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Treatment de-intensification strategies for head and neck cancer

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Abstract

Increasingly, squamous cell carcinoma of the oropharynx (OPSCC) is attributable to transformation resulting from high-risk human papillomavirus (HPV) infection. Such cancers are significantly more responsive to treatment than traditional tobacco- and alcohol-associated squamous cell cancers of the head and neck. Conventional management with definitive chemoradiation, surgery and adjuvant radiation, or radiation given with altered fractionation schemes, while effective, incurs long-term morbidity that escalates with treatment intensity and significantly impairs quality of life. Recent trials have suggested that less intensive treatment regimens may achieve similar efficacy with decreased toxicity. In this article, we review the primary strategies used for de-escalation of treatment, which include the reduction of radiation dose, substitution and/or elimination of concurrent radiosensitising chemotherapy, and the use of minimally invasive surgery. We discuss the rationale behind these approaches and the preliminary data demonstrating the success of de-escalation, as well as potential considerations raised by treatment de-intensification in HPV-associated OPSCC.

Keywords

Head and neck; Oropharynx; Human papillomavirus; Oropharyngeal neoplasms; Clinical trial; Radiotherapy; Chemotherapy; Surgery; Carcinoma; Squamous cell

1. Introduction

Epidemiologic trends from the 1980s onward have demonstrated a decline in the incidence of squamous cell cancers in the larynx, hypopharynx, and oral cavity [1], related to the parallel decline in tobacco use. However, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) over this same period has increased, attributable to the rise of high-risk human papilloma-virus (HPV) infection leading to HPV-associated OPSCC [2,3]. The incidence of HPV-associated OPSCC now accounts for over 70% of newly diagnosed OPSCC in the United States [3]. The virus is thought to be transmitted sexually, and a high

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lifetime number of sexual partners is associated with an increased risk of oropharyngeal cancer, regardless of the presence of established risk factors including tobacco and alcohol use [4,5]. Clinical and demographic factors differ between patients with HPV-positive and HPV-negative disease; patients with HPV-positive OPSCC are typically younger and more likely to have nodal involvement than their HPV-negative counterparts [6].

HPV is a DNA virus that is implicated in the carcinogenesis of neoplasms in the cervix, oropharynx, and anus [7,8]. HPV DNA integrates with the host DNA, allowing for the production of viral proteins E6 and E7. These proteins interfere with the activation of host tumour suppressor proteins p53 and Rb, respectively [9]. While HPV-negative tumours commonly harbour mutated p53, HPV-associated OPSCC is typically p53 wild type [10,11]. Inactivation of Rb by E7 results in the overexpression of p16, a marker commonly used to identify HPV-associated cases [12]. Data from The Cancer Genome Atlas observed complex mutational patterns including loss of TRAF3, activating mutations of PIK3CA, and amplification of E2F1 in HPV-associated oropharyngeal cancers, pointing to aberrant activation of NF- κ B, other oncogenic pathways, and cell cycle dysregulation as critical in the pathogenesis of these tumours [11]. Non-HPV-associated cancers have also been shown to have higher expression of the epidermal growth factor receptor (EGFR) than their HPV-associated counterparts [13]. Additionally, HPV-associated tumours may be less hypoxic [14], another factor predicted to enhance response to radiotherapy.

As both EGFR expression and p53 status are correlated with treatment responsiveness and survival, these biologic differences would be expected to contribute to differential outcomes in OPSCC based on HPV status. In fact, in multiple prospective trials published over the past decade, HPV positivity has conferred improved prognosis for patients with OPSCC compared with patients with similar stage HPV-negative tumours [14–23]. Eastern Cooperative Oncology Group (ECOG) 2399 was the first prospective study to demonstrate improved outcomes in patients with HPV-associated disease. In this trial, patients with HPV-positive tumours had a superior response to induction chemotherapy (82% versus 55%, $p = 0.01$), chemoradiotherapy (84% versus 57%, $p = 0.007$) and improved 2-year overall survival (OS) (95% versus 62%, $p = 0.005$) [16].

The effect of HPV status on clinical outcomes was validated by Ang et al. in their retrospective analysis of the Radiation Therapy Oncology Group (RTOG) 0129 study cohort, in which 63.8% of patients with stage III–IV OPSCC were found to have HPV-associated cancers [15]. OS at 3 years was 82.4% in patients with HPV-associated disease and 57.1% in patients with non-HPV-associated cancer ($p < 0.001$). The risk of death increased significantly with each additional pack-year of smoking. Patients were thus grouped by risk: those with HPV-associated disease and ≤ 10 pack-year smoking history as well as those with HPV-associated disease, >10 pack-year smoking history, and N0–N2a disease were deemed low-risk, with a 3-year OS of 93%; those with HPV-associated disease, >10 pack-year smoking history, and N2b–N3 disease were intermediate-risk, with a 3-year OS of 70.8%. Of note, no patients with HPV-associated disease were classified as high-risk, with a 3-year OS of 46.2%.

However, the current standard of care for OPSCC is derived from older trials of head and neck cancer patients with predominately HPV-negative disease, potentially representing overtreatment of favourable-risk, HPV-positive patients. Given the different aetiology, natural history [24–26], biomolecular signature [11,27], and treatment responsiveness, it is now accepted that HPV-positive and HPV-negative OPSCCs are distinct diseases to be studied separately in trials. Consequently, a number of clinical trials are underway to investigate strategies for the de-intensification of treatment in patients with HPV-associated OPSCC in order to minimise morbidity while maintaining excellent outcomes.

2. Rationale for treatment de-intensification

In medically fit patients with locally advanced head and neck cancer, the non-surgical standard of care is radiotherapy to a dose of 70 Gy with concurrent cisplatin, determined by prospective randomised trials as well as a meta-analysis of over 17,000 patients [28–30]. While these publications demonstrated improved OS in patients treated with concurrent chemoradiation (5-year OS 33.7% versus 27.2% without chemotherapy) [28], this regimen incurs notable acute and long-term morbidity. For the treatment-responsive HPV-associated cancers, current therapies may be more intensive than necessary to achieve cure. Increasing the intensity of therapy with some combination of surgery, chemotherapy and/or radiation therapy has been shown to increase treatment-induced toxicity [31] as well as cost [32]. Published rates of gastrostomy tube placement, for example, range from 5% [33] to as high as 85% [34], depending on the patient population and the therapeutic modalities used.

Large portions of the pharyngeal axis and soft tissues in the neck receive high doses of radiation in patients undergoing definitive management for OPSCC; the toxic effects are augmented by radiosensitising chemotherapy. The rates of acute and late grade 3 toxicity are approximately 80% and 25%–60%, respectively [15,29,30]. Frequently occurring acute toxicities include dermatitis, mucositis, and dysphagia [23,24]. Long after the completion of definitive therapy, many patients endorse chronic dysphagia and xerostomia, which negatively impact their quality of life [35,36]. At 24 months after the receipt of radiotherapy (with or without chemotherapy) to the head and neck, 15% of patients were found to have grade 2 swallowing dysfunction, and 8% of patients had progressive dysphagia [37]. Patients with oropharyngeal primary cancers, who received chemoradiotherapy, or who underwent bilateral neck irradiation were more likely to have severe persistent dysphagia, underscoring the morbidity of present-day standard treatment for OPSCC patients.

Moreover, chronic effects such as dysphagia and speech-related toxicity have been shown to occur in a radiation dose-dependent fashion [38–43]. Increasing dose to the supraglottic larynx is also associated with an increased likelihood of swallowing dysfunction [43]. Stricture and feeding tube dependence increase when the volume of pharyngeal constrictors receiving 70 Gy exceeds 50% and 30%, respectively, and aspiration increases when >50% of the pharyngeal constrictors receive 65 Gy [44,45]. Dysphagia increases with every 10 Gy above 55 Gy given to the superior and middle pharyngeal constrictors [46]. Therefore, a notable strategy for lessening treatment morbidity is to reduce the dose and volume of normal tissue irradiated. The adoption of intensity-modulated radiotherapy (IMRT) has already been shown to reduce the likelihood of late toxicities including xerostomia and

dysphagia [43,47,48]. Nonetheless, further efforts should be made to reduce radiation-related morbidity, and radiation dose reduction may lead to improved functional outcomes, particularly if the dose is lowered below 55 Gy with regard to dysphagia.

The addition of chemotherapy to radiation is known to increase rates of acute and chronic toxicity. The Intergroup trial noted a 52% rate of grade 3 toxicity in the radiotherapy alone group, compared to a rate of 89.5% in the chemoradiotherapy cohort. Renal and hematologic toxicity, as well as nausea and vomiting, were significantly worse with the addition of cisplatin, and a trend for worsened mucositis was observed. Both arms including chemotherapy demonstrated a 10% increase in the placement of a gastrostomy tube when compared to radiotherapy alone (not significant) [30]. The Groupe Oncologie Radiotherapie Tete et Cou (GORTEC) 94-01 trial also demonstrated worse grade 3–4 toxicity (30%–56%) with the addition of concurrent chemotherapy, though the number of patients in this subset was small, precluding detailed toxicity analysis [29]. Disturbingly, 10-year results of RTOG 91-11 demonstrated increased non-cancer mortality in the concomitant chemo-radiation arm (30.8%) when compared to the induction chemotherapy arm (20.8%) and the radiation-alone arm (16.9%), suggesting the current system of monitoring and grading late effects of treatment may be inadequate [49]. Worth noting, however, is that larynx cancer patients have higher baseline comorbidity and thus late cisplatin-related toxicity may not be mirrored in the more medically fit HPV-positive OPSCC patient population.

Concern for treatment-induced morbidity has prompted the initiation of multiple trials aiming to reduce treatment-related toxicity. Defining appropriate candidates for treatment de-intensification is critical in maintaining the excellent outcomes historically seen in patients with HPV-associated OPSCC. Several groups are currently examining how to best re-classify the American Joint Committee on Cancer (AJCC) staging groups for this patient population. The International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) group recently proposed a new staging system for HPV-associated OPSCC [50]. Examining the 5-year OS of a multi-institutional, international cohort of over 1900 patients with HPV-associated OPSCC, the authors used a recursive partitioning analysis to create the novel staging system. Using the AJCC 7th edition tumour node metastasis (TNM) classification, the proposed ICON-S stage groupings are stage I (T1–T2N0–N2b), stage II (T1–T2N2c or T3N0–N2c), and stage III (T4a–T4b or N3). The proportion of patients alive in the validation cohort at 5 years with ICON-S stage I, II, and III disease was 88%, 81%, and 65%, respectively. Metastatic disease (M1) is classified as ICON-S stage IV. It is worth noting that while smoking pack-years were shown to impact OS, the ICON-S staging system does not account for smoking history. An alternate grouping was proposed by Huang et al. using a recursive partitioning analysis that included AJCC 7th edition TNM stage, age, and smoking pack-years to derive the following four valid prognostic groups for survival: group I (T1–3N0–N2c with ≤20 pack-years), group II (T1–3N0–N2c with >20 pack-years), group III (T4 or N3 and age ≤70 years), and group IVA (T4 or N3 and age >70 years); with a 5-year median OS of 89%, 64%, 57%, and 40%, respectively [51]. Patients with lower T and N stage disease and minimal smoking history are thus the ideal candidates for possible de-intensification of therapy. Current trials explore de-intensification of treatment largely in this patient population (Table 1).

3. De-intensification trials for HPV-associated OPSCC

3.1. Reducing chemotherapy-related toxicity

One strategy for reducing chemotherapy-related toxicity is the replacement of cisplatin with cetuximab, a monoclonal antibody targeting the EGFR extracellular ligand binding domain. This anti-EGFR therapy was approved by the regulatory bodies in both the United States and Europe for the treatment of patients with locally advanced head and neck squamous cell carcinoma on the basis of the Bonner trial, which demonstrated improved 3-year OS in those treated with combined cetuximab and radiotherapy when compared to radiotherapy alone, 55% versus 45%, respectively ($p = 0.05$) [52]. On subgroup analysis, the survival was greatest among patients with oropharyngeal primary cancers, younger age, high nodal stage, and low tumour stage—factors typical of HPV-associated cases. Furthermore, grade 3 toxicity was similar between the two groups, with the exception of higher rates of acneiform rash (17% versus 1%, $p < 0.001$) and infusion reaction (3% versus 0%, $p = 0.01$) in the cetuximab arm. That cetuximab did not appear to increase the severity of typical radiation-induced toxicity, such as mucositis and dysphagia, rendered this therapy an enticing candidate for treatment de-escalation.

A recently published secondary analysis based on p16 status confirmed the association between p16 status and improved outcome; moreover, the addition of cetuximab to radiotherapy had its greatest benefit in HPV-associated OPSCC (locoregional control and OS hazard ratio 0.31 and 0.38, respectively) [53].

RT0G 1016 (NCT01302834) explored the replacement of cisplatin with cetuximab. This phase III non-inferiority trial stratified patient by T stage, N stage, Zubrod performance status, and smoking history and compared cetuximab concurrent with accelerated radiotherapy (70 Gy given six fractions per week for 6 weeks) to cisplatin days 1 and 22 with the same accelerated radiotherapy course for 987 patients with p16 positive stage III/IV OPSCC. Accrual for this trial has been completed, and the estimated primary completion date is in 2020. The Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in Human Papillomavirus + Oropharyngeal Squamous Cell Carcinoma trial (NCT01874171) is a randomised phase III trial currently accruing patients with stage III–IVa HPV-associated OPSCC with ≥ 10 pack-year smoking history that used a similar study schema (cisplatin-based chemoradiotherapy to 70 Gy versus cetuximab concurrent with the same radiation) to compare toxicity outcomes between the two cohorts. The Trans-Tasman Radiation Oncology Group is also enrolling on a similar phase III trial (NCT01855451), but with weekly cisplatin, in order to examine symptom severity. Ultimately these studies will confirm or refute the idea that cetuximab plus 70 Gy achieves similar rates of cure as cisplatin plus radiation, and will also better delineate the toxicities associated with either approach, which may differ based on smoking history and T stage.

An alternative de-intensification approach is the omission of chemotherapy. The ongoing HN-002 trial (NCT02254278) is a large randomised phase II study of nearly 300 patients assessing two different de-escalation strategies. Eligible patients are those with HPV-associated T1–T3 tumours with N0–N2b nodal status and ≥ 10 pack-years smoking history, falling under the low-risk classification put forth by Ang et al. [15]. Patients are randomised

to receive accelerated radiotherapy alone to 60 Gy given six fractions a week over 5 weeks versus 60 Gy using standard fractionation over 6 weeks with dose-reduced weekly cisplatin (40 mg/m² weekly, total 240 mg/m [2]). Retrospective data suggest that the weekly chemotherapy schedule results in significantly reduced severity of mucositis compared to the traditional schedule of delivery every 3 weeks [54]. Notably, both arms represent a 10 Gy reduction in total radiotherapy dose. The primary end-point of the study is 2-year progression-free survival of at least 85% as well acceptable swallowing function based on the MD Anderson Dysphagia Inventory. This combination efficacy and toxicity end-point is novel, and demonstrates the emphasis of selecting therapies in which patients are likely to be cured, but also have minimal long-term morbidity.

3.2. Reduction of radiotherapy dose

Because radiotherapy-related toxicity is dose-dependent, Chera et al. conducted a phase II study examining the dose reduction of radiotherapy in low-risk patients with minimal smoking history who underwent chemo-radiation for T0–3 N0–2c M0 HPV-associated OPSCC (NCT01530997). Treatment was limited to 60 Gy IMRT delivered over 6 weeks with concurrent weekly cisplatin (30 mg/m²). All patients received post-treatment biopsy of the primary site and resection of involved nodes at 4–14 weeks following completion of therapy, possibly reflecting the investigators' uncertainty about whether 60 Gy would suffice to eradicate gross disease. The pathologic complete response rate was 86%. The rates of grade 3 toxicities compare favourably to historical controls [55], with a gastrostomy tube rate of 39% and a 0% rate of long-term feeding tube dependence on this study. These results are particularly impressive given data demonstrating that undergoing post-treatment neck dissection after radiotherapy or chemo-radiotherapy significantly increases the likelihood of feeding tube dependence 24 months after completing therapy (relative risk [RR] 7.66, 95% confidence interval [CI] 2.07–10.89) [56]. The group is conducting larger follow-up studies without the need for biopsies and resection of neck nodes, however these early data suggest that de-escalation 60 Gy plus weekly cisplatin may suffice in appropriately selected patients.

The NRG HN-002 (HN002 study by NRG, group comprising National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group) trial, previously mentioned for its omission of cisplatin, also explores radiotherapy dose reduction in both arms. In the low-risk arm, radiation-alone is given to a dose of only 60 Gy in standard 2 Gy fractions, albeit in an accelerated fashion with the delivery of six fractions per week rather than five. The standard five fractions per week schedule is used in the arm with concurrent dose-reduced cisplatin.

Chemoselection, the use of induction chemotherapy to identify patients with disease sensitive to therapy, has been incorporated in a novel paradigm administering lower doses of radiation in chemotherapy responsive HPV-associated cancer. ECOG 1308 (NCT01084083), a phase II trial, examined a de-intensification strategy of radiation dose reduction based on response to induction chemotherapy in patients with resectable stage III–IV T3–4b N0–3 HPV-associated OPSCC. In this study, patients received 3 cycles of induction chemotherapy with cisplatin, paclitaxel, and cetuximab. Patients with a clinical complete response at the primary site went on to receive radiotherapy to 54 Gy using standard 2 Gy fractions over

5½ weeks with concurrent cetuximab. Patients with a clinical partial response or stable disease at the primary site received a more aggressive regimen, with radiotherapy to 69.3 Gy in 2.1 Gy fractions over 6½ weeks with concurrent cetuximab.

Early results of this trial are excellent. Seventy-one percent of patients demonstrated a clinical complete response at the primary site. One-year progression-free survival rates ranged from 87% in patients without a complete response who received 69.3 Gy plus cetuximab up to 97% in the most favourable subset of patients. Toxicity results were also promising, with only 1% of patients exhibiting grade 4 toxicity (lymphopenia) and low rates of grade 3 toxicity [57]. The lower IMRT dose used in the favourable arm of this study has also been shown to ameliorate late toxicities, reaching a statistically significant improvement in patient-reported difficulty swallowing solids (100% versus 35%) [58]. This finding is critical, as it supports the hypothesis that doses <55 Gy are less likely to impair swallowing function [46], suggesting that de-escalation of radiotherapy dose to 60 Gy may not be sufficient to significantly improve the incidence of dysphagia.

The Quarterback Trial (NCT01706939), a phase III non-inferiority trial, is currently recruiting participants to further explore chemoselection using induction chemotherapy in patients with stage III–IV non-metastatic HPV-associated OPSCC, nasopharynx cancer, or head and neck cancer of an unknown primary with 20 pack-year smoking history. Patients will receive three cycles of docetaxel, cisplatin, and 5-FU induction therapy. Those with a clinical complete response will undergo a 2:1 randomization to reduced- (56 Gy) or standard- (70 Gy) dose radiotherapy with weekly carboplatin and cetuximab or carboplatin only.

3.3. Reducing surgical morbidity

Surgical resection is a modality often applied in the management of OPSCC. Until recently, a mandibulotomy was required to gain sufficient access to the oropharynx for resection, resulting in severe functional and cosmetic detriments [59]. Nearly 25% of these patients were noted to have severe complications, while operative mortality was around 3% [60]. Recent technological advancements led to the development of transoral approaches including transoral robotic surgery (TORS), which utilises miniaturised instruments to perform resection of select pharyngeal tumours through the open mouth. When coupled with magnification, it allows for accurate dissection without the morbidity and functional deficits of open surgery [59,61]. Some studies suggest that TORS may improve rates of margin-negative mucosal resections, potentially reducing the need for adjuvant chemotherapy in addition to radiotherapy [62].

While minimally invasive surgery reduces morbidity, the treatment-related toxicity is still considerable, particularly in patients who receive adjuvant treatment with radiotherapy or chemoradiation. For instance, one analysis showed a 0% rate of gastrostomy tube use in T1/T2 OPSCC patients treated with TORS alone versus a 44.4% rate of gastrostomy tube use and a 22.2% rate of gastrostomy tube dependence 1 year after TORS in patients who required adjuvant therapy [63]. To further reduce morbidity after surgery, ongoing trials explore reducing the dose of adjuvant radiotherapy or eliminating adjuvant chemotherapy in patients with pathologic evidence of extracapsular extension (ECE)—a departure from the

standard of care adjuvant chemoradiation established for these patients based on the combined analysis of EORTC 22931 and RTOG 9501 [64].

ECOG 3311 (NCT01898494) was therefore designed to explore the combination of TORS and risk-based, de-intensified adjuvant radiotherapy or chemoradiotherapy in patients with clinical T1–2 N0–1 HPV-associated OPSCC. Patients deemed low-risk (margin-negative resection, N0 or N1 disease, no ECE) after resection are observed, intermediate-risk patients (negative but ≥ 1 mm margin, +ECE, N2a, or 2–4 involved lymph nodes) receive adjuvant radiotherapy alone with 50 versus 60 Gy using standard daily fractionation, and high-risk patients (>1 mm ECE, positive margins, or ≥ 5 lymph nodes positive) are treated with 66 Gy and weekly cisplatin. Results of this trial will determine if the combination of minimally invasive surgical techniques with reduced intensity adjuvant therapy proves to be less toxic than current standard of care management, and may justify a follow up phase III trial comparing TORS and reduced dose post-operative radiation therapy with standard chemoradiation.

Similar to ECOG 3311, the Post-operative Adjuvant Treatment for HPV-Positive Tumours trial (NCT02215265) also calls for risk-based stratification after TORS. While the low-risk classification is the same as ECOG 3311, the other risk group criteria vary. The intermediate-risk criteria are negative margin, $\geq pT3$ disease, or $pT1-2$ disease with $pN2a/b$, perineural invasion, lymphovascular invasion, or negative but close margin (<5 mm). These patients receive either 60 Gy in 2 Gy fractions over 6 weeks or 50 Gy in 2 Gy fractions over 5 weeks. The high-risk criteria include positive margin or ECE, and these patients are assigned to receive 60 Gy with or without concurrent cisplatin.

Eliminating adjuvant chemotherapy in postoperative patients with ECE is yet another strategy for minimizing treatment-associated morbidity. The Washington University group published provocative data suggesting that the presence of ECE may not affect disease-free survival (DFS) in surgically managed patients. In their retrospectively assembled experience of 151 $p16 +$ OPSCC patients after TORS, the 3-year DFS of patients with and without ECE were 89% (95% CI 84%–95%) and 94% (95% CI 83%–100%), respectively [65]. A study out of the University of Pittsburgh yielded similar findings [66], with a 5-year update showing a disease specific survival of 89.3% (95% CI 73.9%–98.1%) in patients with ECE and 84.8% (95% CI 64.4%–94.1%) in patients without ECE [67]. The Washington University group has also published a retrospective comparison of patients with ECE that received either adjuvant radiotherapy alone or chemoradiation. In the analysis, 48 patients received radiation alone while 65 were treated with chemoradiation. The 3-year DFS rates were similar at 94.5% in the radiation alone cohort and 91.8% in the chemoradiation group ($p = 0.74$) [65].

Bearing in mind these data from small, single institution retrospective series, the Post Operative Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related P16 + Oropharynx Cancer trial (NCT01687413) was designed to investigate the role of adjuvant chemotherapy in patients with ECE. In this study, T1–4a node-positive patients with HPV-associated OPSCC with ECE but negative margins receive either standard 60 Gy with concurrent weekly cisplatin or 60 Gy without chemotherapy.

Finally, a Mayo Clinic phase II trial (NCT01932697) is exploring the use of an accelerated hyperfractionation with twice daily radiation in post-operative cases. The total radiation dose of 36 Gy is delivered in 20 fractions in 1.8 Gy twice daily dosing 5 d/week with concurrent weekly docetaxel. This reduced radiation dosing is inspired by studies showing lower doses are able to control disease in anal cancer, another HPV-associated squamous cell cancer [68]. Eligible patients must have at least one of the following risk factors: lymph node >3 cm, two or more metastatic lymph nodes, perineural invasion, lymphovascular invasion, ECE, pT3, or microscopic pT4a tumour stage. The combined results of these surgical trials should yield more information on proper risk stratification and adjuvant treatment selection in the coming years.

4. Conclusions

The aforementioned ongoing trials will elucidate many of the current questions regarding the standard of care management of HPV-associated OPSCC. In the future, these patients will likely be managed with de-intensified therapies, whether it is through de-intensification of surgery and adjuvant treatment, omission, substitution or reduction of the dose of chemotherapy, and/or the reduction radiotherapy dose. Appropriate selection of patients for treatment de-intensification is critical in order to avoid jeopardizing the excellent outcomes that are achieved with the current standard of care therapy in this patient population; therefore de-intensification is presently not recommended outside of a clinical trial. A better understanding of the molecular alterations underlying HPV-associated disease should be elucidated to provide further opportunities for targeted therapies with less toxicity. If these approaches prove adequate, the quality of life of patients should be significantly improved.

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Table 1

De-intensification trials in HPV-associated OPSCC.

Trial	Phase	N	Inclusion criteria	Treatment
Chemotherapy de-intensification trials				
RTOG 1016 (NCT01302834)	III	706	T1–2, N2a–3, or T3–4, any N, HPV-positive OPSCC	Cetuximab versus high-dose cisplatin concurrent with accelerated IMRT (70 Gy in 6 weeks)
De-ESCALaTE HPV (NCT01874171)	III	304	Stage III–IVA HPV-positive OPSCC (T3N0–T4N0, T1N1–T4N3). Excludes > N2b, >10 PY	Cetuximab versus high-dose cisplatin concurrent with RT (70 Gy)
TROG 12.01 (NCT01855451)	III	200	Stage III (excluding T1–2, N1) or IV (excluding T4, N3, or M1) HPV-positive OPSCC if <10 PY. If >10 PY, only N0–2a	Cetuximab versus weekly cisplatin concurrent with RT (70 Gy) once per week
Radiotherapy de-intensification trials				
NRG HN-002 (NCT02254278)	II	296	T1–2, N1–2b, or T3, N0–2b disease and <10 PY HPV-positive OPC	Reduced-dose IMRT (60 Gy) with/without weekly cisplatin
NCT01530997	II	40	T1–3, N0–2c HPV-positive OPSCC if <10 PY or >5 years of abstinence	IMRT (54–60 Gy) with weekly cisplatin (30 mg/m ²)
ECOG 1308 (NCT01084083)	II	80	Resectable stages IIIA/IIIB and IVA/IVB HPV-positive OPSCC (p16-high or HPV-16 ISH positive)	IC, then response-adapted RT (54 or 66–70 Gy) with cetuximab
The Quarterback Trial (NCT01706939)	III	365	Stage III/IV (M0) HPV-associated OPSCC/unknown primary/nasopharynx. Excludes active smokers/>20 PY	IC with TPF: patients with CR/PR randomly assigned 2:1 to carboplatin with RT (56 versus 70 Gy) per week. Non-responders receive standard RT.
De-intensification of surgery/adjuvant therapy				
ECOG 3311 (NCT01898494)	II	377	Resectable stage III–IVB p16-positive OPSCC	TORS then risk-adapted post-operative treatment (observation/50 versus 60/66 Gy with weekly platinum)
PATHOS trial (NCT02215265)	II/III	242	Resectable T1–T3, N0–2b HPV-positive OPSCC. Excludes active smokers with N2b disease	TORS then re-adapted post-operative treatment (observation/50 versus 60Gy/60 Gy with or without weekly cisplatin)
ADEPT (NCT01687413)	III	500	Transoral resected p16-positive OPSCC (R0 margin), T1–4a, pN positive with ECE	Post-operative adjuvant 60-Gy RT with or without weekly cisplatin
NCT01932697	II	40	P16-positive OPSCC (R0 margin), stage I–IVB. Excludes <10 PY or smoking within 5 years	Surgery followed by hyperfractionated IMRT (36 Gy/20 fractions BID) + weekly docetaxel

Abbreviations: ADEPT, Post Operative Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related P16 + Oropharynx Cancer; CR, complete response; De-ESCALaTE, Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in Human Papillomavirus + Oropharyngeal Squamous Cell Carcinoma; ECE, extracapsular extension; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; HPV, human papillomavirus; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; ISH, in situ hybridization; N, number of patients; NRG-HN002, HN002 study by NRG (group comprising National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group); OPSCC, oropharyngeal squamous cell cancer; PATHOS, Post-operative Adjuvant Treatment for HPV-Positive Tumours; PR, partial response; PY, pack-years; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; TORS, transoral robotic surgery; TPF, docetaxel, cisplatin, fluorouracil; TROG, Trans Tasman Radiation Oncology Group.

Adapted from the review by Bhatia and Burtneiss [69].