Locally advanced head and neck squamous cell cancer: treatment choice based on risk factors and optimizing drug prescription

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Despite the policy changes to decrease tobacco consumption and therapeutic advances in this disease, squamous cell carcinomas arising from the head and neck (HNSCC) continue to represent a common neoplasm and a leading cause of cancer-related mortality in Europe and worldwide. Although different approaches have been evaluated, no treatment has currently been shown to be superior to cisplatin (Platinol, Corden Pharma) based chemoradiation in locally advanced HNSCC. Based on retrospective subgroup analyses from multiple large clinical trials, human papillomavirus (HPV) status has been shown to be a validated prognostic factor in oropharyngeal tumors. Patients with HPV-related tumors, especially those who are non-smokers, have generally excellent outcome as their tumors are highly sensitive to both chemotherapy and radiation, whereas those with tobacco-related and HPV-negative tumors, who continue to represent substantial number of cases in Europe, have worse prognosis with tumors that are more resistant to treatment. The goal of treatment de-intensification in patients with favorable risk is to avoid long-term and late toxicity, but this must be achieved without compromise of treatment efficacy. For those with risk factors that portend a worse prognosis, the question remains whether addition to or modification of conventional treatment regimens would improve upon therapeutic index. Innovative clinical trial designs specifically tailored to these risk groups are urgently needed.

Key words: chemoradiotherapy, head and neck cancer, human papillomavirus, induction chemotherapy, locally advanced, risk stratification

Introduction

Tumors arising from the head and neck are the seventh most common neoplasms worldwide. In 2010, an estimate of 634,760 new cases were diagnosed and 356,705 deaths occurred secondary to these tumors globally [1, 2]. In Europe, head and neck tumors ranked sixth in 2010 with ∼113,825 new cases or an incidence of 4.2 cases every 100,000 inhabitants, and they represented the seventh leading cause of cancer death [3]. The vast majority of head and neck malignancies, both worldwide and in Europe, are squamous cell carcinomas (HNSCC) by histology [4].

In over three quarters of new cases, HNSCC are diagnosed at a localized or locally advanced stage which, by and large, portends a curable prognosis. Their definitive treatment involves a multidisciplinary team of surgeons, radiation oncologists and medical oncologists, as well as dentists, nutritionists, among other health care professionals, who are essential to ensure the optimal and timely delivery of treatment and recovery from adverse effects after therapy.

Treatment decisions for locally advanced HNSCC, including the delivery of single versus multiple modality therapy, and the sequence of administration if multimodality therapy is indicated, have classically been based on tumor-related factors, such as primary site and stage, as well as patient-related characteristics, such as age, performance status and pre-existent comorbidities [5]. Anatomical site not only determines the resectability and functional outcome [6, 7], but also has prognostic implications. For instance, HNSCC of hypopharyngeal origin tends to have a worse prognosis compared with tumors of other primary sites with the same stage [8]. Regarding stage, the main objective of staging is to categorize tumors based on their long-term outcome, such that tumors with small primary lesions (T stage) and more extensive nodal involvement (N stage) may harbor a similar prognosis as those with larger primaries but more limited nodal extension. Typically, tumors with the same overall stage should have comparable outcomes and the more advanced the tumor stage, the worse the prognosis. Lastly, age and performance status are important variables on which treatment selection should be based, since both have been shown to be relevant predictive factors for treatment benefit in large randomized clinical trials and in the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) [9, 10].
2) How can the results of adjuvant chemoradiation treatment
in patients with high-risk resected tumors be further improved? Several clinical trials are assessing the addition of systemic agents either concomitantly or sequentially, to adjuvant chemoradiation in this setting. Systemic agents which are being evaluated using such chemo-additive strategies include different erbB/HER-pathway agents such as anti-EGFR monoclonal antibodies (e.g. nimotuzumab (NCT00957086)), or small molecule tyrosine kinase inhibitors with antitumor activity against multiple members of the erbB/HER family receptors (e.g. lapatinib (NCT00424255) or afatinib (NCT01427487)). Another strategy being investigated involves the use of non-platinum cytotoxic chemotherapeutic agents. For instance, the randomized phase II study RTOG 0234 compared the triplet combinations of cetuximab with weekly cisplatin and radiation versus cetuximab with weekly docetaxel (Taxotere) and radiation. Both the treatment arms were deemed feasible and tolerable, but the docetaxel-containing arm appeared to achieve better disease-free survival when compared with historic controls receiving high-dose cisplatin and radiation from the RTOG 9501 study [14]. As a next step, it would seem appropriate to launch a randomized comparison of the docetaxel–cetuximab–radiation triplet against standard chemoradiation in the high-risk population.

unresectable disease and organ preservation approach
This section includes locally advanced HNSCC in which complete resection is not feasible, and also those cases in which despite resectability, an upfront surgical approach is avoided as it may lead to undesirable functional and/or cosmetic deficits.

Several meta-analyses have confirmed the superiority of chemoradiation compared with radiotherapy alone in this setting [10, 15, 16]. The absolute improvement in 5-year survival ranges between 5% and 9% [10, 15, 17]. A recently published meta-analysis in patients with oral cavity and oropharyngeal cancers showed that this benefit could be even higher [16].

the induction chemotherapy controversy
While the benefit of chemotherapy delivered concomitantly with radiation treatment is well established, the role of induction chemotherapy remains controversial. The MACH-NC meta-analysis showed that in comparison to radiotherapy alone, the magnitude of survival benefit from concomitant chemoradiation was superior to that achieved from induction chemotherapy followed by radiation [10, 15]. However, none of the modern era induction chemotherapy trials using taxane-based triplets, or those evaluating sequential therapy of induction chemotherapy followed by concurrent chemoradiotherapy (Table 1), were included in the meta-analysis.

Several induction chemotherapy or sequential therapy trials warrant highlighting. Two phase III studies compared the triplet induction regimen TPF (docetaxel, cisplatin and 5-fluorouracil (5-FU)) with the doublet induction regimen PF (cisplatin and 5-FU) as their main research question. In these two studies, the induction chemotherapy was followed by radiation alone (EORTC 24971/TAX 323 study) [18], or by carboplatin (Paraplatin, Bristol-Myers-Squibb) based chemoradiation (TAX 324 study) [19]. In both the studies, an improvement in OS and progression-free survival (PFS) were observed in the TPF arm compared with PF arm. However, neither of these two studies contained a conventional cisplatin-based chemoradiation arm without induction chemotherapy. A phase III trial from the Spanish Head and Neck Cancer Cooperative Group (TTCC) compared conventional cisplatin-based chemoradiation alone as control, against two sequential therapy arms with the same chemoradiation preceded by TPF and PF as induction regimens, respectively [20]. The study met its primary goal of finding a statistically significant reduction in time to treatment failure between the sequential therapy arms and the control arm; however, a statistically significant difference in OS was not observed. Interestingly, concerns about the feasibility of combining TPF as an induction regimen and conventional high-dose cisplatin at 100 mg/m² as a concurrent regimen became apparent, as a reduced compliance in both radiotherapy and chemotherapy was observed in the sequential therapy arms. Challenges in appropriate treatment delivery were also observed recently, in a French phase II larynx preservation study, TREMPILIN, in
Table 1. Taxane-based randomized clinical trials of induction chemotherapy followed by radiotherapy or by concomitant chemoradiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>n</th>
<th>Induction chemotherapy</th>
<th>Radiotherapy</th>
<th>Concomitant chemotherapy</th>
<th>CRR %</th>
<th>OS (mo)</th>
<th>PFS (mo)</th>
<th>TTF (mo)</th>
<th>TTP (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 24971/TAX 323</td>
<td>III</td>
<td>177</td>
<td>Docetaxel 75 mg/m² d1 + CDDP 75 mg/m² d1 + 5-FU 750 mg/m² d1-5</td>
<td>Conventional 66–70 Gy</td>
<td>No</td>
<td>33.3*</td>
<td>18.8*</td>
<td>11*</td>
<td>10.5</td>
<td>–</td>
</tr>
<tr>
<td>Vermorken et al. [18]</td>
<td>III</td>
<td>181</td>
<td>CDDP 100 mg/m² d1 + 5-FU 1000 mg/m² d1-5</td>
<td>No</td>
<td>19.9*</td>
<td>14.5*</td>
<td>8.2*</td>
<td>7.8</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>TAX 324</td>
<td>III</td>
<td>255</td>
<td>Docetaxel 75 mg/m² d1 + CDDP 100 mg/m² d1 + 5-FU 1000 mg/m² ×4 days</td>
<td>Primary tumor: 70–74 Gy Neck: Uni/Invol: 50 Gy/60–74 Gy</td>
<td>Carboplatin AUC 1.5 weeks 1–7</td>
<td>17</td>
<td>71*</td>
<td>36*</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>Posner et al. [19]</td>
<td>III</td>
<td>246</td>
<td>CDDP 100 mg/m² d1 + 5-FU 1000 mg/m² ×4 days</td>
<td>Carboplatin AUC 1.5 weeks 1–7</td>
<td>15</td>
<td>30*</td>
<td>13*</td>
<td>–</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hitt et al. [20]</td>
<td>III</td>
<td>155</td>
<td>Docetaxel 75 mg/m² d1 + CDDP 75 mg/m² d1 + 5-FU 750 mg/m² d1-5</td>
<td>CDDP 100 mg/m² day 1, 22, 43</td>
<td>44.5*</td>
<td>27.1</td>
<td>–</td>
<td>5*</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>156</td>
<td>CDDP 100 mg/m² d1 + 5-FU 1000 mg/m² d1-5</td>
<td>CDDP 100 mg/m²/3 week day 1, 22, 43</td>
<td>33.6</td>
<td>–</td>
<td>12.3*</td>
<td>18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>128</td>
<td>No</td>
<td>No</td>
<td>61.5*</td>
<td>37.2</td>
<td>–</td>
<td>13.4*</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>Paccagnella et al. [22]</td>
<td>II</td>
<td>50</td>
<td>Docetaxel 75 mg/m² d1 + CDDP 80 mg/m² d1 + 5FU 800 mg/m² d1-5</td>
<td>Primary tumor: 70 Gy Neck: ≥60 Gy</td>
<td>CDDP 20 mg/m² d1-4 + 5-FU 800 mg/m² 96 h day 1, 43</td>
<td>50*</td>
<td>39.6</td>
<td>30.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51</td>
<td>No</td>
<td>No</td>
<td>21.3*</td>
<td>33.3</td>
<td>19.7</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>TREMPLIN</td>
<td>II</td>
<td>126</td>
<td>Docetaxel 75 mg/m² d1 + CDDP 75 mg/m² d1 + 5-FU 750 mg/m² d1-5</td>
<td>RT 70 Gy</td>
<td>CDDP 100 mg/m²/3week day 1, 22, 43d</td>
<td>–</td>
<td>NR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lefebvre et al. [21]</td>
<td>II</td>
<td>50</td>
<td>Docetaxel 75 mg/m² d1 + CDDP 80 mg/m² d1 + 5FU 800 mg/m² d1-5</td>
<td>Cetuximab 250 mg/m² weeks 1–7</td>
<td>–</td>
<td>NR</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant.
*Combined: TPF and PF arm in comparison to the control arm.
*18 months after treatment completion.
*60 patients were assigned to this treatment arm.
*Larynx preservation protocol. This clinical trial only included squamous cell carcinomas (HNSCC) of the larynx and hypopharynx suitable for total laryngectomy. No global complete response rate is provided. From the 116 patients randomly assigned to the chemoradiation or bio-radiotherapy arms, 93% versus 96% were laryngectomy free at 3 months after treatment completion [65].
*56 patients were assigned to this treatment arm.

CRR, complete response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure; TTP, time to progression; CDDP, cisplatin; 5-FU, 5-fluorouracil; AUC, area under the curve; NR, not reached.
which dose modifications during the induction phase were required in 26% of the patients and only 43% of the patients received all three pre-specified doses of concomitant cisplatin [21].

Another approach to optimize the delivery and dose intensities of the chemotherapeutic agents as well as radiotherapy has been offered in a phase II study of the GSTTTC Italian Collaborative Group. In this study, cisplatin–5FU-based chemoradiation with or without induction TPF was compared [22]. Treatment compliance was better than in the aforementioned Spanish and French studies. Based on the higher response rate observed in the sequential therapy arm (Table 1), the phase III part of this study has been opened to enrollment (H&N07; NCT01086826). In this phase III study, a factorial design is used with the first randomization being induction TPF regimen versus no induction, and a second randomization to cisplatin–5FU-based chemoradiotherapy versus cetuximab-based bio-radiotherapy has been added [23].

GORTEC 2007-02 (NCT01233843) is another phase III trial which compares standard chemoradiotherapy with carboplatin–5FU doublet against an investigational arm with induction TPF regimen followed by concurrent radiotherapy with cetuximab. The INTERCEPTOR trial conducted by the Gruppo Oncologico del Nord-Ovest (NCT00999700) is a similar phase III which compares standard chemoradiotherapy with high-dose cisplatin against an investigational arm with induction TPF followed by concurrent radiotherapy with cetuximab.

Until the results of these clinical trials (H&N07, GORTEC 2007-02, INTERCEPTOR) become available, current treatment guidelines consider induction chemotherapy only as a possible strategy in larynx preservation protocols [24, 25], and not as standard of care in general for locally advanced HNSCC.

The role of anti-EGFR therapy
The addition of the monoclonal antibody cetuximab to radiotherapy has been shown to improve the response rate, PFS and OS when compared with radiation alone in a phase III trial in locally advanced HNSCC [9, 26]. However, results of direct OS comparison between cisplatin-based chemoradiotherapy and anti-EGFR therapy-based bio-radiotherapy from prospectively conducted clinical trials are awaited. Early results from such a comparison in a clinical trial are available from the TREMLIN study. In this phase II larynx preservation study, patients with laryngeal and hypopharyngeal tumors who had achieved at least a partial response after TPF induction therapy were randomized to chemoradiotherapy with cetuximab or bio-radiotherapy with cetuximab [21]. While patients on the cetuximab arm had more skin toxicity within the radiotherapy field, they encountered a lower incidence of severe toxicities and achieved better treatment compliance. There was a non-statistical significant trend to a higher locoregional failure after 18 months in the cetuximab arm, but, as salvage surgery was feasible in many cases, the eventual locoregional control was similar in both arms. In addition, no difference in metastatic recurrence was observed between treatment arms.

Several phase III trials comparing platinum-based chemoradiation with anti-EGFR therapy-based bioradiation are ongoing, to evaluate the strategy of chemotherapy-sparing during the concurrent phase of treatment. The HN.6 study (NCT00820248), a phase III trial led by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), has recently completed recruitment. It compared standard fractionation radiotherapy combined with high-dose concurrent cisplatin against accelerated fractionation radiotherapy combined with the humanized anti-EGFR monoclonal antibody panitumumab. RTOG 1016 (NCT01302834) is also a chemo-sparing phase III trial, which compares the administration of two cycles of high-dose cisplatin against weekly cetuximab, both the agents are given in combination with accelerated, intensity modulated radiation therapy given once daily on days 1 to 4 and twice daily on day 5 (concomitant boost) weekly for 6 weeks. The eligible population in RTOG 1016 is enriched for patients with human papillomavirus (HPV)-associated oropharyngeal cancers.

There are other examples of ongoing trials which also compare chemoradiation with bioradiation during the concurrent phase as part of their design. One example is the GSTTTC randomized study H&N07 (NCT01086826) which utilizes a factorial design and compares four arms, cetuximab-based bio-radiotherapy with or without induction TPF, and cisplatin and 5-FU-based chemoradiotherapy with or without induction TPF [23]. Another example is the TTCC-2007-01 trial (NCT00716391) conducted by the Spanish Head And Neck Cancer Cooperative Group (TTCC). This phase III trial compares two sequential regimens, one with TPF followed by standard chemoradiotherapy with high-dose cisplatin, the other with TPF followed by bio-radiotherapy with cetuximab.

In locally advanced HNSCC, the chemo-additive strategy of adding anti-EGFR therapy to concurrent chemoradiotherapy has been disappointing. The recently presented RTOG 0522 study showed no difference in PFS and OS with the addition of cetuximab to accelerated radiation and concurrent cisplatin [27].

A further strategy to incorporate anti-EGFR therapy into the current treatment regimens for locally advanced HNSCC is to deliver it as maintenance therapy after chemoradiation. This strategy is being utilized in a phase III trial comparing a pan-erbB/HER inhibitor, afatinib, against placebo as maintenance therapy after completion of definitive chemoradiotherapy (NCT01345669). This trial is limited only to locally advanced HNSCC patients whose tumors are HPV-negative.

Outside of clinical trials, cetuximab is also an option to consider for combination with radiotherapy in patients ineligible or unsuitable for cisplatin treatment due to older age or comorbidities such as renal dysfunction, hearing impairment and peripheral neuropathy [28].

HPV and smoking as risk factors
HPV status has added further complexity to the optimal treatment decision in locally advanced HNSCC. In the early 2000, several reports showed a causal relationship between HPV and a subgroup of oropharyngeal cancers [29–31]. Towards the end of that decade, the first retrospective case
series showed that HPV-positive tumors not only had a different etiolog, but also a better prognosis than HPV-negative tumors [32, 33]. At that time, the subgroup analysis of the ECOG 2399 study based on HPV status was published. This subgroup analysis showed that patients with HPV-positive tumors had better OS, as well as better response to both induction chemotherapy with paclitaxel (Taxol, Corden Pharma) and carboplatin and concomitant chemoradiation with weekly paclitaxel [34] (Table 2). Other similar subgroup analyses of prospective studies have since been published, showing a survival advantage of patients with HPV-positive tumors treated with chemoradiation with [35] or without induction chemotherapy [36, 37], or with radiotherapy alone [38, 39] (Table 2).

RTOG 0129 was a randomized phase III trial comparing accelerated-fractionation radiotherapy with concomitant boost with standard-fractionation radiotherapy, combined with 2 cycles versus 3 cycles of concomitant high-dose cisplatin therapy, respectively, in patients with stage III and IV HNSCC. The subgroup analysis of all patients with oropharyngeal tumors enrolled on RTOG 0129, based primarily on their HPV status, showed that patients with HPV-positive tumors had a better 3-year OS rate: 82.4% (95% CI 77.2%–87.6%) in the HPV-positive subgroup versus 57.1% (95% CI 48.1%–66.1%) in the HPV-negative subgroup. The adjusted hazard ratio (HR) for death for HPV-positive versus HPV-negative status was 0.42 (95% CI 0.27–0.66). This HR was adjusted by those factors found to be relevant in the multivariable analysis, including age, race, performance status, tumor stage, nodal stage and tobacco exposure expressed as a number of pack-years. In addition, an improved 3-year PFS rate in the HPV-positive subgroup (73.7%, 95% CI 67.7%–79.8%), in comparison to the HPV-negative subgroup (43.4%, 95% CI 34.4%–52.4%), was also found. This improvement was mainly due to a statistically significant reduction in the local-regional relapse rate of 13.6% (95% CI 8.9%–18.3%) in the HPV-positive subgroup versus 35.1% (95% CI 26.4%–43.8%) in the HPV-negative subgroup [40].

This subgroup analysis also highlighted the role of tobacco smoking as an independent factor associated with worse OS and PFS. It was estimated that the risks of death and cancer relapse increased by 1% for every additional pack-year of tobacco smoking, regardless of the HPV status [40].

### Table 2. Subgroup analysis of clinical trials evaluating human papillomavirus (HPV) status as a prognostic factor

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Intervention</th>
<th>Study population</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>HPV positive</td>
<td>HPV negative</td>
<td>HR</td>
<td>95% confidence interval (CI)</td>
</tr>
<tr>
<td>RTOG 0129 [36]</td>
<td>III</td>
<td>Chemoradiation: Standard fractionation RT + CDDP Accelerated fractionation RT + CDDP</td>
<td>323</td>
<td>206</td>
</tr>
<tr>
<td>ECOG 2399 [34]</td>
<td>II</td>
<td>Induction: carboplatin AUC 6 + paclitaxel 175 mg/m² RT + concomitant paclitaxel 30 mg/m²</td>
<td>96</td>
<td>38</td>
</tr>
<tr>
<td>TROG 02.02 [37]</td>
<td>III</td>
<td>Chemoradiation: RT + CDDP ± tirapazamine</td>
<td>172</td>
<td>102</td>
</tr>
<tr>
<td>TAX324 [35]</td>
<td>III</td>
<td>RT and concomitant carboplatin</td>
<td>111</td>
<td>56</td>
</tr>
<tr>
<td>DAHANCA5 [38]</td>
<td>III</td>
<td>Only control arm: Conventional RT</td>
<td>156</td>
<td>35</td>
</tr>
<tr>
<td>DAHANCA6&amp;7 [39]</td>
<td>III</td>
<td>Conventional vs. accelerated RT</td>
<td>794</td>
<td>179</td>
</tr>
</tbody>
</table>

RT, radiotherapy; CDDP, cisplatin; AUC, area under the curve; TPF, docetaxel + cisplatin + 5-fluorouracil; PF, cisplatin + 5-fluorouracil.

### Table 3. Oropharyngeal cancer risk groups according to RTOG 0129 subgroup analysis [40]

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-year overall survival (OS): 93%</td>
<td>Three-year OS: 70.8% (HR 3.54; 95% CI 1.91–6.57)</td>
<td>Three-year OS: 46.2% (HR 7.16; 95% CI 3.97 to 12.93)</td>
</tr>
<tr>
<td>human papillomavirus (HPV) positive, smoking history &lt;10 pack-years</td>
<td>HPV positive, smoking history ≥10 pack-years, with N0 to N2a disease</td>
<td>HPV negative, smoking history &lt;10 pack-years, T4 tumors</td>
</tr>
<tr>
<td>HPV positive, smoking history ≥10 pack-years, with N2b to N3 disease</td>
<td>HPV positive, smoking history ≥10 pack-years, with N2b to N3 disease</td>
<td>HPV negative, smoking history ≥10 pack-years, with T2 or T3 tumors</td>
</tr>
<tr>
<td>HPV negative, smoking history &lt;10 pack-years, T2 or T3 tumors</td>
<td>HPV negative, smoking history &lt;10 pack-years, T4 tumors</td>
<td>HPV negative, smoking history ≥10 pack-years</td>
</tr>
</tbody>
</table>

years. In addition, an improved 3-year PFS rate in the HPV-positive subgroup (73.7%, 95% CI 67.7%–79.8%), in comparison to the HPV-negative subgroup (43.4%, 95% CI 34.4%–52.4%), was also found. This improvement was mainly due to a statistically significant reduction in the local-regional relapse rate of 13.6% (95% CI 8.9%–18.3%) in the HPV-positive subgroup versus 35.1% (95% CI 26.4%–43.8%) in the HPV-negative subgroup [40].

This subgroup analysis also highlighted the role of tobacco smoking as an independent factor associated with worse OS and PFS. It was estimated that the risks of death and cancer relapse increased by 1% for every additional pack-year of tobacco smoking, regardless of the HPV status [40].
The recursive-partitioning modeling carried out in this subgroup analysis identified HPV status as the main determinant for survival, followed by tobacco smoking exposure (> versus ≤10 pack-years) and then nodal status (N0 to N2a versus N2b to N3) for HPV-positive tumors, or tumor stage (T1 to T3 versus T4) for HPV-negative tumors. Based on these risk factors, oropharyngeal cancer patients were divided into three risk groups, low, intermediate and high risk, with an estimated 3-year OS rate of 93%, 70.8% and 46.2%, respectively (Table 3) [40]. These differences render this classification an important patient selection or stratification tool in the design of future HNSCC clinical trials.

**treatment optimization from an European perspective**

It is clear that the data published in the last few years have identified HPV status as a major determinant of survival in oropharyngeal cancer patients. However, mature results from large, prospective and randomized clinical trials to guide treatment decision based on the HPV status are currently lacking. It is likely that moving forward, clinical trials will need to be specifically designed for HPV-positive versus HPV-negative HNSCC patients, or utilize HPV status as a stratification factor, in order to clarify the most appropriate treatment for these biologically different patient populations.

In order to design clinical trials for HNSCC patients in Europe, certain distinctions between the European and the North American populations should be considered. Similar to North America, the overall incidence of HPV-related tumors is increasing in Europe [41–47]. However, as tobacco and alcohol consumption remains elevated in certain parts of Europe, the incidence of HPV-unrelated HNSCC in such areas is still high [48–50]. This phenomenon leads to different distribution of tumor sites across Europe, which may partly explain the differences in survival between countries [50–52], as well as the varied rates of cancer site origins in phase III trials conducted by European [18, 20] versus North American [19, 36] groups.

International collaboration is essential to conduct clinical trials focused on specific risk groups, to help address the key relevant questions faced in daily practice: ‘can long-term toxicity be avoided in patients with low risk oropharyngeal cancers without comprising their outcome?’ and ‘How can the outcome of high risk patient groups with less favorable prognosis be further improved?’

**strategies to diminish long-term toxicity in low-risk patients**

As the curability of low-risk oropharyngeal cancer patients is high (Table 3), there are growing concerns related to the late toxicity induced by chemoradiation among the long-term survivors [53]. Since HPV-positive tumors have shown a higher sensitivity to induction chemotherapy [34], chemoradiation [34] and radiation [38, 39], different approaches is being evaluated to diminish treatment toxicity. For instance, the RTOG 1016 study (NCT01302834) evaluates whether the substitution of cisplatin with cetuximab, concomitant to accelerated-fractionation radiation, in HPV-positive oropharyngeal tumors, will result in comparable 5-year survival. On the other hand, the E1308 study (NCT01084083) investigates the feasibility of reducing radiotherapy intensity when administered in combination with cetuximab, in HPV-positive oropharyngeal cancer patients who achieved a complete response after three cycles of induction treatment with cisplatin, paclitaxel and cetuximab.

Other de-intensification strategies in favorable risk patient subgroups include the evaluation of alternative induction regimens, besides the commonly used TPF triplet, followed by radiotherapy alone or bio-radiotherapy; as well as the substitution of cisplatin by other less toxic chemotherapeutic agents in concurrent chemoradiotherapy. In addition, new advances in surgical techniques, such as trans-oral robotic surgery (TORS), which brings the promise of improved functional outcome compared with conventional open surgery, have made surgery a potential option in some tumors traditionally considered difficult to access or unresectable. The comparisons of TORS versus radiation-based therapy in early oropharyngeal tumors, or de-intensified combined modality regimens incorporating TORS and post-op radiotherapy versus chemoradiotherapy in locally advanced oropharyngeal tumors, would be of interest, both in terms of disease control and long-term toxicity.

**strategies to improve survival in worse prognosis groups**

This group not only includes patients with intermediate and high-risk oropharyngeal tumors, but also those with locally advanced HNSCC from other primary sites, which continue to be prevalent in many European countries.

The role of sequential therapy versus concurrent chemoradiotherapy in this group of patients still needs to be established. Furthermore, the most appropriate induction regimens, and the most optimal agents to combine concomitantly with radiation, to maximize both compliance and therapeutic index, are unclear and await clarification from prospective clinical trials.

The subgroup analysis of many ongoing clinical trials, such as the GSTTTC Italian Collaborative Group H&N07 trial [23], will shed light on these unanswered questions. However, as the role of unplanned subgroup analyses is mainly to generate hypothesis, the design of prospective randomized trials to specifically evaluate the best treatment approach in the worse prognosis groups is essential. Parallel translational research to evaluate the molecular mechanisms associated with the biological aggressiveness of these tumors is integral.

Lastly, based on the high frequency EGFR gene amplifications in HPV-negative tumors [54, 55], the addition of anti-EGFR targeted agents to such tumors could be beneficial. Several mechanisms of resistance to anti-EGFR treatment have been described [56–64], the evaluation of targeted agents that would potentially overcome this resistance would be of relevance in this setting.
conclusions

Besides the conventional tumor- and patient-based factors that direct therapeutic decisions in locally advanced HNSCC, HPV status and tobacco consumption have emerged as useful risk stratification factors to help predict risks of disease recurrence and long-term survival. Current research directions in this disease focus on treatment de-intensification to minimize long-term toxicity while maintaining disease control among patients with favorable risks of cure; and on the optimization of multimodality regimens among patients with worse prognostic risks. With the emerging era of personalized cancer medicine, molecular profiling to identify key oncogenic drivers in HNSCC brings promise of providing additional insights to enhance treatment choices in the future.

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