Treatment de-escalation in HPV-positive oropharyngeal carcinoma: Ongoing trials, critical issues and perspectives

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Due to the generally poor prognosis of head and neck squamous cell carcinoma (HNSCC), treatment has been intensified, these last decades, leading to an increase of serious side effects. High-risk human papillomavirus (HR-HPV) infection has been recently etiologically linked to a subset of oropharyngeal squamous cell carcinoma (OPSCC), which is on the increase. These tumors are different, at the clinical and molecular level, when compared to tumors caused by traditional risk factors. Additionally, their prognosis is much more favorable which has led the medical community to consider new treatment strategies. Indeed, it is possible that less intensive treatment regimens could achieve similar efficacy with less toxicity and improved quality of life. Several clinical trials, investigating different ways to de-escalate treatment, are currently ongoing. In this article, we review these main approaches, discuss the rationale behind them and the issues raised by treatment de-escalation in HPV-positive OPSCC.

Among head and neck squamous cell carcinomas (HNSCC), those induced by high-risk human papillomavirus (HR-HPV) represent a distinct subgroup1 with unique epidemiologic, clinical and molecular characteristics (Fig. 1).2−3 These tumors mainly affect the oropharynx (particularly tonsil and base of tongue) and their incidence is increasing.4 Considering current trends, and decreasing tobacco and alcohol consumption, it is estimated that HR-HPV will become the dominant etiologic factor for oropharyngeal squamous cell carcinoma (OPSCC) in the coming decades in most Western countries.5,6 Numerous retrospective and prospective studies have demonstrated that patients with HPV-positive OPSCC have markedly improved survival outcomes compared to those with HPV-negative HNSCC.7−8 These favorable outcomes are independent of treatment choice, as long as this conforms to current standard of care.9 Given that these patients are generally young and have a high likelihood of surviving their disease, post-treatment quality of life becomes of paramount importance. Indeed, a significant number of patients will experience severe toxicities including xerostomia, swallowing disorder, pain and stiffness of the neck and ototoxicity. Therefore, de-escalation is becoming a central issue as traditional OPSCC therapies involve high doses of radiation/chemotherapy, which may prove unnecessary for HPV-positive tumors.10,11 The goal of treatment de-intensification is to maintain good cure rates whilst minimizing long-term morbidity. Currently, different approaches to achieve this reduction of treatment-related morbidity are being pursued. These include limiting radiation dose, cisplatin alternatives given concurrently with radiation, modulation of radiation dose according to induction chemotherapy response and integrating minimally invasive surgery into treatment algorithms. These strategies are interesting but raise many questions (e.g. which type of patient should be enrolled and in which trials? How to define precisely a HPV-induced cancer?).

In this article, we review the main ongoing clinical trials for HPV-positive OPSCC, discuss the rationale behind them and several issues raised by treatment de-escalation. We also provide suggestions for future therapeutic approaches.

Ongoing treatment de-escalation trials for HPV-positive OPSCC

Reducing toxicity by replacement of cisplatin with cetuximab.

Among ongoing clinical trials, several are testing the benefits of antiepidermal growth factor receptor (EGFR) therapies and particularly cetuximab (Table 1). Cetuximab is a monoclonal antibody designed to target the EGFR extracellular ligand binding domain. It has been approved by the regulatory agencies of the United States and Europe for the...
Figure 1. Simplified model illustrating the main deregulations induced by the viral oncogenes E6 and E7. E6 and E7 viral oncogenes, by inhibiting TP53 and pRb, respectively, play a key role in the abrogation of cell cycle control, apoptosis and promotion of genetic instability that contributes to the development of cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

treatment of patients with locally advanced HNSCC on the basis of a phase III trial published in 2006. In this study, Bonner et al. reported improved locoregional disease control, progression-free survival and overall survival with the addition of cetuximab to radiation in patients with locally advanced HNSCC. Although subgroup analyses of randomized trials should be interpreted with caution, data reported by Bonner et al. indicate a disproportionate benefit of the addition of cetuximab to radiotherapy in patients with HPV-positive OPSCC (significant improvement in survival with a hazard ratio of 0.62), early T stage (T1–3), advanced N stage (N1–N3), high Karnofsky performance score (90–100) and age less than 65 years old. These results could be attributable to chance alone, however, these parameters are strongly suggestive of HPV-related cancers. Because analysis of HPV status, or its surrogate marker p16, was not done on the tumor samples in this trial, definitive conclusions remain speculative. However, the results of this study, the potential lower long-term toxicity of cetuximab and the fact that HPV-positive patients do well with the standard treatments have contributed to the rationale for using cetuximab in many of the clinical trials on HPV-induced OPSCC.

Several ongoing phase III studies have been designed to compare cetuximab combined with standard dose radiation therapy with cisplatin-based chemoradiation in stage III/IV HPV-positive OPSCC. The Radiation Therapy Oncology Group (RTOG) trial RTOG 1016 compares a regimen of cisplatin (100 mg/m²; on days 1, 22) and accelerated intensity-modulated radiation therapy (70 Gy over 6 weeks) with cetuximab (400 mg/m² loading dose, then 250 mg/m² weekly) and radiation therapy with the same modality. This trial enrolled over 700 p16 positive patients (T1–2 N2a-3, T3–4 any N). The primary end point of RTOG 1016 is overall survival and the study hopes to answer conclusively whether cetuximab can be safely substituted for cisplatin, which is considered the gold standard for chemoradiation, in patients with HPV-positive OPSCC. The original accrual goal of this trial has been met, but data are not mature yet. As it was designed as a noninferiority trial, a sufficient number of deaths must happen to provide the statistical power for analysis. If treatment results exceed those of the statistical hypotheses, the major risk is that potential inferiority will not be ruled out due to wide confidence intervals. A trial from Warwick Medical School, called De-ESCALaTE HPV is based on the same assumption. Three hundred and four patients, with p16-positive stage III–IVb OPSCC, are planned for accrual. In this study, the control arm consists of normofractionated radiotherapy (70 Gy) with cisplatin (100 mg/m²; on days 1, 22, 43) and the experimental arm is based on cetuximab (400 mg/m² loading dose, then 250 mg/m² weekly) and the same radiotherapy. The primary end point of this trial is the rate of severe toxicity (grade 3–5) with the assumption that cetuximab and radiotherapy will lead to less morbidity and better quality of life without a significant difference in overall survival or locoregional control. The Trans-Tasman Radiation Oncology Group has a similar study in Australia that also randomizes HPV-positive OPSCC patients to weekly cetuximab (400 mg/m² loading dose, then 250 mg/m² weekly) vs. weekly cisplatin (40 mg/m²) with concurrent radiation (70 Gy, over 7 weeks). The design of these trials is similar so it will be possible to pool them and perform a meta-analysis if their individual results are not conclusive.

Although cetuximab efficacy in this setting has been demonstrated, it has recently been regarded with caution. Results from the RTOG 0522 study, the BIBW 2992 and the Spectrum trials, despite several limitations (retrospective subgroup analysis, HPV status not evaluated in all patients and relatively short follow up period), suggest a lack of benefit of anti-EGFR therapies in HPV-positive OPSCC. Additionally, several phase II studies in advanced, persistent or recurrent carcinoma of the cervix (the model of HPV-induced carcinogenesis) have shown no benefit from cetuximab combined with cisplatin, as monotherapy, or from erlotinib (EGFR-Tyrosine Kinase Inhibitor) as a single agent. Finally, there is no strong biological evidence supporting the role of anti EGFR therapy in HPV-induced tumors, as EGFR alterations (protein over expression, increased gene copy number or activating mutations) are rare in HPV-positive OPSCC. Moreover, the Cancer Genome Atlas Group have recently investigated the cumulative effect of various mechanisms of biological alteration in HNSCC. The results suggested that EGFR is a relevant oncogenic target in only HPV-negative disease.
Table 1. Ongoing treatment de-escalation and therapeutic vaccination trials in HPV-associated OPSCC

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Studied population</th>
<th>Intervention</th>
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<tr>
<td><strong>Substitution of cisplatin by cetuximab</strong></td>
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<tr>
<td>NCT01302834&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RTOG 1016 Radiation therapy oncology group</td>
<td>III</td>
<td><em>n</em> = 706 Stage III-IV (no T1–2 N0–1)</td>
<td>Radiation therapy (70 Gy) with weekly Cetuximab or weekly Cisplatin (100 mg/m²)</td>
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<tr>
<td>NCT01874171&lt;sup&gt;b&lt;/sup&gt;</td>
<td>University of Warwick De Escalate HPV</td>
<td>III</td>
<td><em>n</em> = 306 Stage III-IVa (no T1–2 N0 and N2b, N2c, N3 if smoking history &gt;10 pack years)</td>
<td>Radiation therapy (70 Gy) with weekly Cetuximab or weekly Cisplatin (100 mg/m²)</td>
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<tr>
<td>NCT01855451&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Trans-Tasman oncology group</td>
<td>III</td>
<td><em>n</em> = 200 Stage III-IV (no T1–2 N1, T4N3 and N2b, N2c, N3 if smoking history &gt;10 pack years)</td>
<td>Radiation therapy (70 Gy) with weekly Cetuximab or weekly Cisplatin (40 mg/m²)</td>
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<tr>
<td>NCT01663259&lt;sup&gt;d&lt;/sup&gt;</td>
<td>University of Michigan</td>
<td>II</td>
<td><em>n</em> = 36 Stage III-IV (no T4 and N3) with smoking history &lt;10 pack years</td>
<td>Radiation therapy (70 Gy) with weekly Cetuximab</td>
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<td><strong>De-intensification of radiation and chemotherapy</strong></td>
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<td>NCT01530997&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Lineberger Comprehensive Cancer Center</td>
<td>II</td>
<td><em>n</em> = 40 T1–3, N0 to N2c with smoking history &lt;10 pack years or &gt;5 years of abstinence</td>
<td>IMRT (54–60 Gy) with weekly Cisplatin (30 mg/m²)</td>
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<tr>
<td>NCT01088802&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
<td>II</td>
<td><em>n</em> = 60 T1–3, any N (resectable)</td>
<td>IMRT, Dose de-escalation (from 70 to 63 Gy and from 58.1 to 50.75 Gy, same number of fractions <em>n</em> = 35 in 7 weeks). Cisplatin will be administered weekly for the first 3 weeks and the last 3 weeks of radiation.</td>
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<tr>
<td>NCT01891695&lt;sup&gt;g&lt;/sup&gt;</td>
<td>University of Virginia</td>
<td>I</td>
<td><em>n</em> = 45 Stage I-IVb</td>
<td>Elective nodal dose de-escalation. Effectiveness of 39.6 Gy (instead of 50 Gy) radiation on tumor control in the cN0 neck</td>
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<td><strong>Induction chemotherapy followed by lower radiation dose</strong></td>
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<tr>
<td>NCT01084083&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Eastern Cooperative oncology group</td>
<td>II</td>
<td><em>n</em> = 80 Stage III, IVa-b</td>
<td>Induction chemotherapy (paclitaxel, cisplatin and cetuximab) followed by low (54 Gy) or standard dose IMRT with cetuximab depending on the response to induction chemotherapy</td>
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<tr>
<td>NCT01706939&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Mount Sinai School of Medecine</td>
<td>III</td>
<td><em>n</em> = 365 Stage III, IV without active smoking within the last 2 years or &gt;20 pack years within the past 20 years</td>
<td>Induction chemotherapy (three cycles of TPF) followed by low (56 Gy) or standard dose (70 Gy) IMRT with weekly cetuximab and carboplatin or carboplatin only, respectively, depending on the response to induction chemotherapy</td>
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<td><strong>Upfront surgery</strong></td>
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<td>NCT01932697&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Mayo Clinic</td>
<td>II</td>
<td><em>n</em> = 40 Smoking &lt;10 pack years</td>
<td>Surgery followed by hyperfractionated IMRT + docetaxel</td>
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<tr>
<td>NCT01898494&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Eastern Cooperative oncology group</td>
<td>II</td>
<td><em>n</em> = 377 Stage III-IVa (no T1–2 N1)</td>
<td>Transoral surgery followed by pathological risk stratification (described within the article): -Low-risk patients do not have adjuvant therapy</td>
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Outcomes from these ongoing trials will provide definitive answers in the next few years.

Should the total dose of radiotherapy be reduced? The relationship between the radiotherapy dose received by the pharyngeal constrictors, base of tongue and supraglottic larynx and long-term swallowing dysfunction is well documented. Dysphagia increases with every 10 Gy above 55 Gy given to the superior and middle pharyngeal constrictors. Stricture and feeding tube dependence increase when the volume of pharyngeal constrictors receiving 70 Gy exceeds 50 and 30%, respectively, and aspiration increases when more than 50% of pharyngeal constrictors receive 65 Gy. Therefore, reducing the dose to limit swallowing disorders is an interesting approach to improve quality of life. Taking into account the excellent prognosis of HPV-positive patients and the fact that these tumors are supposed to be more radiosensitive, several investigators have hypothesized that this strategy is possible. Different approaches have been proposed.

Induction chemotherapy followed by decreased radiotherapy doses in good responders. Since the pioneering work of Ensley et al., numerous trials have validated the concept that the response to chemotherapy predicts future response to subsequent radiotherapy. Consequently, several trials are based on induction chemotherapy to select good responders that could benefit from a reduction in radiation dose.

The Eastern Cooperative Oncology Group trial ECOG 1308 is a phase II study based on this concept. This study recruited 80 HPV-positive patients with stage III or IV resectable oropharyngeal cancers. Patients received three cycles of induction chemotherapy with paclitaxel (90 mg/m² on days 1, 8 and 15), cisplatin (75 mg/m² on day 1) and cetuximab (loading dose of 400 mg/m² on day 1, followed by 250 mg/m² weekly). After induction chemotherapy all patients had clinical and radiological restaging. Patients who achieved a complete response received radiation up to 54 Gy and cetuximab. All patients with partial response or stable disease received the standard dose of radiotherapy and cetuximab. Preliminary results of this study were presented at ASCO 2013. Eighty patients were enrolled, 3 patients (3.8%) had only 1 cycle of chemotherapy and were excluded. Sixty-two patients out of 80 (78%) had a complete response enabling reduced dose radiotherapy whereas 15/80 (18%) received standard dose radiotherapy. One-year progression free survival (PFS) was 91% for patients receiving 54Gy and 87% for those receiving standard dose. Patients with less than 10 pack years of tobacco history and low dose radiation (n = 40/62) had a 1-year PFS of 97%. Grade 3/4 dysphagia was observed in only 17%. These early results suggest that induction chemotherapy appears to identify a group of patients with low 1-year failure rates after reduced dose radiation. However, caution must be exercised as we do not have the benefit of hindsight. De-escalation may be less appropriate for patients with T4 (n = 7/62, 1 year PFS: 86%, 95% CI (0.33-0.98)), N2c (n = 19/62, 1 year PFS: 88%, 95% CI (0.61-0.97)) or significant smoking history (n = 21/62, 1 year PFS: 84%, 95% CI (0.57-0.94)).
Longer follow up and prospective comparison with standard treatment are required to confirm the utility of this approach.

The Mount Sinai School of Medicine is leading a phase III trial in which patients will receive three cycles of Docetaxel, Cisplatin and 5-FU (TPF) induction chemotherapy. Good responders will be randomized on the second phase of this study, where patients will undergo a 2:1 randomization to reduced (56 Gy) or standard (70 Gy) dose radiotherapy with weekly Carboplatin and Erbitux or carboplatin only, respectively. Patients not meeting the response criteria will be treated with standard dose chemoradiation. Three hundred and sixty five patients, with HPV16-positive (determined by both p16 IHC and PCR positivity) oropharyngeal, nasopharyngeal and carcinoma of unknown primary are planned for accrual. This trial, which alternates both radiation dose and chemotherapy, does not include a standard of care treatment arm, but would be expected to have decreased toxicity and equivalent locoregional control and progression-free-survival at 3 years compared to standard therapy.

The rationale behind these studies, where the response to a primary treatment determines the choice of the next treatment, is interesting. Additionally, induction chemotherapy may potentially decrease distant metastases, that are a leading cause of death in HPV-positive patients, and the radiation dose reduction in these trials is significant. However, it is important to highlight that induction chemotherapy followed by radiotherapy is not standard care except in laryngeal preservation. To date, it has not been demonstrated to be as effective as chemoradiation or radiotherapy alone as reported in a comprehensive meta-analysis conducted by Pignon et al. Although TPF induction is superior to PF, direct trials have failed to prove the superiority of TPF induction followed by radiotherapy over concomitant chemoradiation. Additionally, acute grade 3-4 toxicities associated with sequential regimen are significant. Indeed, compliance rates with an entire course of treatment with these regimens are approximately 70% on highly selected patients. However, HPV-positive patients have few comorbidities and should tolerate these treatments well. Finally, in these studies cetuximab or other agents are used in combination with radiotherapy in good responders to induction chemotherapy, which could count against radiation dose decrease in terms of late toxicity.

Is radiotherapy alone sufficient? Chemoradiation is the standard of care for advanced staged OPSCC in numerous institutions but is associated with severe acute and late toxicities. Consequently, radiotherapy alone might represent an alternative option for HPV-positive OPSCC.

Although HPV-positive OPSCCs have more favorable locoregional control and survival outcomes compared to HPV-negative OPSCCs, several authors have reported that distant metastases rates are similar for both and that distant metastases seem to be the leading cause of death in HPV-positive patients, as in cervical cancer. Therefore, a deintensification protocol that withholds or reduces chemotherapy intensity should be considered cautiously and might be best restricted to subgroups least likely to develop distant metastases. O’Sullivan et al. have stratified 382 patients with HPV-positive OPSCCs, treated with radiotherapy alone or concurrent chemoradiotherapy, into two risk groups based on the risk of distant metastases using recursive partitioning analysis. The low risk group (n = 286, 3-year distant and locoregional control rates were, respectively, 93% (95% CI, 89-95) and 95% (95% CI, 91-97)) comprises patients with T1-3 N0-2a tumors, whereas the high risk group (n = 96, 3-year distant and locoregional control rates were, respectively, 76% (95% CI, 65-84) and 82% (95% CI, 72-89)) comprises patients with T4 and/or N3 tumors. Among the low-risk group, radiotherapy alone (mostly accelerated regimens) seems to be equally effective in terms of distant control for N0-2a and N2b minimal smokers (<10 pack/years) but seems to be inferior to chemoradiation for N2c disease. In addition to T4 and N3 disease, the authors concluded that it seemed prudent to exclude N2b heavy smokers (>10 pack/years) and N2c disease from deintensification strategies that do not include conventional chemotherapy. To the best of our knowledge, there is no ongoing trial comparing radiotherapy alone to other treatment standards, but this should be studied as it is known that concomitant chemotherapy is responsible for a significant increase in acute and late toxicities.

Elective nodal dose de-escalation. University of Virginia is leading a phase II trial aiming to study the effectiveness of 39.6 Gy instead of standard dose (50Gy) on nodal control in the clinically uninvolved neck (cN0) of patients with p16-positive OPSCC. Our study uses the same radiation doses that are delivered to lymph nodes in cN0 HPV-induced anogenital disease and explore the opportunity to reduce the radiation dose in HPV-related OPSCCs.

Less invasive surgery: the conceptual role of TORS in treating HPV-driven OPSCC. Surgery and radiotherapy are both highly effective, as single modalities, for the management of early-stage (T1–2N0) oropharyngeal cancers. Advanced OPSCC can be treated by primary surgery followed by radiotherapy, or by primary chemoradiation. During the last decade, there was a shift from surgical to non surgical regimens due to the improvements in locoregional control and quality of life with the advent of intensity modulated radiotherapy (IMRT) and concurrent chemotherapy. However, as direct comparison of these strategies is lacking, therapeutic decisions are mainly based on institutional preferences. The debate has been relaunched by the introduction of transoral robotic surgery (TORS). TORS permits resection of selected oropharyngeal tumors through the open mouth, without the morbidity and the functional deficit usually related to open surgery. The FDA approved its use in 2009 for the treatment of T1 and T2 tumors of the oropharynx. Although the data for TORS are still in their early phase, oncologic results appear promising. Like any surgical approach, TORS...
allows more appropriate use of postoperative adjuvant therapy based on pathologic staging. This valuable information has the potential to spare or diminish substantially the need for high-dose radiation or concurrent chemoradiation in patients who are expected to do well. Moreover such benefits are increased if the resection can be accomplished with low morbidity, which is the case with TORS. Based on these advantages, several trials use up front transoral surgery followed, or not, by postoperative adjuvant therapy.

The ECOG 3311 is a phase II trial in which patients with stage III and IVa p16-positive OPSCC treated by transoral surgery and neck dissection are stratified into 4 arms according to their pathological results. Patients staged as T1-T2/N0-N1 with negative margins undergo exclusively transoral surgical (ARM A). Patients with clear/close margins, <1mm extra capsular spread (ECS), 2-4 metastatic LN, perineural invasion and/or lymphovascular invasion are randomized between ARM B (low-dose IMRT, 50Gy/25 Fractions) and ARM C (standard-dose IMRT, 60 Gy/30 Fractions). Patients with positive margins, >1mm ECS or ≥5 metastatic LN undergo standard-dose IMRT (66Gy/33Fractions) with weekly chemotherapy (cisplatin 40 mg/m²) (ARM D).

The Washington University School of Medicine is leading a phase III trial to study the optimal intensity of adjuvant therapy required in p16 positive OPSCC who have had all known disease removed surgically (with clear margins) by a minimally invasive approach, and who have ECS in their lymph nodes. Patients are randomized to receive either radiation alone (IMRT, 60 Gy/30Fx) or radiation (IMRT, 60 Gy/30Fx) and weekly cis-platinum (40 mg/m²) during therapy.

These strategies make particular sense for the patients with clinical N0 and N1 disease. If clear margins are achieved, then the goal may be to perform surgery alone. Indeed, risk of neck recurrence without postoperative radiotherapy is less than 5% for patients staged as pN0-1, but may increase up to 20% for pN2 disease.38,39 For more advanced OPSCC, these strategies may help to determine the optimal postoperative adjuvant therapy based on objective criteria provided by the pathologic assessment. Indeed, traditional pathologic risk features may not be as meaningful in the selection of adjuvant therapy regimens and doses in HPV-initiated disease.40 Finally, transoral surgery is not only limited to TORS and other minimal invasive surgical modalities exist (e.g. endoscopic laser surgery, transoral conventional surgery). However, it is probable that robotic surgery facilitates tumor en-bloc resection with clear margins especially for more advanced disease. Prospective trials are urgently needed to assess the benefits for patients of these new surgical approaches.41

**Issues of concern**

**Do we really need to de-escalate treatment?** Most studies suggest that patients affected with HR-HPV-related OPSCC have a better prognosis than their HPV-negative counter-parts. However, cancer related death will affect up to 20% of HPV-positive OPSCC which is not insignificant when compared to other good prognosis malignancies.47,8 Additionally, several authors have reported that distant metastases are as frequent among HPV-positive and negative OPSCC and that it seems to be the leading cause of death in HPV-positive patients.25,26 In this context is treatment de-escalation a good option? Although, this question goes against the grain, it remains a legitimate one. The main objective should be to improve outcomes, especially since these patients can tolerate more intensive treatment than those with HPV-negative tumors, most probably due to less comorbidities. On the other hand, it is true that treatment-related late toxicities are a serious matter of concern especially in younger and healthier patients who will suffer serious social and economic consequences. Taking into account the favorable outcomes of HPV-induced OPSCC, a safe reduction of treatment intensity might be envisaged but in selected patients.

**Selection of patients for treatment de-escalation trials.** There is increasing evidence that HPV-induced OPSCCs represent a heterogeneous group, particularly in term of prognosis. The data produced by Ang et al.7 have shown that HPV-positive patients with a high nodal category (N2b-N3) and more than 10 pack years smoking history have an increased risk of disease progression and death (3-year overall survival rate of 70.8% (95%CI, 60.7–80.8)) compared to nonsmokers who have the lowest risk of death (3-year overall survival rate of 93% (95%CI, 88.3–97.7)). Consequently, treatment de-escalation would be inappropriate for patients with increase oncological failure risk and should only be considered for low risk patients. This highlights a central issue regarding patient selection. Should only nonsmoking HPV-positive patients be included in such studies? If this is not the case, is 10 pack years the appropriate threshold? Should patients with massive nodal involvement be excluded? Are there other clinical or biological parameters to take into account? Currently, there is no consensus on these matters. However, the majority of ongoing trials have taken into account some of these parameters to select patients with better prognosis. Moreover, de-escalation trials should be limited to the oropharynx, which is the only anatomic site within the upper aerodigestive tract where the oncogenic role of HR-HPV is clearly established.

**The risk-benefit balance.** To what extent could treatment be de-escalated and for which patients remains an open question of paramount importance. While the concept of decreasing treatment intensity is attractive, both patients and physicians may be reluctant to embrace the possibility of worse outcomes in exchange for the possibility of improved tolerability. This psychological barrier is well illustrated in a recent study42 in which 51 patients, with OPSCC treated with chemoradiation, were asked what potential difference in cancer survival was acceptable to prefer radiotherapy over chemoradiation (considering the fact that radiotherapy induces less
Although p16 overexpression is a reliable surrogate marker monly used assay for enrolment in de-escalation trials. Consequently, there is a risk of under-HPV16-negative by polymerase chain reaction and In-Situ approximately 15% to 20% of p16-positive OPSCCs are ablly identify HR-HPV-related tumors. The detection of HPV infection. Indeed, several authors have reported that approximately 15% to 20% of p16-positive OPSCCs are HPV16-negative by polymerase chain reaction and In-Situ Hybridization. Consequently, there is a risk of under-treating a proportion of OPSCC patients falsely considered as HPV-driven which can be harmful for patients and have major medico-legal consequences. The use of stepwise algo-rithms, that combine different HPV tests as a strategy to compensate for the limitations of individual tests, should be considered to better classify HPV-induced from non HPV-induced OPSCC until a reliable single assay is developed.

**Future therapeutic approaches**

**Therapeutic vaccine.** Therapeutic vaccines, against HPV, aims to induce cytotoxic T-lymphocyte responses to HPV early regulatory proteins (mainly E6 and E7) to eliminate infected cells. Numerous strategies are being explored and published data come from HPV-induced ano-genital malignancies. A recent phase II trial testing a therapeutic vaccine composed of HPV16 E6 and E7 peptides in women with HPV16-positive high-grade vulvar intraepithelial neoplasia (HG-VIN), provided promising results. After 12 months follow-up, 15 of 19 patients had clinical responses with a complete response in 9 that was maintained at 24 months of follow-up. One patient developed an invasive carcinoma at 6 month and 3 of 6 patients with partial response developed a cancer at, respectively, 13, 30 and 42 months. Knowing that the rate of spontaneous regression of HG-VIN is less than <1.5%, the authors suggested that these good outcomes are probably related to vaccination.

John Hopkins Hospital is leading a phase I trial evaluating the safety and feasibility of an HPV-DNA vaccine against HPV16 E7-protein delivered by electroporation in HPV-induced OPSCC. Cyclophosphamide, an immuno-modulatory agent, is given in addition to the vaccine to enhance immune responses against HPV-infected cells. Two other phase I studies are currently recruiting participants. The NCT01462838 trial aims to show that vaccination with a p16INK4a peptide is safe and can induce a p16INK4a-specific T-cell response in advanced HPV-induced ano-genital and HNSCC (these malignancies being associated with p16 overexpression). The Realistic study (NCT01598792) aims to demonstrate that a vaccine based on a genetically modified strain of the bacterium Listeria monocytogenes encoding HPV16 target antigen is safe and is able to boost the immune system of patients with HPV-positive OPSCC. Thirty-six patients who have completed standard protocol chemoradiation or surgery are planned for accrual.

**The programmed death-1/Programmed death ligand-1 (PD-1/PD-L1) immune checkpoint.** Recent works have suggested that HPV-induced tumors use the PD-1/PD-L1 pathway as an adaptive mechanism against antitumor immunity. This pathway belongs to the immune checkpoints that regulate negatively the immune response (Fig. 2). Indeed, several authors have shown that PD-L1 expression is common in HPV-positive OPSCC. Lyford-Pike et al. found its expression in 70% (14/20) and Ukpo et al. in 49% (68/138) of HPV-positive tumours compared to 29% (2/7) and 34% (14/41) in HPV-negative tumors, respectively. Additionally, Pai et al. have recently proposed a model in which tumor infiltrating lymphocytes, present in HPV-induced OPSCC, secrete IFN-gamma that induce PD-L1 expression on tumor cells localized on tumor periphery at the interface with the inflammatory stroma. Engagement of the PDI receptor on activated T cells by its ligand PD-L1 results in negative T-cells regulation, which protects cancer cells from immune elimination. These findings need to be confirmed. However, they may provide a rationale to develop strategies to target this pathway as effective blockade of PD1/PD-L1, with monoclonal antibodies, has shown to reverse T-cell anergy and improve outcomes in patients affected with melanoma, lung and renal cancer.

The phosphoinositide 3-kinase (PI3K) pathway. The PI3K signaling pathway, a critical signal transduction system, plays a key regulatory role in many cellular process including cell proliferation, survival, motility and angiogenesis. Numerous studies have revealed that many components of this pathway are commonly altered in a wide spectrum of human cancers. Recent publications exploring the mutational landscape of HNSCC, have reported that activating mutations in PIK3CA (gene encoding for the catalytic subunit p110α of PI3K) are found in 6–8% of HNSCC but were more frequent in HPV-positive tumors, however, in these studies, few HPV-positive samples were included. Two recent studies confirmed this finding in larger cohorts of OPSCC. Indeed, Nichols et al. observed PIK3CA activating mutations (codons 542, 545 and 1047) in 13 of 46 HPV-positive OPSCC (28%) and in 4 of 41 HPV-negative OPSCC (10%), which was statistically significant (p = 0.03). Chiosea et al. have found PIK3CA mutations in 23 of 75 (31%)
patients with HPV-positive OPSCC, and when they include other potentially activating genetic alterations of the PI3K signaling pathway (PIK3CA amplification, HRAS mutation and PTEN loss) up to 45% (34/75) of the whole cohort was affected. Additionally, several studies exploring the preclinical efficacy of PI3K-targeted therapy in animals model, inoculated with HPV-positive patient-derived tumorgraft harboring PIK3CA activating mutations or HPV-positive HNSCC-derived cell lines, showed promising results. These works provide a rationale for testing PI3K-pathway inhibitors in the subset of HPV-positive patients harboring PIK3CA mutations. It is also interesting to note that the high rate of PIK3CA mutations could account for the potential lack of benefit of anti-EGFR therapies in HPV-positive OPSCC, as constitutive deregulation of the PIK3CA gene could bypass the EGFR-initiated signaling cascade.

**Conclusion**

Treatment deintensification is a reasonable goal in selected HPV-positive OPSCCs in the setting of controlled clinical trials since survival rates are higher than in HPV negative patients. This reduction needs to be achieved without jeopardizing the good survival results of HPV-positive patients, and taking into account the risk of metastatic relapse in this patient subgroup. To safely de-escalate treatment, heavy smokers and patient with advanced disease should not be included because current data indicate that they still bear a relatively poor prognosis even though their tumor is HPV-induced. Ongoing trials are based on established therapeutic modalities (e.g. radiotherapy, chemotherapy, EGFR-targeting therapy and surgery) and the first results can be expected in the coming years. Until that time, de-intensification should not be considered the standard. Finally, a better understanding of specific molecular alterations underlying HPV induced tumorigenesis will provide ample opportunities to target more selected pathways.

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References


