Has the time come for de-escalation in the management of oropharyngeal carcinoma?

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Over the course of the last two decades, there has been a decrease in the incidence of head and neck cancers thanks to a decreasing prevalence of smoking. However, a new risk factor has been coming to the fore: human papillomavirus infection (HPV). HPV-positive oropharyngeal squamous cell carcinoma (HPV+OPC) is more sensitive to chemotherapy and radiotherapy, which translates to a much better prognosis with conventional treatment protocols than tumours that are HPV-negative. Traditional therapeutic interventions are associated with substantial morbidity and have a great impact on patient quality of life. The main focus is on identifying an ideal group of HPV-positive patients who could receive de-intensification treatment regimens aimed at avoiding the late toxicity of treatment. Various strategies are considered, such as reduction in radiotherapy dose following induction chemotherapy, radiotherapy alone, minimally invasive surgical techniques, and substituting platinum-based chemotherapy. The first generation of de-escalation randomised phase III trials have now been published. The following review summarizes the current knowledge and treatment of oropharyngeal carcinoma.

Key words: oropharyngeal carcinoma, human papillomavirus (HPV), treatment de-escalation/de-intensification, prognostic and predictive markers

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INTRODUCTION

Head and neck cancers represent the sixth most common malignancy worldwide. There are approximately 630,000 new patients diagnosed annually, with 350,000 succumbing to the disease[1]. HPV+OPC incidence has steadily increased in many parts of the world during recent decades[2,3]. While in the past, head and neck cancer was diagnosed predominantly in older people with a habit of excessive alcohol consumption and smoking, nowadays we are seeing an increasing incidence of oropharyngeal carcinomas in patients who are younger, in good health, with good social backgrounds and social status, who often do not present with risk factors such as smoking or alcohol abuse[3,4]. The substantial increase in incidence of HPV+OPC has been attributed to a probable increase in HPV infection[4]. This increase could be due to changes in sexual practices (lifetime number of oral sexual partners) within the affected population[5]. HPV-positive tumours are diagnosed preferentially in the oropharyngeal region, especially in the tonsil and tongue base, and they represent a new subgroup of tumours with various biological, epidemiologic and molecular characteristics (Table 1) (ref.[4,6,7]).

Patients suffering from HPV-associated carcinoma respond better to treatment, and have a lower risk of locoregional recurrence, as well as lower incidence of secondary primary carcinoma[8,9]. HPV-positive tumours are charac-

terised by high-expression p16 (ref.[10]), a protein that is involved in head and neck cancer pathogenesis. HPV status is considered the most important prognostic indicator in head and neck cancer, reflected by the inclusion of p16 status in the eighth edition of the American Joint Committee on Cancer Staging System (Table 2) (ref.[4,10,11]). However, there is currently no evidence that the new staging of HPV+OPC should drive clinical decision-making. There is global consensus about the need for treatment de-escalation (reduction of toxicity while preserving anti-tumour efficacy) for patients with HPV+OPC (ref.[12,13]). Since surgery coupled with concomitant chemoradiation (CRT) is the cornerstone of a curative treatment in head and neck cancers, the current clinical studies focus primarily on minimally-invasive surgical procedures, administered radiation dose reduction, and nephrotoxic cisplatin dose substitution/reduction.

Chemotherapy de-intensification, replacement of cisplatin.

Cetuximab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR) (ref.[14]). EGFR is involved in the activation of several oncogenic pathways and is overexpressed in up to 90% of patients with head and neck cancer[14]. EGFR expression is a strong, independent, prognostic factor in squamous cell carcinomas of the head and neck (HNSCC). High EGFR ex-

Table 1. Characteristics of patients with HPV-positive and negative oropharyngeal carcinoma.

	HPV-negative OPC	HPV-positive OPC
Risk factors	Alcohol, tobacco use	Sexual behaviour, HPV infection, immunosuppression
Incident trends	Decreasing	Increasing
Age	Older men	More likely to be younger (aged < 60 years) men
Tumour location	All sites	Base of the tongue, tonsil
Stage	Variable	Advanced stages (small T, massive N involvement)
Radiological image	Any	Cystic nodal involvement
Histopathological features	Keratinising	Baseloid, Non-keratinising
Tumour differentiation	Any	Undifferentiated
Outcomes	Worse OS and PFS	Better OS and PFS
Locoregional recurrence	Higher	Lower
Metastatic dissemination	Often within 2 years, lung	Later (> 2 years), unusual locations other than just lung (i.e., skin, liver, brain)
Second primary tumours	Common	Less common

OPC, oropharyngeal carcinoma; HPV, human papillomavirus; OS, overall survival; PFS, progression free survival; N, lymph node; T, tumor

Table 2. New TNM staging system classification for HPV-related OPSCC patients 8th edition, developed by The International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S).

Characteristics	7th edition TNM	8th edition TNM
Stage classifications	Stage I (T1N0) Stage II (T2N0) Stage III (T3N0 or T1-T3N1) Stage IVa (T4aN0-1 or T1-T4aN2) Stage IVb (T4b or T1-T4bN3) Stage IVc (M1)	Stage I (T1-T2N0-N1) Stage II (T1-T2N2 or T3N0-N2) Stage III (T4 or N3) Stage IV (M1)
Main N (lymph node) differences	N1: metastasis in a single ipsilateral lymph nodes, <3 cm N2a: metastasis in a single ipsilateral lymph node >3 cm but <6 cm. N2b: metastasis in multiple ipsilateral lymph nodes, <6 cm N2c: metastasis in bilateral or contralateral lymph nodes, <6 cm	N1: ipsilateral metastasis in lymph node(s), <6 cm N2: bilateral or contralateral metastasis in lymph node(s), <6 cm[a]
Main T (tumor) differences	T4a: tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate or mandible T4b: tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base or encases carotid artery	T4: tumor invades any of the following: larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, mandible, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base or encases carotid artery[b]

HPV, human papillomavirus; ICON-S, The International Collaboration on Oropharyngeal cancer Network for Staging; M, metastasis; N, lymph node; OPSCC, oropharyngeal squamous cell carcinoma; T, tumor; OS, overall survival
[a] Because 5-years OS was similar among N1, N2a and N2b, they re-termed the N categories.
[b] Because 5-years OS was similar among T4a and T4b, they were no longer subdivided and it was re-termed as T4

pression is associated with poorer clinical outcomes in HPV-negative patients with HNSCC (ref.[15]). HPV+OPCs were less likely to overexpress EGFR (ref.[15,16]). The use of cetuximab in HPV-positive patients is based on the results of the Bonner et al. study, which demonstrated the effectiveness of cetuximab in locally advanced HNSCC. In this trial, bioradiotherapy with cetuximab was shown to significantly improve overall survival (OS) compared with radiotherapy (RT) alone (median 49.0 months vs 29.3 months) in patients with HNSCC (ref.[17]). In secondary analysis the impact was evaluated of p16 protein and HPV DNA status on outcomes in patients with OPC.

These data suggest that regardless of p16 status, patient outcomes were improved by the addition of cetuximab to RT compared with RT alone. Therefore, although p16 status is a strong prognostic biomarker, it does not seem to predict the effect of cetuximab. This subgroup analysis suggested that a more pronounced benefit from cetuximab may be exhibited in the p16-positive population compared with the p16-negative population; however, no significant interaction between treatment groups and p16 status could be shown[18]. There were several limitations to this study. This was a retrospective analysis of HPV status in a previously unselected population, and the sample size of

the p16-positive subgroup was small, precluding statistical analysis. The medical community has long been awaiting the results of the RTOG 1016 and De-ESCALATE, phase III studies, which examined the effectiveness of replacing cisplatin with cetuximab in HPV+OPC. RTOG 1016 was a randomised, multicentre, non-inferiority trial in patients with locally advanced HPV+OPC. 987 patients were enrolled, of whom 849 received accelerated intensity-modulated RT (70 Gy in 35 fractions) with either concurrent cetuximab (loading dose followed by cetuximab weekly) or high-dose cisplatin. The goal of the study was to determine if substitution of cisplatin with cetuximab would result in a comparable 5-year OS. After a median follow-up of 4.5 years, RT plus cetuximab did not meet the non-inferiority criteria for OS (77.9% vs 84.6%) and progression free survival (PFS) (67.3% vs 78.4%) (ref.[19]). Estimated 5-year rates of local-regional failure were also better in the cisplatin arm (9.9% vs 17.3%) (ref.[19]), and there was no significant difference in distant metastasis between the cetuximab and cisplatin arms. Proportions of moderate to severe toxicity (acute and late) were similar between groups[19]. The international, randomised controlled trial De-ESCALATE has a similar design. 334 patients with low-risk (non-smoker or lifetime smoker with <10 pack-year smoking history) HPV+OPC were randomly assigned to receive either high-dose cisplatin or cetuximab (loading dose followed by seven weekly infusions) in addition to a standardised RT (70 Gy in 35 fractions). The primary outcome of this study was overall severe toxicity events (grade 3-5), and secondary outcomes included OS, time to recurrence, quality of life, and swallowing outcomes. Results of this trial show that, not only did cetuximab result in similar rates of severe and all-grade toxicity to cisplatin, but it importantly resulted in poorer 2-year OS (97.5% vs 89.4%) and higher rates of locoregional recurrence (6.0% vs 16.1%) (ref.[20]) and distant metastases than did standard cisplatin therapy. The spectrum of toxicity varied substantially between the two groups, with skin toxicity and infusion reactions more common in the cetuximab group and gastrointestinal and labyrinthine symptoms predominating in the cisplatin group. Equally, there was no difference between the groups in quality of life or swallowing outcomes[20]. Results of both studies further support cisplatin as the radiosensitiser as the standard of care in all eligible patients with head and neck cancer even for low-risk HPV-positive patients. The purpose of the Trans-Tasman Radiation Oncology Group 12.01, phase III trial is to compare the treatment-related side effects (both acute and longer term) between the cisplatin and cetuximab regimens. Both treatments would be given weekly for the duration of the radiotherapy (70 Gy in 35 fractions). Preliminary results are anticipated soon. These findings will help determine the optimal treatment for patients with HPV+OPC (ref.[21]).

Immunotherapy. Over the past few years immune checkpoint inhibitors have changed treatment paradigms in many malignancies, and are currently under investigation in head and neck cancer as well. Nivolumab and pembrolizumab (both anti-PD-1 antibody) are recommended as category 1 in recurrent and/or metastatic head and neck cancer (non-nasopharyngeal cancer) if the disease progresses during or after platinum-based chemotherapy[22]. Based on the phase III CheckMate 141 study, the OS benefit of nivolumab was independent of p16 status, although the benefit was more pronounced in the p16-positive OPC (ref.[23]). The Keynote-012 study, which investigated the efficacy of pembrolizumab, also observed a higher response in patients with recurrent or metastatic HPV+OPC (ref.[24]). The role of RT and the synergy with immunotherapy as adjuvant or concomitant treatment for advanced HPV+OPC is still under investigation. HPV+OPC are believed to benefit more from immunotherapy than HPV-negative disease, because HPV-positive tumours express viral antigens and because of tumour location in lymphoid tissues (tonsils or base of tongue). Viral antigens can be recognised as foreign by the patient's immune system, leading to immune recognition and activation. Tumour location of HPV+OPC leads to the presence of a higher level of CD8+ and PD-1 tumour infiltrating lymphocytes, which may play a crucial role in the better response of HPV+OPC to immunotherapy[25,26].

Reduction of total radiation dose

Morbidity caused by RT is dose-dependent. The degree of dysphagia, stricture formation, feeding tube dependence and aspiration can be reduced if the total radiation dose to the pharyngeal constrictors is limited to 52–55 Gy, and increases substantially if more than 50% of the superior and 30% of the middle pharyngeal constrictors have been subjected to 70 Gy or more[27-29]. Moreover, HPV-positive status is associated with an increased risk of stroke or transient ischemic attack following RT for head and neck cancer[30]. Therefore, reducing the dose to limit swallowing disorders is an interesting approach to improving the quality of life. Taking into account the excellent prognosis of HPV-positive patients and the fact that these tumours are assumed to be more radiosensitive, several investigators have hypothesised that this strategy is possible. Different approaches have been proposed. Several trials are based on induction chemotherapy to select good responders that could benefit from a reduction in radiation dose. The other de-intensification treatment strategy currently subject to clinical research is overall radiation dose reduction (Table 3) (ref.[6,12,13]).

ECOG 1308 was the first phase II trial evaluated as to whether complete clinical response (cCR) to induction chemotherapy (IC) could select patients with HPV+OPC for reduced radiation dose (from 69 to 54 Gy) as a means of sparing late sequelae. In this study IC (Cisplatin, Cetuximab, and Paclitaxel) was used as a biomarker of responsiveness, and the demonstrated radiation dose could be reduced in a subset of patients with HPV+OPC showing tumour sensitivity to chemotherapy. Fifty-six patients (70%) achieved a primary-site cCR to IC and 51 patients continued to receive cetuximab with IMRT 54 Gy. After a median follow-up of 35.4 months, 2-year PFS and OS rates were 80% and 94% respectively, for patients with primary site cCR treated with 54 Gy of radiation) (ref.[31]). Responders to IC who received reduced-dose radiation appeared to have significantly less late swallowing

Table 3. Selection of treatment de-escalation trials for HPV-driven oropharyngeal cancer.

Name study	Phase	n	Population	Design
Substitution of cisplatin by cetuximab				
RTOG 1016 NCT01302834	III	987	Stage III-IV	RT (70 Gy) with high-dose Cisplatin or weekly Cetuximab
De Escalate NCT01874171	III	304	Stage III-IVa	RT (70 Gy) with high-dose Cisplatin or weekly Cetuximab
NCT01855451	III	200	Stage III-IV	RT (70 Gy) with weekly Cetuximab or weekly Cisplatin
Induction chemotherapy followed by lower radiation dose in good responders				
ECOG 1308 NCT01084083	II	80	Stage III-IV	Paclitaxel, Cisplatin and Cetuximab followed by low (54 Gy) or standard dose IMRT with Cetuximab
Quarterback NCT01706939	III	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				
Optima NCT02161562	II	62	Stage III-IV	Patients (pts) are classified as low-risk (T3, N2b, 10 ≤PYH) or high-risk (T4 or N2c or >10 PYH) All pts receive 3 cycles of carboplatin and nab-paclitaxel and dose/volume adapted RT 1) Low-risk pts with 50% response received low-dose RT alone to 50 Gy. 2) Low-risk pts with 30–50% response OR high-risk pts with 50% response received low-dose CRT 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.
De-intensification of surgery/adjuvant therapy				
ECOG 3311 NCT01898494	II	377	Stage III-IVb	TORS then risk adapted post-operative treatment (observation/50 vs 60/66 Gy with weekly platinum)
PATHOS trial NCT02215265	II/III	242	Stage T1-3, N0-2b	TORS then re-adapted post-operative treatment (observation/50 vs 60/66 Gy with or without weekly platinum)
ADEPT trial NCT01687413	III	500	Stage T1-4a, pN positive with ECE	Post-operative adjuvant RT 60 Gy with or without weekly platinum

ADEPT, Post Operative Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related P16+Oropharynx Cancer; De-ESCALATE, Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in Human Papillomavirus+oropharyngeal Squamosus Cell Carcinoma; ECE, extracapsular extension; Gy, Gray; HPV,human papillomavirus; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; N, number of patients; OPSSC,oropharyngeal squamosus cell carcinoma; PATHOS, post-operative Adjuvant Treatment for HPV-Positive Tumors; PR, partial response; PY, pack-years; RT,radiotherapy; RTOG,Radiation Therapy Oncology Group; TORS, transoral robotic surgery; TPF, docetaxel, cisplatin, fluorouracil, ECOG; EasternCooperative Oncology Group; CRT, chemoradiotherapy; PYH, pack/years

dysfunction (40% vs 89%) or impaired nutrition (10% vs 44%) (ref.[31]). However, among patients with good prognosis (non-smoking patients with less than T4 tumours and ipsilateral nodes smaller than 6 cm) who achieved a complete primary site response to IC, the 2-year PFS rate was 96% (ref.[31]). This supports the importance of careful patient selection for treatment deintensification approaches. The 15-Gy reduction in radiation dose seemed to improve measured swallowing outcomes and nutritional status[32]. Similarly, results of the phase II OPTIMA clinical trial indicate that patients with HPV–positive head and neck cancers can receive substantially lower radiation doses safely and effectively if they respond to IC initially. Sixty-two patients received three cycles of IC (carboplatin and nab-paclitaxel), and those who responded well received one of two de-escalated treatment regimens: 50 Gy of RT alone (RT50 arm) for low-risk disease (≤T3, ≤N2B, ≤10 pack-year smoking history), or 45 Gy of chemoradiation therapy (CRT45 arm) for high-risk disease (T4 or ≥N2C or >10 pack-years). Patients without a favourable response received regular-dose CRT to 75 Gy (CRT75 arm). All patients also received de-escalated RT volumes limited to the first echelon of univoled nodes. All low-risk patients and 32 of the 34 (94%) of the high-risk patients were progression-free at two years following treatment[33]. 2-year OS were 100% for low-risk patients and 97% for high-risk patients[33]. Side effects from de-escalated therapy were significantly improved compared to standard treatment. Rates of grade 3 or higher mucositis were 16% for RT50, 46% for CRT45 and 60% (ref.[33]) for CRT75. Based

on these results, favourable response to IC appears to be a powerful biomarker for dose and volume CRT de-escalation. Outstanding survival and high response to IC suggest that completion neck dissection may not be necessary. Further evaluation of induction-based de-escalation in large multicentre studies is justified. The Quarterback is an active phase III randomised, non-inferiority trial. A total of 365 patients with locally advanced HPV+OPC will be treated with 3 cycles induction chemotherapy (Docetaxel, Cisplatin, and 5-FU). Partial or complete responders are randomised to receive a reduced (56 Gy) or standard (70 Gy) dose RT with weekly carboplatin. Patients not meeting the response criteria are treated with standard dose chemoradiation (up to 70 Gy). The primary endpoint is equivalent locoregional control and PFS at 3 years[34]. Very preliminary outcomes based on 23 patients enrolled and 20 randomised were presented at the ASCO meeting in 2017, and the 2-year PFS were 87.5% for those patients receiving standard doses and 83.3% (ref.[35]) for those patients receiving dose deescalation. Toxicity and quality of life data were not included.

Minimally invasive surgical techniques

Concerns relating to CRT (including the development of metachronous radiation-induced sarcomas and the deleterious systemic effects of cytotoxic drugs) have brought surgery back into the spotlight as a primary treatment option for OPC. The last de-intensification treatment approach consists of incorporation of minimally invasive surgical techniques such as trans-oral robotic surgery (TORS). TORS for operable HPV+OPC is increasingly considered an alternative to CRT as a consequence of fast functional recovery and high effectiveness in terms of tumour control[36-38]. While minimally invasive surgery reduces morbidity, the treatment-related toxicity is still considerable, particularly in patients who receive adjuvant treatment with RT or CRT (in patients with pathologic evidence of extracapsular extension (ECE) or close/positive margins in the primary resection specimen). For instance, one analysis showed a 0% rate of gastrostomy tube use in T1/T2 OPC 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[39]. TORS, like most treatments, can have important treatment-related adverse effects. The most common and serious complication of TORS is postoperative haemorrhage, with an incidence rate ranging from 3 to 8% (ref.[40]). This potentially fatal complication frequently requires a second surgical procedure to control the bleeding[41,42]. Moreover, TORS-based treatment is criticised because a large percentage (about 50%) of patients will still receive adjuvant CRT or RT, despite the disease being sufficiently manageable with concomitant CRT only (for advanced-stage disease) or RT only (for early-stage disease)[43,44]. Early-stage disease is amenable to single-modality treatment (surgery vs RT) with similar efficacy in terms of tumour control. However, as of now, it remains unclear which treatment provides better functional recovery[45-47]. The method for reducing

the percentage of adjuvant treatment is selecting patients for TORS (e.g. without radiographic ECE) (ref.[48,49]). The ORATOR, phase II study, if successful, will provide a much-needed randomised comparison of the conventional strategy of primary RT vs the novel strategy of primary TORS. The trial is designed to provide a definitive quality of life comparison between the two arms[50]. This is currently in progress with an estimated completion date of June 2021. To further reduce morbidity after surgery, ongoing trials explore reducing the dose of adjuvant RT or eliminating adjuvant chemotherapy in patients with risk factors (ECE, positive surgical margins). There are three trials (PATHOS, ADEPT and ECOG 3311) currently underway evaluating the role of de-escalated CRT or observation following primary surgery (TORS combined with a staging neck dissection) for stage III/IV disease[28]. ECOG 3311 is a phase II trial that involves patients after a transoral resection and neck dissection. A major focus was appropriate patient selection. Thus, patients who had clinical or radiographic evidence of matted nodes, and those for whom transoral resection was anticipated to result in positive surgical margins, were not enrolled. Patients are separated into risk groups based on lymph node positivity, ECE, and positive surgical margins. The aim of the study is to determine if it is possible to avoid adverse side-effects of post-surgical radiation and chemotherapy in low-risk patients (negative surgical margins, zero to one node involved with no ECE) and if reduced-dose RT is effective. Primary endpoints included both the feasibility of a large multi-institutional TORS trial (which has now been demonstrated) and the 2-year PFS. Secondary outcomes included toxicity, swallowing function, patient-reported outcomes, and the risk group distribution of these surgeon-selected patients for inclusion[51]. The Adjuvant De-escalation, Extracapsular Spread, p16 Positive, Transoral (ADEPT) trial is a phase III randomised clinical trial, which studies the intensity of adjuvant therapy in patients who have had their disease removed surgically by a minimally invasive approach, and who have ECE. After surgery, patients are randomised to receive either radiation alone (60 Gy), or radiation and weekly cisplatin during therapy[52]. This trial also de-escalates adjuvant RT fields, wherein radiation is not delivered to the primary bed in patients with completely resected T1 or T2 disease. Retrospective analysis showed that locoregional control was not compromised and g-tube use was decreased when primary bed radiation was eliminated[53]. The primary endpoint of the trial examines the impact of transoral laser surgery followed by less intensive adjuvant treatment on swallowing function in patients with HPV+OPC, as well as the effect of this approach on locoregional control and survival[52]. The PATHOS, phase II/III trial will investigate the benefit of CRT in the high-risk group. Patients with positive margins or ECE are randomised between RT 60 Gy with or without concomitant chemotherapy. The low risk group will have no adjuvant therapy as per standard treatment. The medium risk group will be randomised to receive either standard (60 Gy) or de escalated (50 Gy) postoperative RT (ref.[54]). These three studies should add

to our understanding of the survival and functional outcomes that result from de escalation of adjuvant therapy in patients with high risk OPC.

Prognostic factors in HPV-OPC

HPV infection status is now well known as one of the most significant prognostic factors in HPV+OPC patients, followed by smoking history (selecting a cutpoint of 10 pack-years), N category (for HPV-positive tumours), and T category (for HPV-negative tumours) (ref.[55,56]). HPV+OPC patients have a substantially higher rate of OS, with up to 28% absolute reduction in risk of death compared to HPV-negative individuals[57]. However, there is a group of HPV-positive patients who have treatment failure, resulting in poor prognosis in real-world clinical practice. Distant failure is equivalent to that for HPV-negative disease, but may manifest later and in more unusual locations than lungs (i.e. skin, liver, and brain) (ref.[58,59]). It is important to identify the ideal patient group for treatment deintensification and to define prognostic risk groups to avoid undertreating the poorer-risk subset in HPV+OPC.

Prognostic risk groups. The landmark RTOG 0129 study stratified 266 patients with OPC and led to the identification of low-, intermediate-, and high-risk groups of patients based on response to CRT. The low-risk group consists of patients with HPV+OPC and a less than 10 pack-year (PY) history of tobacco use or more than 10 PY history and a single metastatic neck node. These patients had 3- and 8-year OS rates of 93% and 81% (ref.[56,60]), respectively, stimulating de-escalation treatment protocols. The intermediate-risk group consists of patients with >10 PY smoking history, or with multiple nodes and/or >6 cm nodal disease and 3-year OS significantly lower (71%) (ref.[56,60]). Patients with advanced T4 primaries, multiple lymph nodes, and smoking histories of more than 10 PYs have an increased risk of disease progression and death and should not be considered for de-escalation trials[59].

Smoking. The negative impact of smoking on HPV-positive patient's prognosis has been shown by several authors. HPV status of the tumor was the major determinant followed by number of PY of tobacco smoking (≤ 10 vs > 10) (ref.[56]). Smoking patients with HPV-positive tumours represent a clinical challenge due to their intermediate prognosis and significantly worse RT outcome compared to HPV-positive patients with a history of no or less-heavy smoking[61,62]. Compared to p16-negative patients, p16-positive patients had significantly better PFS (28.9% absolute increase at 10 years) and OS (32.1% absolute increase at 10 years) (ref.[63]). Smoking negatively impacted outcome; in the p16-positive subgroup, smokers never had significantly better PFS than former/current smokers (24.2% survival benefit at 10 years) (ref.[63]). The risks of death and cancer relapse significantly increased by 1% for each additional pack-year of tobacco smoking[64]. Therefore, clinicians should strongly encourage smoking cessation amongst all head and neck cancer patients. There are scarce data on the relationships between smoking during treatment and the incidence and severity of radiotherapy-related complications. Some studies have reported a negative impact of continued smoking on treatment tolerance and outcomes in patients with head and neck cancer[65,66]. However, the data from other studies do not confirm this hypothesis[67].

Positive surgical margins and ECE. Historically, positive surgical margins and ECE are the two most important risk factors in stratification of patients with head and neck cancer into a high-risk group that profits from adjuvant concomitant cisplatin-based treatment or RT alone[68,69]. The definition of an adverse feature in the context of HPV is an area of active research. ECE is reported to occur in approximately 60% of patients with regional neck metastasis and further decreases the prognosis of head and neck cancer patients[70,71]. The prognostic significance of ECE in HPV+OPC is a matter of debate. ECE does not have the same adverse prognostic significance in HPV+OPC as compared to HPV-negative tumours[72]. The key consideration for all surgical access in oncology is resection of the primary tumour with sufficient margins without a high risk of causing long-term functional impairment. The safety margin is considered the main indicator of oncological radicality[73]. The impact of the surgical margins on the outcome of HPV+OPC patients remains equivocal. Some studies showed evidence that positive margins were associated with poor outcome in terms of disease-free survival and mortality, but some studies failed to show this impact[72,74,75]. These findings raise questions regarding the additional benefit of postoperative CRT in this group. ECE and surgical margins remain a mysterious condition and much progress still needs to be made, both at the clinical and basic research levels. Clinical trials also use different definitions for negative margins and ECE. There are currently no standardised histological diagnostic criteria for ECE and positive surgical margins. This lack of standardisation calls for the introduction of internationally accepted reproducible criteria for its diagnosis[49].

CONCLUSION

The oropharynx plays an essential role in swallowing and speech. Treatment modalities are heavily influenced by the aim of reducing the risk of functional disability where possible. Thinking of better prognosis in patients with HPV+OPC urge us to assess whether through deintensification of a standard treatment it is possible to achieve the same level of effectiveness and minimise adverse side-effects in young patients in good clinical condition. Clinical studies focus on radiation dose reduction, and the option of replacing nephrotoxic cisplatin and promoting minimally-invasive surgery within the treatment algorithm is discussed. Recent results from two trials, RTOG 1016 and De-ESCALaTE, provided similar conclusions that concurrent systemic therapy is important in the management of HPV+OPC, and modification or elimination of systemic therapy will be problematic. The increasing incidence of HPV+OPC, which often presents with small primary tumours, has reinvigorated the debate

surrounding whether surgery or radiation is the optimal single-modality treatment of early-stage OPC. Whether primary TORS followed by appropriate adjuvant treatment results in survival and functional outcomes equivalent to (or better than) standard CRT is a bigger question. The standard of care for the definitive non-operative management of cisplatin-eligible patients with advanced disease is CRT for a total dose of approximately 70 Gy with concurrent high-dose cisplatin. For patients undergoing initial surgical resection, adjuvant CRT with concurrent high-dose cisplatin is recommended for those with positive surgical margins and/or extranodal tumour extension.

Although the prognosis of HPV+OPC is better than that of HPV-negative OPC, currently the treatment of these two entities is identical. Less-intense treatment is an option only in the setting of clinical trials. Patients with HPV+OPC should be offered clinical trial options whenever they are available. Furthermore, deintensification in an unselected population of patients with HPV+OPC has proven short-sighted. Treatment de-escalation is potentially conceivable in a select population of patients with low-risk HPV+OPC. However, this population must be specifically defined with clinicopathologic factors, or personalised approaches to treatment using risk estimates from published nomograms must be developed.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies discussing the role of HPV as etiologic agent of oropharyngeal carcinoma, its epidemiology, treatment and prognosis. The search was performed as broadly and comprehensively as possible. Scientific articles from 1985 to 2019 were searched using the Medline/PubMed, Scopus and Web of Science databases and references from relevant articles using the terms "HPV", "oropharynx cancer", "epidemiology", "prevalence", "treatment", "de-intensification", "de-escalation", "radiotherapy", "chemotherapy", "prognosis". All searches were up to date as of July 2019. Publications from the last 10 years were preferred.

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