, institution specific, and has not been studied in a controlled manner. The eastern cooperative oncology group (ECOG) is currently conducting a prospective randomized phase II study (ECOG3311) in which patients with HPV-associated T1-2, N1-N2b OPSCC all have transoral surgery followed by risk-adapted adjuvant radiation and chemotherapy.[18]

Omission of Radiation

There is no question that single modality treatment with TLM and TORS alone will significantly reduce toxicity. Interestingly, most patients (70%-80%) who receive TLM and TORS receive adjuvant RT.[16] Currently on the ECOG3311, only ~11% of enrolled patients are being observed after transoral surgery (ie, not receiving postoperative radiation and chemotherapy).[18] Thus, omission of RT may be a reality for only a small number of patients.

Grant et al[19] reported on 69 patients treated with TLM alone at the Mayo Clinic; 44 patients who did not have indications for RT and 25 patients who did have indications for RT in the neck, but refused. The 5-year local control for the entire group was 94% and the 5-year local-regional control for those with and without RT indications was 84% vs 74%. However, in a multicenter TLM study, patients who did not receive adjuvant RT had worse overall and disease-free survival.[16] One may argue that all patients with node-positive OPSCC require adjuvant RT because of the risk of occult disease in the ipsilateral retropharyngeal (~20%)[20] and cranial level II nodes that are not surgically treated. Even in those who are node negative, the retropharyngeal nodes may still be at risk.

What about excluding the primary site from the RT treatment volume? Many patients do not have indications for postop RT related to the primary site (margin not close and no perineural invasion). In patients with indications for RT to the neck (multiple positive nodes or extranodal tumor extension) but no indications at the primary site, it is reasonable to exclude the primary site operative bed from the RT target volume.

Historically, a negative margin was considered to be ≥5 mm, close margins were <5 mm, and positive was tumor on the inked en bloc specimen. The definition of pathologic margins is different with transoral surgical procedure. There is no close margin designation and a negative margin is defined as a negative inked margin, regardless of distance.[21] Margins are defined and interpreted differently with transoral surgeries because margins are carefully mapped intraoperatively under better visualization (as compared to conventional surgical techniques). Furthermore, for resection of the tonsil, the superior constrictor muscle is taken with the resection and is considered a natural barrier of spread. The mean superior constrictor thickness is ~2 mm, and even though tumor often abuts this muscle, because it is considered a barrier to spread, what historically would be considered a close margin is considered negative with transoral surgery. Thus, close margins are not defined with transoral surgeries and the reported rate of positive margins is low <10%, and therefore one could argue that the primary site need not be treated with RT.

Omission of the primary site in intensity-modulated radiotherapy (IMRT) plans will reduce the mean dose to the primary site to ~40 Gy.[22] Mean doses to the contralateral parotid and pharyngeal constrictors are not significantly reduced; however, the mean dose to the oral cavity is reduced by a mean of 20 Gy.[22] With primary site avoidance IMRT plans, swallowing function may not be improved. From the prospective series from Haughey et al, patients with swallowing function scores of 0-2 (normal swallowing to mild dysphagia) were not significantly different between patients treated with TLM alone (47/52 patients) or TLM plus adjuvant RT (103/117); $P = 0.79$. Thus, even the complete omission of RT did not improve swallowing function. This suggests that sparing the primary site with IMRT may not result in less dysphagia.

The low-dose radiation bath associated with IMRT techniques makes it difficult to completely avoid or spare the primary site. Proton RT (especially intensity-modulated proton therapy) has the advantage of eliminating the low-dose bath resulting in better avoidance of the primary site. The Mayo clinic is currently conducting an observational study of patients with OPSCC who have indications for RT only to the neck after transoral resection, and neck dissection will be treated with