Clinical and Translational Radiation Oncology 8 (2018) 4–11

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Treatment de-escalation for HPV-driven oropharyngeal cancer: Where do we stand?

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ARTICLE INFO

Article history:
Received 30 August 2017
Revised 28 October 2017
Accepted 29 October 2017
Available online 4 November 2017

Keywords:
Human papillomavirus (HPV)
Oropharynx/oropharyngeal
Cancer/neoplasm
Treatment de-escalation/de-intensification

ABSTRACT

HPV-driven oropharyngeal cancers have significantly better survival rates than tobacco and alcohol induced head and neck cancers. As HPV-positive patients are younger, healthier and far more likely to survive their disease, long-term treatment side effects are becoming a major issue. This has led the scientific and medical community to reassess the current treatment protocols in order to develop less toxic strategies while maintaining good oncological outcomes. In this article, we discuss the ongoing treatment de-escalation trials and highlight the issues raised by these studies.

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Introduction

Human Papillomavirus (HPV)-driven oropharyngeal squamous cell carcinoma (OPSCCs) represent a distinct disease from other head and neck squamous cell carcinomas (HNSCC) that are traditionally induced by excessive tobacco and alcohol consumption [1]. One of their most striking clinical feature is their very good prognosis, the risk of death of HPV-positive patients being half of their HPV-negative counterparts [2,3]. These favorable outcomes have led the medical community to implement a new staging system dedicated to this emerging disease [4] and to examine treatment de-escalation opportunities. Indeed, our current treatment paradigm might expose HPV-positive patients to overtreatment

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https://doi.org/10.1016/j.ctro.2017.10.005

and unnecessary toxic effects. It is likely that less intensive treatment regimens could achieve similar efficacy with less toxicity and an improved quality of life. There are currently many ongoing trials aiming to de-intensify treatment. Four main strategies are under active investigation: 1) radiation combined with cetuximab instead of cisplatin, 2) Induction chemotherapy followed by decreased radiation doses and/or volumes for good responders, 3) radiation alone instead of chemoradiation, 4) Transoral surgery followed or not by postoperative radiotherapy.

In this article, we will discuss the rationale behind these different strategies and highlight several issues raised by treatment de-escalation. We will also comment the outcomes of the few de-intensification studies that were recently published.

Replacement of cisplatin with cetuximab

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 (Table 1). Cetuximab is a monoclonal antibody that targets epidermal growth factor receptor (EGFR). EGFR is involved in the activation of several oncogenic pathways and is overexpressed in up to 90% of HNSCC [5].

The rational that encourages the use of cetuximab in HPV-positive patients is mainly based on the study of Bonner et al. [5]. This study, that was published in 2006, has demonstrated that the addition of cetuximab to radiation provides better oncological outcomes than radiation alone in locally advanced HNSCC [6] (median overall survival improvement from 29.3 to 49 months). Interestingly, if we take a closer look at the data it is striking to observe that patients with oropharyngeal cancer, small primary, significant nodal involvement, good health and younger age are those who have the greatest benefit from cetuximab [6]. Although, these parameters could be attributable to chance alone, they strongly recall HPV-driven HNSCC. The second point behind this concept is that Cetuximab is « supposed to be less » toxic than cisplatin especially in the long run, even if to date there is no direct comparison. Finally HPV-positive patients do well independently of treatment choice, as long as conforms to the standard of care [2,3,7].

However many have recently questioned this rationale as the evidence supporting the replacement of cisplatin by cetuximab is not very strong [8,9]. On a mechanistic level, the existing data are conflicting. Many studies have shown an inverse correlation between HPV status and EGFR alterations [10]. Moreover integrative analysis of gene expression and gene copy numbers have shown that HPV-driven OPSCC are characterized by a lack of EGF pathway activation [11,12]. On the other hand a few in vitro-studies studies have found evidence of enhanced EGFR activation in HPV-positive cell lines [13]. Clinical data are also conflicting (Table 2). Several studies assessing the role of anti-EGFR therapies in HNSCC have shown more benefit for HPV-negative patients than for their HPV-positive counterparts [14–17]. On the other hand, some trials have reported that the benefit is independent from HPV-status [18,19], or a trend toward improved efficacy in

Table 1
Selection of treatment de-escalation trials for HPV-driven oropharyngeal cancer (details available at www.clinicaltrials.gov).

Identifier	Phase	Population	Intervention
Substitution of cisplatin by cetuximab			
NCT01302834[a] RTOG 1016	III	N = 987 Stage III-IV	RT (70 Gy) with Cisplatin (100 mg/m^2 X2) or weekly Cetuximab
NCT01874171[a] De Escalate HPV	III	N = 304 Stage III-IVa	RT (70 Gy) with Cisplatin (100 mg/m^2 X3) or weekly Cetuximab
NCT01855451	III	N = 200 Stage III-IV	RT (70 Gy) with weekly Cetuximab or weekly Cisplatin (40 mg/m^2)
Induction chemotherapy followed by lower radiation dose in good responders			
NCT01084083[a] ECOG 1308[25]	II	N = 80 Stage III-IV	Paclitaxel, cisplatin and cetuximab followed by low (54 Gy) or standard dose IMRT with cetuximab depending on the response to IC
NCT01706939 Quarterback trial	III	N = 365 Stage III-IV	3 Cycles TPF followed by low (56 Gy) or standard dose (70 Gy) IMRT with weekly cetuximab + carboplatin or carboplatin only, depending on the response to IC
Induction chemotherapy followed by reduced (chemo)radiation dose and volume in good responders			
NCT02258659[a,b] OPTIMA trial	II	N = 62 Stage III-IV	Patients (pts) are classified as low-risk (≤T3, ≤N2B, ≤10 PYH) or high-risk (T4 or ≥N2C or >10 pack/years) All pts receive 3 cycles of carboplatin and nab-paclitaxel and dose/volume adapted radiotherapy 1) Low-risk pts with ≥50% response received low-dose radiotherapy alone to 50 Gy 2) Low-risk pts with 30–50% response OR high-risk pts with ≥50% response received low-dose chemoradiotherapy to 45 Gy 3) All other pts, i.e. poor responders, receive regular-dose CRT All pts also received de-escalated RT volumes limited to the first echelon of uninvolved nodes. CRT consisted of paclitaxel, 5-FU, hydroxyurea, and 1.5 Gy twice daily RT every other week. Primary site biopsy and neck dissection performed after de-escalated treatment for pathologic confirmation
Radiation therapy alone (standard or reduced dose)			
NCT02254278[a] NRG HN002	II	N = 295 Stage III-IV	Reduced dose IMRT (60 Gy) with or without cisplatin (40 mg/m^2)
Upfront surgery			
NCT01898494 ECOG 3311	II	N = 377 Stage III-IVa	Transoral surgery followed by pathological risk stratification: – Low-risk patients do not have adjuvant therapy – Intermediate-risk patients are randomized between 50 and 60 Gy – High-risk patients undergo RT (66 Gy) with weekly cisplatin (40 mg/m^2)

[a] Accrual completed.
[b] Very preliminary data [52] (1 year median follow-up) were presented during ASCO 2017 showing promising rates of response to induction chemotherapy and high rates of pathological response after dose reduced radiotherapy. Severe mucositis and PEG tube dependency at 3 months post RT were correlated with RT dose ($p = .03$ and $<.001$ respectively). Longer follow-up needed to consider survival results.

Table 2
Trials assessing the role of anti-EGFR therapies in HNSCC patients.

Identifier	Population	Intervention
Greater benefit for HPV-negative than HPV-positive patients		
RTOG 0522-Trial [16] (Phase III)	895 TT naïve stage III–IV HNSCC (235 p16 + /86 p16-)	Concurrent accelerated RT plus cisplatin with or without cetuximab
SPECTRUM-Trial [14] (Phase III)	657 R/M HNSCC (99 p16 + /344 p16−)	Panitumumab in combination with chemotherapy versus chemotherapy alone as first line therapy
LUX HN1 Trial [15] (Phase III)	483 R/M HNSCC (49p16 + /208 p16−)	Afatinib compared with methotrexate as 2nd-line treatment in R/M patients progressing on or after platinum-based therapy
BIBW 2992-trial [17] (Phase II)	124 R/M HNSCC (17 p16 + /48 p16−)	Afatinib vs Cetuximab following any line of prior platinum based therapy
Benefit independent of HPV-status		
Bonner Study [19] (Phase III)	424 TT naïve stage III–IV HNSCC (110 p16− vs 75 p16+)	Cetuximab + RT vs RT alone cetuximab
Extreme-Trial [18] (Phase III)	442 R/M HNSCC(337 p16− vs 44p16+)	Cetuximab + Cisplatin + 5 Fu vs Cisplatin + 5 FU

R/M: Recurrent /Metastatic; HNSCC: Head and Neck squamous cell carcinoma; TT: treatment.
Comment: p16 status was retrospectively assessed in the Extreme trial [18] and in the Bonner study [19]. In the Bonner study [19], the interaction test is close to significance (p = .085 for OS) and suggests a greater benefit in HPV-positive patients.

HPV-positive patients [18]. These outcomes should, however, be interpreted cautiously as these trials have studied different population (recurrent/metastatic vs. treat naïve patients), were based on different anti-EGFR inhibitors (Panitumumab, Afatinib or Cetuximab) and have used different HPV-status definition. The final answer to this relevant issue is expected soon. The biggest trial (RTOG 1016) has enrolled almost 1000 patients by 2014 and data analysis is planned in 2018.

Less "aggressive radiation/chemoradiation regimens

The relationship between the radiotherapy dose received by the pharyngeal constrictors, the 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 [20]. 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 [21,22]. Therefore, reducing the radiation doses or volumes to limit swallowing disorders is an interesting approach to improve quality of life.

Induction chemotherapy followed by decreased radiation doses or volumes in good responders

Several investigators have assumed that decreased radiation dose is feasible and safe in some HPV-positive patients through the use of induction chemotherapy (IC) as a mean for patient selection. The rationale behind this approach is supported by the following points. Firstly, numerous trials have validated the concept that the response to chemotherapy predicts future response to subsequent radiotherapy [23]. Secondly, HPV-positive tumors are supposed to be more radiosensitive than their HPV-negative counterparts [24]. Finally, doses comparable to adjuvant radiation doses would be adequate to treat patients with subclinical disease. Several studies based on this strategy are ongoing and some have already been published (Table 1).

The ECOG 1308 trial [25] is the first published study based on that concept. In this trial 80 patients were enrolled to receive 3 chemotherapy cycles (paclitaxel, cisplatin and cetuximab) followed by weekly cetuximab and low radiation dose (54 Gy) in complete responders or standard dose (70 Gy) in patients with partial response or stable disease. Three patients were excluded because they had only 1 cycle of chemotherapy and 13 had major protocol deviation for unclear reasons (5 complete responders received 70 Gy and 8 patients with partial response or stable disease had 54 Gy). The IC regimen was well tolerated as 96% of patients received all planned cycles, without major delays or increase in toxicity burden. Of note, 14 patients had cisplatin dose reduction, 2 switched to carboplatin and Cetuximab dose was reduced in 18 patients. The median follow-up was 23 months and the 2 years PFS estimates for the 51 complete responders treated with a decreased dose was 80% (95% CI 0.65–0.89). Interestingly, analysis of treatment failures showed that patients with T4 (2-years PFS: 50%; 95% CI 0.11–0.80), N2c (2-years PFS: 73% : 95% CI 0.44–0.89) and smokers >10 pack-years (2-years PFS: 65%; 95% CI 0.41–0.82) have poor outcomes compared with those with less than 10 pack-years of tobacco history and less advanced tumor stages (<T4N2c) who had a 2 years PFS of 96% (95% CI 0.71–0.99). Regarding post treatment toxicity, data were limited to 51 patients (42 treated with low radiation dose and 9 with standard dose). At 12 months, significantly fewer patients treated with 54 Gy of radiation had difficulty swallowing solids (40% v 89%; p = .011) or impaired nutrition (10% v 44%; p = .025), although the interaction between toxicity and more advanced disease has not been reported.

Chen et al. [26] performed a single arm phase II trial (NCT01716195), in which 44 patients with stage III/IV p16-positive OPCs received 2 cycles of IC (paclitaxel and carboplatin given 21 days apart) followed by radiation combined with paclitaxel. Interestingly, the radiation dose was reduced in complete or partial responders (54 Gy, n = 24) but also in those with less than partial or no responses (n = 20, 60 Gy instead of the standard 70 Gy). All patients completed IC, except 1 patient who had an allergic reaction to paclitaxel and was subsequently treated with carboplatin alone. 37 of 44 patients (84%) received all planned cycles of weekly paclitaxel during radiation and the remaining 7 (16%) missed doses for various reasons (toxicity, social or personal reasons). At a median follow up of 30 months, 1 patient developed distant metastases and 3 had locoregional recurrence (all these patients had partial or less than partial response to IC). The 2-years PFS and locoregional control were respectively 92% (95% CI 77–97) and 95% (95% CI 80–99). The 2-years freedom from grade 3 or worse mucosal and esophageal adverse events was 85% (95% CI 80–90) for patients treated with 54 Gy and 86% (95% CI 80–90) for those who received 60 Gy (p = .47). These outcomes, achieved with 15–20% decreased radiation doses, compared favorably with that obtained in the ECOG 2399 trial [3], that used the same protocol except that radiation was given to a dose of 70 Gy, and with other historical controls treated with standard chemoradiation regimens.

The Mount Sinai School of Medicine is leading a phase III trial (Quarterback study – NCT01706939) in which patients receive three IC cycles composed of Docetaxel, Cisplatin and 5-FU (TPF) [27]. On the second phase, good responders are randomized (2:1

randomization) to reduced (56 Gy) or standard (70 Gy) dose radiotherapy with weekly Carboplatin and Cetuximab or Carboplatin alone, respectively. Patients not meeting the response criteria are 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 alters 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. Very preliminary outcomes were presented at ASCO 2017 meeting and the 2-years PFS for patients receiving 56 Gy and standard dose were respectively 87.5% and 83% [28]. Toxicity and quality of life data were not presented.

Unlike the above-mentioned studies that have focused on radiation doses reduction to decrease toxicity, Villaflor et al. have examined whether radiation volume de-escalation was safe and effective (NCT01133678) [29]. The investigators justified this approach by the 3 following points 1) the majority of loco regional failures after chemoradiation occurs within the radiation field and particularly in the gross tumor volume/highest risk radiation volume [30], 2) Conventional radiation elective nodal volumes are based on historic surgical data regarding the risk of occult lymph node metastasis and it has been demonstrated that under certain circumstances radiation volumes can be safely reduced [31] (e.g. elimination of elective radiotherapy to the retropharyngeal and contralateral uninvolved neck in limited tonsilar cancers), 3) reduction of radiation volumes should translate into improved quality of life. In their study, patients with locally advanced HNSCC received two cycles of IC (cisplatin, paclitaxel, cetuximab ± everoli mus). Good responders (≥50% reduction in the sum of tumor diameters) received a dose of 75 Gy (1.5 Gy twice daily every other week) in a single planning target volume (PTV1) encompassing exclusively gross disease expanded by 1.5 cm combined to concomitant chemotherapy (paclitaxel, fluorouracil, hydroxyurea). Non responders (<50% response) received the same chemotherapy regimen and a dose of 45 Gy on an elective planning target volume (PTV2), encompassing PTV1 and the first uninvolved nodal echelon, followed by a sequential boost to PTV1 to a dose of 75 Gy. Ninety-four patients stage IVa/b HNSCCs were enrolled, among which there were 59 HPV-positive OPSCCs. 43 patients received everolimus as part of their IC regimen as this drug was discontinued on interim analysis after 50 patients due to futility. One patient with sepsis and declining performance status during IC was removed from the study and treated with a decreased intensity CRT regimen, but subsequently died due to progressive disease. Three patients died during IC (sepsis in 2 cases, cardiac arrest in 1 case). IC response was evaluable in 89 patients. Thirty-seven patients (41.6%) were good responders (GR) among which 30 HPV-positive patients, and 52 (58.4%) had no response (NR). One patient died during CRT due to toxic megacolon and among the 88 patients who completed CRT, 9 died from disease progression and 1 due to catheter associated sepsis.

There was a trend for improved progression-free (P = .086) but not overall survival (P = .94) for GR versus NR. The 2-years PFS and OS were 86.0% and 83.5% for GR and 68.7% and 85.4% for NR, respectively. The majority of LRF (12/13-92.3%) were in-field failures within the RT treatment volume and 11/12 (91.7%) occurred in the highest risk volume (PTV1). With respect to HPV-positive patients, the 2-years PFS for GR was 93.1% against 74.0% for NR (p = .10). NR were significantly more likely to undergo G-tube placement during treatment (50.0% GR versus 73.5% NR, p = .040) and be G-tube dependent at 6-months follow-up (5.7% GR versus 32.6% NR, p = .005). The authors concluded that elimination of elective nodal coverage in patients with GR to IC did not appear to compromise outcomes, suggesting that occult nodal disease in GR may be cleared with chemotherapy alone, and resulted in significantly decreased late toxicity. Based on these results, the same group has enrolled patients with HPV-positive OPSCC in a phase II trial of IC response-stratified RT dose and volume de-intensified therapy with pathologic validation of response (see Table 1, NCT02258659 [27]).

The rationale behind these studies, where the response to a primary treatment determines the choice of the next treatment, is very relevant. Additionally, IC may potentially decrease distant metastases that are a leading cause of death in HPV-positive patients [32].

However, although impressive, these outcomes raise several issues. Firstly, the excellent survival rates reported in these studies do not guarantee long-term tumor control as the data are not "mature" yet. Similarly, the follow-up periods are too short (23 months in ECOG 1308 [25], 30 months in NCT01716195 [26] and 24 months in NCT01133678 [29]) to provide a clear and precise picture of long and very long-term toxicities. Indeed swallowing disorders, chronic pain and osteoradionecrosis, that have major impact on quality of life, can occur up to 5–10 years after chemoradiation completion [33]. Secondly, it is legitimate to wonder whether this strategy taken as a whole is a true de-escalation of total therapeutic toxicity burden, given the lengthy IC that preceded the initiation of de-escalated RT that is, however, combined to CT. For instance, 6 out of 94 (6.3%) patients enrolled in NCT01133678 had treatment related fatal complication [29]. Thirdly, as IC followed with radiation is not a standard of care except in laryngeal preservation, these trials lack direct comparison with a standard chemoradiation arm.

Chemoradiation with decreased dose of radiation and chemotherapy

Chera et al. [34] have recently conducted a phase II study (NCT01530997) evaluating the efficacy of a de-intensified chemoradiation therapy regimen in 44 "low risk" HPV-positive patients (T0-3, N0-2c and minimal/remote smoking history). Treatment consisted in 60 Gy IMRT (instead of the standard 70 Gy) with concurrent weekly 30 mg/m^2 cisplatin (instead of 100 mg/m^2 on day 1, 22 and 43). The primary study endpoint was pathologic complete response (pCR) rate based on required biopsy of the primary site and dissection of pretreatment positive lymph node regions, regardless of radiographic response. Following treatment, the clinical complete response rates (based on physical examination and neck CT-scan performed 4–8 weeks after treatment completion) at the primary site and in the neck were respectively 98% and 60%. Surgical evaluation was performed in 43 patients at a mean of 9 weeks. Six patients had partial pathological response (microscopic residual foci in 4 patients) and the pCR rate was 86% (98% for the primary site and 84% for the neck lymph nodes). The investigators also reported early evidence of decreased toxicity compared with other standard regimens.

This study provides very provocative, proof-of-principle data that de-escalation with reduced CRT (representing a 40% reduction in chemotherapy and 14% reduction in RT dose) results in high pCR rate, a possible surrogate for long-term local-regional disease control. The investigators have chosen pCR as the primary endpoints because they were concerned that de-intensified CRT may have inferior outcomes, and from the patient safety standpoint, pathologic assessment may be more robust than imaging based clinical response.

However several important limitations must be highlighted. The trial focused on a very favorable risk cohort of HPV-driven OPSCC and radiation alone could have been sufficient in some of these patients (T1-2 N0-1 and potentially T3N2a-b) [28]. The follow-up period is very short (median 14, 3 months) especially for the toxicity assessment, which is the final goal of any

de-escalation strategy. Finally, post CRT positron emission tomography/CT was not used to guide the need for any surgery. In recognition of these shortcomings, the investigators are currently conducting a follow-up study (NCT02281955) [27]. Patients will receive the same de-intensified CRT regimen, followed by a 12-weeks post-CRT positron emission tomography/CT scan to guide the use of surgery. Patients with moderate smoking histories are eligible, and chemotherapy is omitted for T0-2 N0-1 patients.

Lee et al. [35] have recently reported preliminary outcomes from a study testing the assumption that early-treatment hypoxia assessment with functional imaging (F-FMISO PET) may help to select which HPV-positive patients can safely receive a 10-Gy dose reduction to metastatic lymph node(s). Thirty-three patients were enrolled of which 30% received reduced radiation dose. At the median follow-up of 32 months (range, 21–61 months), the 2-year locoregional control rates and OS were 100%. The 2-year distant metastasis–free rate was 97%. Hypoxia on imaging was confirmed pathologically. This study highlights the potential role of functionnal imaging to alter radiation dose and warrants further investigations.

Removal of chemotherapy

Several studies have demonstrated that amongst HPV-positive patients some have an extremely low oncologic failure risk (especially non-smokers with less than T4 or N2c-N3 disease) [32,36]. For these patients the addition of chemotherapy to radiotherapy does not seem to significantly increase overall survival benefit, suggesting that chemotherapy may be omitted completely. Chen et al. [37] have reported very good outcomes in a series of 19 HPV-positive OPSCCs treated exclusively by radiation, including 17 (74%) patients with stage III/IV and 18 (79%) non-smokers (<100 cigarettes in a lifetime). The 3-years overall survival and locoregional control rates for patients with stage III/IV disease were 81% and 88%, respectively. Among the 18 HPV-positive patients who were never-smokers, the 3-years rates of overall survival and locoregional control were 100% for both.

The NRG Oncology cooperative group has completed the accrual of a phase II study (HN002) randomizing patients to chemoradiotherapy (60 Gy in six weeks with weekly 40 mg/m^2 cisplatin) versus moderately accelerated radiotherapy alone (60 Gy in five weeks with 6 fractions per week). This trial recruited only patients with early to moderate stage T1-T2, N1-N2b or T3, N0-N2b and a lifetime cumulative smoking history inferior to10 pack-years.

Alternative to the "conventional" photon beam therapy

Using a different radiation type could help reduce side effects and improve long-term functional outcomes. Indeed, proton beam therapy allows to reduce the dose to normal structures, especially for OPSCC [38], and a retrospective case matched study has suggested reduced use of feeding tube or weight loss in patients treated with proton therapy compared to IMRT, with similar DFS [39]. Predicted toxicities using each treatment could be used to individualize which treatment to allocate to each specific patient [40]. A randomized trial (NCT01893307 [27]) is currently under way to compare these two forms of radiation, evaluating tumor related outcomes as well as patient reported and physician graded toxicities.

Less invasive surgery: the role of TORS in treating HPV-driven OPSCC

Since the end of the 90's there was a progressive shift from surgical to non-surgical treatment for OPCs due to the improvements in locoregional control and quality of life with the advent of intensity modulated radiotherapy and concurrent chemotherapy. However, as direct comparison of these strategies is still lacking, therapeutic decisions are mainly based on physician and/or institutional preferences. The debate has been relaunched by the introduction of transoral robotic surgery (TORS). TORS permits resection of selected pharyngeal tumors through the open mouth, without the cosmetic deformity, the morbidity and the functional deficits 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 [41–43].

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 upfront transoral surgery followed, or not, by postoperative adjuvant therapy.

The ECOG 3311 (NCT01898494) [27] is a phase II trial, lead by the Eastern Cooperative Oncology Group, in which 511 patients with stage III/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 a surgical treatment (ARM A). Patients with close margins, <1 mm extra capsular spread (ECS), 2–4 metastatic LN, perineural invasion and/or lymphovascular invasion are randomized between ARM B (low-dose IMRT, 50 Gy/25 Fractions) and ARM C (standard-dose IMRT, 60 Gy/30 Fractions). Patients with positive margins, >1 mm ECs or >5 metastatic LN undergo standard-dose IMRT (66 Gy/33Fractions) with weekly chemotherapy (cisplatin 40 mg/m^2) (ARM D). The primary endpoint is 2-years PFS. This study has now completed recruitment and is in follow-up.

The Washington University School of Medicine is leading a phase III trial (NCT01687413) [27] 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. 496 patients are randomized to receive either radiation alone (IMRT, 60 Gy/30Fx) or radiation (IMRT, 60 Gy/30Fx) and weekly cisplatin (40 mg/m^2) during therapy. The endpoints are disease free survival and PFS.

In the PATHOS trial (NCT02215265) [27], run by the Cardiff Clinical Trials Unit in the UK, 242 patients with HPV-positive cancer (T1-3, N0-2b) treated by transoral surgery and neck dissection are stratified into 3 groups according to their pathological results. Patients without adverse histological features will not receive any adjuvant treatment. Patients with T3 tumours (or T1T2 tumours with additional risk factors), N2a or N2b disease with evidence of perineural and/or vascular invasion or close margins (15 mm) are randomized between 2 post-operative radiation doses (60 Gy in 30Fx over 6 weeks or 50 Gy in 25Fx over 5 weeks). Finally, those with tumors of any T or any N stage with positive (<1 mm) margins around the primary tumor specimen and/or cervical lymph node extracapsular spread are randomized between 2 post-operative radiation regimen (60 Gy in 30Fx over 6 weeks or 60 Gy in 30Fx over 6 weeks with concurrent Cisplatin). The endpoint of this phase II study is swallowing function. If an improvement in swallowing function is demonstrated compared to control, then a larger phase III study will be undertaken.

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 [44,45]. 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 [46]. 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 en-bloc resection with clear margins especially for more advanced disease. Prospective trials are needed to assess the benefits for patients of these new surgical approaches.

Issues raised by treatment de-escalation

A few years ago, many were legitimately concerned by treatment de-intensification due to the underlying potential oncologic failure risks. Today, this concept is overall well accepted by the medical and scientific community but major issues remain still unanswered.

Are all HPV-positive patients potential candidates?

Despite the generally good prognosis for HPV-driven OPC, around 20% of patients die from their disease [2,3,7]. The overall principle guiding treatment is *primum non nocere* (first do no harm). Consequently treatment de-intensification is only conceivable in "low risk" patients, compromising patient's safety being unacceptable. The data produced by several groups have shown that HPV-positive patients with advanced primary (T4), high nodal category (N2c-N3) and a smoking history superior to 10–20 pack years have an increased risk of disease progression and death [2,32,36]. 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, what is the appropriate smoking threshold? Do we need to differentiate current from former smokers and if yes, what is the appropriate definition of former tobacco consumption? Should patients with large nodal involvement be excluded and does this include patients with cystic nodal metastasis? Are there other clinical or biological parameters to take into account beyond tumor HPV-status? 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. The American Joint Committee on Cancer eighth edition staging system devoted to HPV-driven OPC might potentially help to select the most suited patients for treatment de-escalation. This new classification better differentiates the prognosis of patients according to their TNM stage [4]. However the main shortcoming is that smoking history is still not taken into account. Finally, 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.

To what extent could treatment be de-escalated?

To what extent could treatment be de-escalated without jeopardizing the survival results is a crucial question. Indeed, the benefit/risk balance between decreased toxicity and cancer control is potentially narrow. 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 study performed by Brotherston et al. [47] 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 side effects than chemoradiation). Nearly 70% of patients were unwilling to risk a 5% or less drop in survival probability to switch from chemoradiation to radiation alone. Therefore, tumor control must remain the main concern of treatment de-escalation strategies. Patients' expectations and priorities have not been well evaluated, and de-escalation strategies should focus on outcomes that matter to patients [48].

HPV-testing reliability?

Accurate classification of OPSCCs, according to their etiology, is mandatory before inclusion into these clinical trials. However, to date there is no consensus regarding the type of tests that are required to reliably identify HPV-related tumors. p16 immunostaining is the most commonly used assay for enrolment in de-escalation trials. Although p16 overexpression is a reliable surrogate marker for HPV infection in the oropharynx, its performance may be confounded by a lack of specificity for oncogenic HPV infection. Indeed, approximately 8% to 20% of p16-positive OPC are HPV16-negative by polymerase chain reaction and In-Situ Hybridization [49]. This means that these tumors are not HPV-driven, with the exception of possible technical issue. Additionally, several seminal studies have shown that the prognosis of p16-positive/HPV-negative tumors is significantly worse than that of p16-positive/HPV-positive cases [50]. Consequently, there is a risk of undertreating a proportion of patients falsely considered as HPV-driven which can be harmful for patients and have medico-legal consequences. The use of stepwise algorithms, 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 [51]. Several RNA-ISH platform are currently under developement to directly identify E6/E7 mRNA (HPV oncogenes), that are considered as the definitive proof of viral involvement. As these platforms use formalin fixed paraffin embedded tissue, they could be easily implemented, in a near future, in routine pathological laboratories.

Conclusion

Treatment de-intensification is a reasonable goal in selected HPV-positive OPSCCs within the strict framework of controlled clinical trials. Numerous studies exploring different strategies are currently ongoing and the first published outcomes are promising, although they come from small phase II trials with clearly insufficient hindsight. Results from large phase III trials, particularly those exploring the substitution of Cisplatin by Cetuximab, are expected soon.

De-escalation deserves continued careful consideration to carve out the delicate balance of cure and toxicity for the sake of a growing population of patients. We caution the medical community to remain committed to the conduct of rigorously constructed clinical trials that will ultimately lead to specific management for HPV-driven OPSCCs.

Conflict of interest

The authors have nothing to disclose.

Funding

No Funding.

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