The rationale for HPV-related oropharyngeal cancer de-escalation treatment strategies

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The treatment paradigms for head and neck squamous cell cancer (HNSCC) are changing due to the emergence of human papillomavirus-associated tumors (HPV-related), possessing distinct molecular profiles and responses to therapy. Retrospective studies have suggested that HPV-related HNSCCs are more frequently cured than those caused by tobacco. Current clinical trials focus on the reduction of treatment-related toxicity and the development of HPV-targeted therapies. New treatment strategies include: 1) dose reduction of radiotherapy, 2) the use of cetuximab instead of cisplatin for chemo-radiation 3) less invasive surgical options, i.e. trans-oral robotic surgery and trans-oral laser microlaryngoscopy, and 4) more specific treatment attempts, including immunotherapeutic strategies, thanks to increasing comprehension of the molecular background of HPV-related HNSCC. Whereas recently published data shed light on immune mechanisms, other studies have focused on specific vaccination against HPV-related HNSCC. A crucial problem is patient selection to the chosen bias. Truly HPV-related cancers (p16-positive and HPV DNA-positive) with biomarkers for good response to therapy could be included in randomized trials aiming for less severe and better tailored therapy.

Key words: oropharyngeal cancer, HPV-related, surgery, radiotherapy, chemotherapy, treatment de-escalation.

Introduction

Head and neck squamous cell carcinoma (HNSCC) can be divided into two different clinical entities based on their association with high-risk subtypes of human papilloma virus (HPV16 and HPV18). Dissimilarities in the prognosis and molecular profile of these tumors have attracted much attention in recent years, in part because of increasing rates of HPV infection in HNSCC; however, the underlying mechanisms and detailed genetic profiles that set these tumors apart are still elusive [1]. Most HPV-initiated cancers arise in the oropharynx (OPC), originating in the tonsil or at the base of the tongue. The percentage of OPCs that are HPV positive differs significantly among countries and is < 20% in Eastern Europe compared to > 50% in the Western part of the world (up to ≥ 80% in Scandinavian countries) [2]. Oropharynxs related to HPV infection differ from non-HPV-related cancers. HPV-related tumors are characterized by superior prognosis in terms of locoregional control, disease-specific survival and overall survival, even if presenting at an advanced stage [3–7]. This phenomenon has been observed for more than two decades, and differences in outcomes between cancers caused by HPV and those caused by alcohol and tobacco persist, despite modern treatment [8]. The improved survival was demonstrated irrespectively of treatment modality, i.e. chemoradiation [9–11], transoral robotic surgery [4] and laser microsurgery [12]. The anatomical site of the tumor origin is of great importance: with respect to prognosis, no survival benefit was observed for non-oropharyngeal tumors [9]. HPV-related status is also a favorable prognostic factor in recurrent or metastatic OPCs [13]. Whether there is a survival advantage also in HPV-related (i.e. p16-positive) non-OPC is still a matter of debate [14]. OPCs, like all other HNSCCs, are staged using the TNM system. The newly learned biological tumor feature, HPV positivity, has improved prognosis, although this has no impact on tumor staging. These data suggest that the current TNM system has limited prognostic value in HPV-related OPCs [15]. This highlights the importance of HPV categorization in studies evaluating the directions and efficacy of OPC treatment and constitute the starting point for treatment modifications [7, 16–18].

Traditional treatment for OPCs includes surgery, radiation therapy (RT), and chemoradiation (CRT). High morbidity and the significant complication rate with open surgery have led to the use of RT or CRT for most OPC patients. Thus, despite excellent local control rates with primary surgery, the trend has shifted toward CRT as the primary treatment for OPCs, with surgery reserved for salvage [19]. However, these non-surgical modalities bear considerable acute and late toxicities. Currently, primary surgical

management has returned to the forefront with the use of trans-oral minimally invasive techniques. Interestingly, it has been shown that HPV-related patients have better baseline and post-treatment overall quality of life (QOL) compared to HPV p16-negative patients, irrespective of treatment modality [20], morbidity and the consequent reduction in QOL. Together with the combination of better prognosis and younger age of HPV-related OPCs it has led to increasing interest in the reduction of treatment-related toxicity, to treatment de-escalation and to the development of HPV-specific therapies. Thus, many patients with HPV-related OPC may not require the aggressive, intensified chemo-radiotherapy given to HNSCC patients today and may achieve excellent survival, avoiding some of the severe side effects along with intensified treatment. The goal of this review is to present current knowledge on this topic.

The mechanisms that underlie the improved prognosis in HPV-related disease have not been fully recognized yet. The following patient- and tumor-related factors should be considered:
• lifestyle risk,
• sensitivity to chemo/radiation therapy,
• immune response.

Lifestyle risk

Pronounced differences in the lifestyle habits between patients with HPV-related and HPV-unrelated OPCs are presented in Table 1. Patients affected by HPV-related cancers are typically younger at diagnosis. Levels of alcohol, tobacco, and marijuana use, as well as the prevalence of the comorbidities diabetes mellitus, chronic obstructive pulmonary disease, anxiety disorders, and major depression, were significantly lower in the HPV-related group, as were the number of total missed treatment days. These differences, as well as those of medical and psychosocial burden, may contribute to the observed discrepancies in treatment adherence and need to be considered in outcomes [21, 22]. Compared to the smoking-related, usually HPV-negative cancers, lower incidence of new primary tumors (as a consequence of different/less hazardous life-style of HPV-positive OPC patients) should be mentioned as one of the reasons for improved survival in the HPV-positive group.

Sensitivity to chemo/radiation therapy

There is a growing amount of data supporting the hypothesis that HPV-related tumors have a better survival rate due to a higher sensitivity to CRT as compared to HPV-unrelated HNSCC [21]. HPV positivity is associated with increased chemo-sensitivity in probably multiple, not yet understood pathways [10, 23–27]. DNA damage in HPV-related and HPV-unrelated HNSCC cell lines occurs by different mechanisms, which illustrate the reasons for the increased sensitivity of HPV-related OPCs [28]. HPV-related tumors have fewer genotypic alterations than negative ones [29], which may increase their sensitivity to DNA-damaging agents. HPV-unrelated cancers carry frequent *TP53* mutations that confer chemo-radioresistance [30]. Expression of p16INK4a dramatically affects radiation sensitivity in HNSCC cells, since p16INK4a over-expression impairs the recruitment of RAD51 to the site of DNA damage in HPV-related cells by down-regulating cyclin D1 protein expression. Consistent with the *in vitro* findings,

Table 1. Comparison of HPV-related and HPV-unrelated HNSCC

HNSCC	HPV-related	HPV-unrelated
Localization	oropharynx	larynx, oral cavity
Age	< 45, young adults	> 45, markedly older; 6th decade
Sex	both	predominantly male
General status at presentation	very good	multiple comorbidities
Risk factors	direct relation between viral infection of the genital organs and the presence of an HPV infection in the oral cavity lowered age of sexual initiation high number of sexual partners lack of condom use oral sex open mouth kissing post-transplantation immunosuppression and HIV-infection [98, 99]	abuses: smoking, drinking
Response to RT/CRT	predominantly good	varies, in most cases moderate
Prognosis	good locoregionally advanced pharyngeal cancers have a 60% lower risk of mortality and a 30% better 5-year survival rate [24, 100, 101]	worth
Histology	poorly differentiated in histological examination [102]	
Profile of gene expression	*p16* overexpression	*TP53* mutation

immunostaining of HNSCC samples revealed that high levels of p16INK4a expression significantly correlated with decreased cyclin D1 expression. These findings reveal an unexpected function of p16INK4a in homologous recombination-mediated DNA repair response and imply p16INK4a status as an independent marker to predict the response of patients with HNSCC to radiotherapy [31]. The enhanced responsiveness of HPV-related cancer cells might be caused by a higher cellular radio-sensitivity due to cell cycle dysregulation and impaired DNA repair [28]. Irradiated HPV-related cell lines progressed faster through S-phase, showing a more distinct accumulation in G2/M. The abnormal cell cycle checkpoint activation was accompanied by a more pronounced increase in cell death after irradiation. The differences between HPV-related and HPV-unrelated HNSCC molecular profiles are presented Table 2 [32–36]. Although the HPV-related cell lines were up to 2.4 times more sensitive to radiation than HPV-unrelated cell lines, they displayed the same relative radio-resistance under hypoxia and exhibited similar patterns of up-regulation of hypoxia-induced genes in response to hypoxia [37]. There were equal frequencies of hypoxic tumors among HPV-related and HPV-unrelated tumors. Data from the randomized DAHANCA 5 trial indicated that HPV-related tumors did not benefit from hypoxic modifications with nimorazole treatment [37].

Immune response

Recently, it was demonstrated that the observed improved survival has a strong immunological component [38–40]. The membrane protein CD200, which functions in immune evasion, was analyzed in several HNSCC cell lines and was found to modulate the response to chemoradiation *in vivo*. Attenuating this might be a potential therapeutic strategy [41]. Previous studies have suggested that treatment failure is caused by the radio-resistance of cancer stem cells (CSCs). Within the group of patients with HPV-related OPCs, a high percentage of CD98-positive tumor cells was associated with a significantly worse five-year overall survival compared to patients with a low percentage of CD98-positive cells. HPV-related tumors showed a lower percentage of cells with CD44 and CD98 expression than HPV-unrelated tumors and harbored fewer cells expressing the CSC enrichment markers CD44 and CD98 [42]. The next observation was made regarding the levels of tumor-infiltrating lymphocytes (TILs). HPV-related tumors often show strong T cell infiltration compared to HPV-unrelated ones; such limited immune cell infiltration was found to be associated with decreased overall survival and increased loco-regional recurrences in HNSCC [38, 40]. Tumor-infiltrating lymphocytes can be used to stratify HPV-related patients into high-risk and low-risk groups. CD3+ and CD8+ T cells can be used as markers to predict disease progression and highlight the importance of TILs in determining the response to chemoradiation in HNSCC patients. Hence, the combination of CRT with novel immunotherapies that activate T cells might be useful in HNSCC patients characterized by low levels of CD8+ TILs at baseline, perhaps by enhancing the treatment response and improving disease outcome [20].

Little is known about changes in HPV-specific immune responses and immune cell phenotypes in OPC patients undergoing radical treatment [43]. One study has pointed towards a potential increase in immunosuppressive influences after potentially curative treatment. In order to target effectively HPV-infected tumor cells after treatment, an immune response of considerably greater magnitude than the natural immune response is needed. As a result, the authors initiated the REALISTIC phase I trial where adjuvant vaccination with HPV16 E7 protein expressed by live recombinant Listeria (ADXS11-001) will be given to OPC patients following standard therapy. This trial will investigate the safest dose of vaccine that will induce a strong systemic HPV16 E7-specific T cell response.

Patient selection for treatment de-escalation

Mechanism differentiating the treatment response

HPV-related HNSCCs respond favorably to radiotherapy as compared to HPV-unrelated HNSCCs; however, it is

Table 2. HPV-positive and HPV-negative HNSCC molecular profiles

Molecular change	HPV-positive	HPV-negative
Viral DNA integration into host DNA	yes	no
DNA lesions (carcinogen adducts, breaks)	background level	frequently detected
Mutations in crucial genes e.g. *TP53*	infrequent, no	frequent
Failure of TP53 suppressor function	binding of cellular proteins by viral proteins: E6 (p53) and E7 (Rb)	dysfunction protein produced by mutated gene
TP16 expression	overexpression	common low expression following gene methylation
Loss of heterozygosity	uncommon	frequent
Chromosome instability	induction of centrosome instability	increased general instability
Chromosome aberrations	occasional chromosome loss	gross deletions
Oncogenic pathway	disrupting p53 and pRb molecular pathways	carcinogen exposure → DNA lesion → mutation → mutator phenotype → cancer

difficult to conclude that the improved clinical outcome is only attributable to the intrinsic radio-sensitivity of HPV-infected cells. More likely, it is a complex interaction among intrinsic mechanisms of radio-responsiveness and the tumor microenvironment, including cells of the immune system. Thus, grouping together patient-related and tumor-related features is a crucial problem for appropriate patient selection for de-escalation treatment.

The selection of "true" positive OPCs

The debate regarding the preferred method of detecting HPV infection is still ongoing [44]. p16 is used as an immunohistochemical stain and is a surrogate marker for HPV. A remarkable finding is the survival of patients with p16-positive but HPV DNA-negative OPC, which is significantly different compared with patients with truly HPV-related OPC. The survival curve of this discordant group almost converges with the survival curve of patients with HPV-unrelated OPC. Furthermore, the patient characteristics of this discordant group resemble those of HPV-unrelated patients [45]. The clinical observations confirmed that the terms p16-related tumors and HPV-related tumors cannot be used interchangeably, and p16 staining should be followed by alternative tests. In general, HPV presence is detectable at the protein (p16), DNA and mRNA level. According to the guidelines of the College of American Pathologists, a histopathological examination (protein) has been supplemented with a requirement to add the $p16^{INK4A}$ assay (DNA) by the polymerase chain reaction (PCR) method performed using fresh or frozen tissue specimens as well as paraffin-embedded specimens and smears. Commercially available HPV genotyping tests and sequencing methods are currently in use [46]. A separate group of tests based on a PCR technique, determining the level of viral expression, includes the analysis of viral transcripts of the E6/E7 genes (mRNA) using reverse transcriptase PCR (RT-PCR). The test for viral oncogenes E6 and E7 is thought to be a "gold standard" by some authors as these oncogenes interact with cellular proteins such as p53 and pRB [47, 48]. Fluorescence *in situ* hybridization (FISH) detects HPV DNA with high specificity but relatively low sensitivity of 85–88%.

Summing up, in patients with OPCs it is absolutely necessary to assess HR HPV DNA. In HR HPV DNA(+) patients viral genotyping pointing at HPV 16 and 18 should be considered. The $p16^{INK4A}$ expression test combined with the HPV DNA test increases the sensitivity of the assay. The HPV mRNA test may be a valuable supplement, but it is not absolutely required. Among many methods to analyze HPV in a tumor tissue the following are used the most frequently: immunohistochemical (IH) detection of $p16^{INK4A}$, *in situ* hybridization (ISH) and PCR. In the case of lymph nodes (diagnostic material collected with various techniques) immunohistochemistry is recommended in order to assess HPV 16 and/or $p16^{INK4A}$.

The diagnostic algorithm of HPV-associated HNSCC has to be based on two parameters combined: tumor features (HPV DNA or *p16*) and the HPV E6/7 test [49, 50]. A combined method of detecting HPV DNA using PCR and

GP5+/6+ starters, and an immunohistochemical analysis of the $p16^{INK4A}$ expression, has sensitivity of 96–97% and specificity of 94–98%. A strong relationship between the classification of a tumor as HPV-associated and a prognosis (assessed based on disease-dependent survival rates) is confirmed only when both parameters are used together. What is more, seronegative patients with regard to E6/E7 antibodies have a significantly higher risk of death despite $p16^{INK4A}$ overexpression, as this parameter can be modulated by other causative factors that are independent of HPV [51].

The patient's individual immune response

High levels of TILs have been used to stratify HPV-related patients into high-risk and low-risk groups (three-year survival: HPV-related/TIL (high) = 96%, HPV-related/TIL (low) = 59%). The survival of HPV-related/TIL (low) patients did not differ from HPV-unrelated patients. The prognostic model (AUROC) for HPV-related tumors using a combination of TIL levels, heavy smoking, and T-stage was significant. This model was developed and validated in multi-center examinations, and it suggests that the immune response, reflected by TIL levels in the primary tumor, has an important role in the improved survival seen in most HPV-related patients, and is relevant to the clinical evaluation of HPV-related OPCs [52].

Multivariate analysis of tumor- and patient-related variables

The general condition of the patient, as well as co-morbidities, habits, locoregional tumor advancement (T, N status), and HPV status, should be considered. When stratified by the risk of death, OPC patients could be classified into three different groups: low, intermediate, and high risk related to HPV-related non-smokers, HPV-related smokers, and HPV-unrelated smokers, respectively [10] The risk of death in HPV-related patients was decreased by 58%. In univariate analysis, smoking appears to be one of the main prognostic factors [10, 53] and an independent predictor in multivariate analysis: 0% failure for non-smokers, 17.9% for smokers [18] and a possible direct effect on treatment response and disease control [54]. No difference was apparent among minimal smokers [55]. On the other hand, the accuracy of patient-reported smoking history is suboptimal; thus, its use as a prognostic marker for treatment selection has potential uncertainty [56]. In other models, co-morbidities were the most important prognostic factor in HPV-related patients and the second most important factor in HPV-unrelated patients [57].

Imaging techniques

Imaging techniques play a role in patient selection and decision making in determining the treatment strategy. Tumor uptake of 18F-fluorodeoxyglucose (FDG) on pre-treatment positron emission tomography (PET) and gross tumor volume (GTV) have been identified as potential prognostic factors for both survival and loco-regional failure [58], but others have found that imaging biomarkers are predominantly related to T- or N-stage and asso-

ciated with HPV-unrelated status [59, 60]. Capturing data from multiple methods, i.e. contrast enhanced CT, MRI, and FDG PET/CT, would better define the disease, treatment planning and follow-up. The development of specific imaging protocols, a common imaging repository for review and subsequent data analysis, and a direct correlation between anatomic/functional imaging with prospectively collected whole tumor specimens are the key considerations for future OPC imaging efforts [17, 61].

To summarize, an increasing cohort of patients with HPV-related OPC may be given better-tailored therapy; however, before de-intensified treatment is administered, additional biomarkers are necessary in combination with HPV-related status in order to predict and select patients who will respond favorably to therapy [62, 63]. Selection of appropriate patients for treatment de-intensification and the method by which treatment should be de-intensified, however, remain areas of ongoing controversy [64].

Surgical de-intensification

Optimal surgical management of HPV-related tumors needs to be different from HPV-unrelated tumors [65]. This population of significantly younger patients with improved prognoses is a good group for trans-oral, minimally invasive, function-sparing techniques. The definition of trans-oral resection (TOR) requires the removal of OPC completely with sound oncologic margins. TOR consists of trans-oral robotic surgery (TORS) or trans-oral laser microsurgery (TLM). These techniques might include the use of electrocautery, a carbon dioxide laser, a thallium-YAG laser or other tissue ablation techniques. The technique may include *en bloc* or piecemeal removal of the tumor, but complete margin clearing is a *sine qua non* condition. Recent advances in surgical techniques reduce morbidity and permit ready recovery in terms of speech and swallowing [66, 67]. TOR is effective as a primary treatment modality in both subsets of patients, with HPV-related and HPV-unrelated OPCs, however, other studies have suggested that HPV status has a significant impact on TORS effectiveness. Even as a single modality, without adjuvant therapy, TOR may be adequate treatment for HPV-related OPCs [64]. In a subset of non-smoking patients with HPV-related OPC, excellent oncologic and functional outcomes are possible with TOR and neck dissection alone [64, 68].

Adjuvant radiotherapy/chemo-radiotherapy

The role of postoperative RT in patients with HPV-related OPC treated by TOR is a subject of current research. Reduction of radiation dose and sparing of chemotherapy have the potential to reduce morbidity and improve short- and long-term QOL [69]. Following TOR, patients with OPC should receive protocol-defined risk-based adjuvant therapy based on established criteria, including the adequacy of surgical resection, margin status, the presence and number of lymph node metastases, extracapsular spread (ECS), HPV status, and smoking. Radiation oncology considerations [17] propose three risk categories after TOR. The low-risk group (negative margins, no evidence of perineural invasion, N0 or N1 neck with no ECS) would

not receive adjuvant therapy but rather a watchful waiting policy. The high-risk patients (positive margins, two or more metastases, ECS) would be assigned to receive post-operative chemoradiation. The remaining patients, classified as intermediate risk (close margins, perineural invasion at the primary site, two metastatic nodes with no ECS), would be investigated to generate data supporting the use of the treatment scheme, probably RT alone or biologic therapy.

The Eastern Cooperative Oncology Group (ECOG) subsequently confirmed the de-escalation treatment direction in the prospective ECOG 3311 trial. The aim was to study TORS surgical resection followed by low-dose or standard dose intensity-modulated radiation therapy (IMRT) in resectable T1–T2, N0–N2, p16+ OPCs, with no evidence of distant metastasis. Any trans-oral approach is intended to have negative margins. Patients are then stratified as low, intermediate, and high risk based on surgical margins, metastatic lymph nodes, ECS and smoking history. Low-risk patients with negative margins and no nodal metastases will be observed. High-risk patients with positive margins or ECS will undergo standard post-operative concurrent CRT with CPPD 40 mg/m^2 and 60 Gy in 33 fractions. Patients with intermediate risk will receive RT alone, and will be randomized to either 60 Gy or 50 Gy fractionated daily over 30 or 25 fractions, respectively. For patients randomized to 60 Gy, the ipsilateral nodal regions involved in the carcinoma and the primary surgical site will receive a 10-Gy boost to a total of 60 Gy.

Until now, a few reports have demonstrated that 8–37% of patients were spared radiation and 48–74% of patients did not require chemotherapy after TORS [70–72]. This selective approach has the potential to reduce toxicity and the risk of late complications and reserve treatment modalities for second primary tumors or recurrences. Some authors have suggested that HPV status may reduce the overall prognostic significance of nodal category [73], and ECS was not shown to be predictive of poor prognosis in surgically treated patients with p16INK4A-positive OPCs [74]. Primary outcome measures, i.e. local control, disease-specific survival, and overall survival, indicate that the oncologic outcomes of TORS are comparable to those of CRT. Preliminary data are encouraging, with overall survival rates at one year exceeding 90%, and at two years exceeding 80%. Local failure rates are reported to be between 0% and 3%, with median follow-up rates ranging from 18 months to two years. Regional recurrence rates varied between 2% and 8%, while distant disease was reported in 1–9% [68, 69].

A phase II trial, ORATOR (Radiotherapy vs. TORS), is going to compare RT to TORS in early-stage OPCs [75]. The trial is designed to provide a definitive QOL comparison between the two arms [75]. Patients will be randomized by HPV status and assigned to either a control arm that will receive definitive IMRT 70 Gy +/– cisplatin every three weeks (100 mg/m^2) or an experimental arm that will undergo TORS along with selective neck dissections +/– adjuvant CRT. In the latter group, adjuvant IMRT will use 64 Gy in 30 fractions. If successful, the study will provide a much-needed randomized comparison of the conven-

tional strategy of primary RT versus the novel strategy of primary TORS.

However, for patients with high risk, resected HNSCC, the standard treatment constitutes adjuvant RT combined with high-dose cisplatin. HPV/p16-positive OPCs who received adjuvant CRT with one dose weekly cisplatin had three-year overall survival rates of 86% and 91%, and three-year recurrence-free survival of 82% and 84%. This finding proved that weekly cisplatin in the adjuvant setting is a good treatment for patients with HPV-related OPCs to preserve survival and minimize toxicity [76]. Secondary outcome measures confirm the beneficial, acceptably low morbidity offered by TORS: a significant positive impact on patient QOL and post-treatment function. Initial, limited QOL data have shown that speech, eating, social, and overall QOL domains tend to decrease from baseline but remain high at three months post TORS. Patients receiving TORS alone report better health-related QOL, compared to individuals receiving TORS and adjuvant radiation or chemo-radiation [73, 77].

To summarize, the only transoral surgical approaches for OPC that have been studied prospectively are TORS and TLM. Functional outcomes are diminished following TOR for T3/T4 OPC compared with T1/T2. The current knowledge supports the recommendation that trials should be limited to T1/T2 cancers. So far, the de-intensification study objectives should be: 1. to demonstrate the efficacy of TOR in multicenter surgical trials, 2. to measure and compare the toxicities and functional outcomes from surgical and non-surgical therapies, and 3. to assess the cost of surgical and non-surgical treatment modalities [16]. The possible reduction of dose in adjuvant RT is due to a combination of the reliable margin status achieved following TOR and the inherent better prognosis of HPV-related OPCs. Although initial feasibility and case series reports are encouraging, further validation through well-designed randomized control trials is required prior to widespread shifts in accepted treatment paradigms.

Definitive radiotherapy/chemo-radiotherapy de-intensification

In early stage disease (I/II), single modality treatment is recommended and RT is still more popular than TORS [7, 16]. Loco-regionally (III/IV) advanced OPC requires any given combination and sequence of surgery, RT, and CRT. The addition of chemotherapy to radiotherapy improves loco-regional control and overall survival [78, 79]; however, retrospective analysis of three Radiation Therapy Oncology Group (RTOG) trials proved a 35% rate of severe late toxicities [80]. A reduction in the standard dose of definitive RT in primary RT/CRT is the first way to decrease toxicity. Using the volumetric information from daily image-guided radiotherapy (IGRT) scans, a significant difference in response rates to irradiation in HPV-related and unrelated OPCs was demonstrated [81]. Rapid initial regression between day one and the beginning of the second week in HPV-related and unrelated tumors (33% vs. 10%) was noted [81]. RTOG 0129, a phase III trial, focused on patients with advanced stage HNSCC, treated by CRT

followed by surgery for residual primary N2-N3 nodal disease. It showed that patients with HPV-related OPCs have a more favorable prognosis, in part due to the natural biology of the cancer and in part because these tumors are more radio-sensitive [10, 82]. Replacement of cisplatin with cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR) for CRT, is another strategy. Cisplatin is still considered the gold standard for CRT, but cetuximab may be less toxic with comparable treatment results in retrospective analyses [83–86]. A possible correlation of HPV/p16 and EGFR status on the effect of RT in combination with cetuximab has not been sufficiently investigated. It has been shown that HPV oncogenes do not modulate the anti-EGFR antibody response in HNSCC; thus cetuximab treatment should be administered independently of HPV status [87]. According to some studies, p16 positivity is associated with a favorable outcome in OPC patients treated with RT and cetuximab [88], but others found that patients with HPV-related OPCs and longer follow-up times showed superior outcomes with concurrent cisplatin versus cetuximab [89].

The Eastern Cooperative Oncology Group has initiated a phase II study to investigate de-intensification of radiotherapy (ECOG 1308). The trial includes patients with stage III and IV resectable disease treated with induction chemotherapy using paclitaxel, cetuximab, and cisplatin. Those who had a complete response (CR) then received weekly cetuximab + low dose IMRT (54 Gy in 27 fractions). Patients who experienced less than CR received definitive standard-dose IMRT (69.3 Gy in 33 fractions) and weekly cetuximab. Preliminary results presented at the American Society of Clinical Oncology (ASCO) 2013 reported an overall response rate of 86%, with decreased toxicity compared to historical outcomes [23].

The RTOG 1016 trial is a randomized phase III study aiming for a direct comparison of concurrent CRT: RT + cisplatin vs. RT + cetuximab in stage II–IV HPV-related OPCs. Randomization is stratified by low and high T stage, low and high N stage, and smoking history (< 10 or > 10 packs/year). Both arms of the trial will use accelerated fractionation IMRT (70 Gy in 6 weeks). Importantly, this study has two main objectives. First, the survival on the cetuximab/RT arm cannot be inferior to the cisplatin/RT arm. The second objective is that the acute toxicity in the cetuximab/RT arm will be reduced by at least 50%, whereas the long-term swallowing function is similar or even better. If both objectives are met, concurrent cetuximab may be considered an effective and less toxic alternative to cisplatin [16].

A similar study in Europe, the De-ESCALaTE HPV trial, will accrue 304 patients with HPV-related-OPCs over three years. HPV-related patients will be randomized to receive cisplatin + RT (arm A) or cetuximab + RT (arm B), and will then be followed up for two years. HPV-unrelated patients will enter into the registration cohort study. Parameters such as acute and late severe toxicity, dysphagia, quality of life, loco-regional recurrence, and overall survival will be assessed.

Different treatment approaches might be essential in determining outcome results [90]. Patients with locally advanced OPCs, stratified according to Ang's risk profile

(low, intermediate, and high risk), were treated with either surgery followed by radiotherapy (surgical series) or CRT with/without induction docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy. The CRT effect was significantly higher in the low- and intermediate-risk groups, as these patients had better survival when treated with CRT compared with open surgery followed by RT [90].

Novel therapies

Everolimus, an inhibitor of the mammalian target of rapamycin, as well as the multi-tyrosine kinase inhibitors sorafenib (targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and RAF) and sunitinib (targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, stem cell factor receptor, the RET proto-oncogene and colony-stimulating factor) have shown remarkable antitumor effects against various tumor entities, with moderate side-effects. These drugs are administered orally, which should lead to higher patient compliance and less hospitalization. HPV-related HNSCC has exhibited a higher sensitivity to the drugs compared to HPV-unrelated HNSCC [91].

Another very attractive strategy for potentially de-escalating RT or CRT regimens is therapeutic vaccination. Therapeutic vaccines have been developed in activation of the immune response against cancer cells. This group of trials is currently investigating the hypothesis that the *Listeria*-based HPV vaccine ADX 11-001 induces circulating and tumor infiltrating specific T cell antigens in HPV16+ OPC patients. An example of such a study is REALISTIC, a phase I study being funded by Cancer Research UK (CRUK) to investigate the use of ADXS-HPV for the treatment of HPV-related head and neck cancer. This study was initiated in October 2013, and the main objectives are to investigate the safety and efficacy of ADXS-HPV in patients presenting with HPV-related OPCs and who have been treated with surgery, RT, or a combination of them. The investigators propose that the therapeutic HPV vaccine could eliminate the standard use of chemotherapy and RT as adjuvant treatments for HPV-related OPCs. To date, there are no recommendations for introducing the vaccination as an adjuvant or neoadjuvant strategy.

The potential influence of de-escalation treatment for metastasizing and recurrent patterns in HPV-related tumors

Metastatic lymph nodes (LN) negatively affect prognosis, but their impact on OPC survival has diminished in HPV-related cases. This finding provides a rationale for additional studies into the prognostic significance of LN metastases in OPC cohorts of defined HPV status, and supports the concept that HPV-related OPC is a disease distinct from "classical" OPC, with unique prognostic features [92]. LN regression and regional control after primary RT/CRT in HPV-related versus HPV-unrelated OPC were found to be crucial to the outcome [82]. The initial radiologic complete nodal response and ultimate LN resolution were similar in both groups at 12 weeks but higher in the HPV- related group at 36 weeks. The three-year re-

gional control rate was higher in the HPV-unrelated cases. HPV-related nodes involute more quickly than HPV-unrelated nodes but undergo a more prolonged process to eventual final involution. Post-radiation neck dissection is advisable for all N3 cases, but it may be avoided for selected N2 HPV-related cases with significant LN involution if they can undergo continued imaging surveillance [93].

As HPV-related OPCs have prolonged survival and lower local recurrence rates, distant metastases (DM) have become the main cause of death. There is still concern that the de-escalation strategies may negatively affect the control of distant metastases and therefore finally compromise survival [94]. A subgroup among HPV-related tumors suitable for de-intensification treatment strategies according to their lower risk of DM was analyzed. Patients with T1–T3, N0–N2, and N2b, smoking less than 10 packs per year, were found to comprise a subgroup among the HPV-related patients with the lowest risk for DM, regardless of the treatment used [95].

The salvage of HPV-related OPC failures is still under debate. Treatment options for patients with recurrent OPCs based on HPV status include salvage neck surgery, hypo-fractionated re-irradiation, chemo-embolization, and chemotherapy [96]. In a retrospective analysis of the EXTREME trial (Erbitux in First Line Treatment of Recurrent or Metastatic Head and Neck Cancer), the median survival of patients with incurable metastatic disease in HPV-related OPCs was improved more than in HPV-non-related tumors with the addition of cetuximab to 5-fluorouracil and platinum-based chemotherapy. This result proved the survival benefits of multimodal, aggressive chemotherapy plus cetuximab and suggests that HPV status has prognostic value in recurrent and/or metastatic tumors [97]. The prognostic impact of EGFR over-expression and imaging biomarkers on loco-regional failure was predominantly related to their association with HPV-unrelated status and T- or N-stage, respectively. Among HPV-related OPC patients treated with uniform CRT, only T4 stage, N3 stage, and smoking contributed to risk stratification for failure [60]. The SPECTRUM study (Panitumumab Efficacy in Patients With Recurrent/Metastatic Head Neck Cancer) demonstrated an improvement in overall survival in HPV-related tumors.

To summarize, patients with truly HPV-related OPCs (p16-positive and HPV DNA-positive), with biomarkers for a good response to therapy (e.g. low MHC class I or CD44 expression, or high numbers of CD8+ tumor infiltrating lymphocytes), could be included in randomized trials aiming toward treatment de-intensification. New treatment strategies may include: 1. dose reduction of radiotherapy, 2. the use of cetuximab instead of cisplatin for chemo-radiation 3. less invasive surgical options, i.e. trans-oral robotic surgery and trans-oral laser microlaryngoscopy, and 4. more specific treatment attempts, including vaccination and immunotherapeutic strategies thanks to increased comprehension of the molecular background of HPV-related HNSCC.

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