Essential news of current guidelines: head and neck squamous cell carcinoma

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Summary Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common cancer and accounts for 890,000 cases and 450,000 deaths worldwide annually. HNSCC is a heterogeneous disease affecting mainly elderly patients, who frequently suffer from significant comorbidities. Due to the aggressive tumor biology and high recurrence rates after curative treatment, it is essential to follow the evidence-based treatment recommendations outlined in the international guidelines, although it has to be emphasized that relevant data gaps and controversies exist such as the role of induction chemotherapy, de-intensification strategies or the role of immunotherapy in the locally advanced and recurrent/metastatic setting. These topics will be addressed in this article. Most importantly, interdisciplinary management of HNSCC patients is key for the optimal management at all disease stages.

Keywords Head and neck squamous cell carcinoma · Guidelines · Immunotherapy · Surgery · Chemoradiation

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common cancer and accounts for 890,000 new cases and 450,000 deaths worldwide annually [1]. While alcohol and tobacco consumption are regarded as the major risk factors for HNSCC development, human papilloma virus infection (HPV) has been identified as contributing to the development of oropharyngeal HNSCC in a sub-group of patients [2, 3]. The HPV-positive population shows a more favourable prognosis compared to HPV-negative disease [3].

It is essential for the optimal management of HNSCC patients that a multidisciplinary team is involved including radiation oncologists, medical oncologists, oral and maxillofacial and head and neck surgeons and nutritionists. Standard treatment options include surgery, (chemo)radiation, chemotherapy and immunotherapy.

While the recent National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines provide comprehensive recommendations regarding the diagnosis, therapy and follow-up of HNSCC, additional guidelines such as the American Society of Clinical Oncology (ASCO) guidelines or the German S3 guidelines deal with certain aspects such as treatment deintensification of HPV-positive oropharyngeal carcinomas or distinct subsites such as oral cavity or laryngeal carcinomas [4–9].

Although the NCCN guidelines are regularly revised and reflect the most recent evidence generated by clinical trials until 2022, the ESMO, ASCO and S3 guidelines, which were last updated between 2019–2021, are still valid and their recommendations are a widely accepted standard of care. Despite a rapidly evolving field it has to be noted that the treatment of locally advanced (LA) and recurrent/metastatic (R/M) disease is challenging, relevant data gaps exist and only a few practice-changing trials have been reported during the last couple of years.

It is the aim of this brief report to address the most relevant and controversial recommendations made by the aforementioned guidelines for the management of non-nasopharyngeal HNSCC from a medical oncologist’s point of view. Since early stage I/II HNSCC is commonly treated with single-modality treatment
(i.e., surgery or radiotherapy) accompanied by a good prognosis, the focus will be laid on non-nasopharyngeal LA and R/M HNSCC.

**International guidelines**

**Locally advanced HNSCC**

Is there a role for induction chemotherapy?

There has been an ongoing debate regarding the status of induction chemotherapy (ICT) during the last couple of years. Since the incorporation of ICT failed to show an overall survival (OS) benefit in multiple clinical trials, the relevance of ICT is decreasing. Studies such as the RTOG 91–11 study, which evaluated the role of ICT followed by radiotherapy, CRT and radiotherapy alone, demonstrated that laryngectomy-free survival was improved in the ICT (hazard ratio [HR] = 0.75; 95% confidence interval [CI], 0.59 to 0.95; \( p = 0.02 \)) and chemoradiation (CRT; HR = 0.78; 95% CI, 0.78 to 0.98; \( p = 0.03 \)) arm compared to radiotherapy alone (but the laryngeal preservation rate was inferior for ICT compared to CRT) [10].

Nevertheless, ICT is regarded as a valid option for larynx preservation attempts, while the use of ICT outside of this scenario is discouraged following the ESMO guidelines [6]. Since there is no consensus within the NCCN panel members on this matter as well, ICT is stated as a category 3 option is most scenarios (except for larynx preservation purposes) [7]. There is broad consensus across the guidelines that the preferred ICT regimen consists of cisplatin, docetaxel plus 5-FU.

What is the optimal platinum dose in combination with definitive/postoperative radiotherapy?

The optimal cisplatin dose and schedule is a matter of ongoing discussion. High-dose cisplatin 100 mg/m² given on day 1, 22 and 43 concurrently to radiotherapy (RT) is regarded as the standard of care across the guidelines [6, 7]. Since the toxicity of this regimen is substantial, alternative chemotherapy regimens with comparable efficacy but less toxicity would be desirable.

Recently, the prospective randomized phase II/III JCOG1008 study conducted in 261 high-risk Asian LA-HNSCC patients scheduled for postoperative chemoradiation evaluated the efficacy and safety of bolus cisplatin 100 mg/m² given every 3 weeks vs. weekly cisplatin 40 mg/m². At a median follow-up of 2.2 years weekly cisplatin was shown to be noninferior with respect to the primary endpoint OS at 3 years (72% vs. 59%, HR 0.69; 95% CI 0.37–1.27) [11].

Likewise, the CONCERT phase III study demonstrated the noninferiority of weekly cisplatin 40 mg/m² to bolus cisplatin 100 mg/m² in terms of locoregional control rates (LCR) at 2 years (56.39% vs. 60.9%) in 278 LA-HNSCC patients treated with definitive CRT [12].

Of note, postoperative RT with weekly cisplatin given at 30 mg/m² showed inferior LCR compared to three-weekly cisplatin 100 mg/m² and should be avoided [13].

Irrespective of the schedule employed it must be emphasized that the delivery of a cumulative cisplatin dose of 200 mg/m² is crucial.

For patients unfit for cisplatin the ESMO guidelines suggest carboplatin combined with 5-FU or cetuximab concomitant to RT as well as hyperfractionated or accelerated RT without chemotherapy [6].

Is there a role for de-intensification in HPV/p16-positive oropharyngeal carcinoma?

It is well known that p16/HPV-positive oropharyngeal carcinoma (OPC) patients have a better prognosis compared to p16/HPV-negative patients. Thus, treatment de-intensification of radiotherapy or chemotherapy in order to minimize treatment-related toxicity is currently being investigated in clinical trials. Examples include a randomised phase II study published recently that demonstrated de-escalated RT in combination with weekly cisplatin results in an excellent 2-year progression-free survival (PFS) rate of 90.5% accompanied by a late severe adverse event rate of 21.3% in low-risk oropharyngeal cancer patients [14]. Since phase III trials for treatment de-intensification are still ongoing, there is broad consensus across the guidelines that—despite a compelling scientific rationale—the treatment strategy of p16/HPV-positive OPC patients remains identical to p16/HPV-negative ones outside of clinical trials [4, 6, 7]. The treatment algorithms of p16-positive vs. p16-negative OPC presented in the NCCN guidelines mainly accommodate the new staging system for p16-positive OPC and do not reflect a different treatment strategy.

Should immunotherapy be given in the neoadjuvant setting or in combination with radiotherapy?

The recurrence rate of stage III/IV disease after curative therapy is about 30–40% in the first 2 years of follow-up and a constant rate of 2–3% per year of second primaries is observed [15–17]. Due to the promising data of immune checkpoint inhibition in the R/M setting and based on the idea of an improved “immune profile” in therapy naïve patients, it is tempting to speculate that immunotherapy administered in the neo-adjuvant setting or concurrently with radiotherapy results in an enhanced immune response to checkpoint inhibitors (CPI) and prolonged survival.

The enthusiasm for the combination of CPI with definitive radiotherapy has been tempered by the disappointing outcomes of three phase III randomized trials (JAVELIN Head and Neck 100, GORTEC-REACH and Keynote 412) [18, 19].

The GORTEC-REACH trial evaluated the efficacy of avembumab plus cetuximab in combination with radiotherapy in LA-HNSCC. The trial missed the primary.
and based on the available evidence [6].

Thus, the hope currently lies in neo-adjuvant immunotherapy approaches followed by surgery (comprehensively reviewed by Nenclares et al. [20]), although long-term survival data are pending.

In summary, immunotherapy remains investigational in early or LA-HNSCC and should not be given outside of clinical trials according to the guidelines and based on the available evidence [6].

### Recurrent/metastatic HNSCC

**What is the optimal first-line regimen in the R/M setting?**

For pre-irradiated patients not amenable to salvage surgery, systemic therapy is the mainstay of treatment. The Keynote 048 phase III study defined a new standard of care in this setting and demonstrated an overall survival (OS) benefit with pembrolizumab alone in the programmed cell death 1 ligand (PD-L1) combined positive score (CPS) ≥1 and CPS ≥20 subgroups (CPS ≥20: HR for OS = 0.61, 95% CI 0.45–0.83), and in combination with platinum/5-FU both in the total population and the predefined CPS-positive populations (CPS ≥1: HR for OS 0.65, 95% CI 0.53–0.8) over the EXTREME regimen [21]. Very recent data demonstrated impressive long-term survival rates (21% at 4 years) in R/M HNSCC patients treated with single agent pembrolizumab, which has never been observed in the pre-immunotherapy era [22]. Of note, neither pembrolizumab alone nor pembrolizumab with chemotherapy improved progression-free survival. The overall response rate for pembrolizumab monotherapy was numerically lower (23.3% vs. 36.1% in the CPS ≥20 population), compared to the EXTREME regimen [21].

The search for a predictive biomarker (beyond PD-L1 expression) to identify patients, who derive the maximum benefit from CPI therapy is still ongoing.

Based on this study the international guidelines recommend either pembrolizumab alone or in combination with chemotherapy as the preferred regimen in the first-line setting [6, 7]. Most notably, there are differences regarding the approval status of pembrolizumab worldwide. In Europe pembrolizumab in combination with chemotherapy is not approved in CPS-negative patients, while this is not the case in the United States. Apart from that, one has to consider that the Keynote 048 trial excluded platinum-resistant patients (= platinum exposure within 6 months), which is reflected in the treatment algorithm depicted in the ESMO guidelines [6].

The NCCN guidelines add pembrolizumab plus cetuximab as a category 2B option. This recommendation is based on a single arm phase II study in 33 R/M HNSCC, which demonstrated an overall response rate with pembrolizumab plus cetuximab of 45% (95% CI 28–62) [23].

Besides immunotherapy regimens, cetuximab-based combination therapy (platinum/5-FU or platinum/taxane) is a valid option (in particular for CPS-negative patients) [24, 25].

Triplet chemotherapy regimens should be avoided due to increased toxicity without additional efficacy.

**What is the optimal second-line regimen in the R/M setting?**

The preferred regimen in the second-line setting depends on previous therapies. CPI-naïve patients or platinum-resistant patients should receive nivolumab or pembrolizumab based on the outcomes of Checkmate 141 and Keynote 040 trials [26, 27].

For patients with previous CPI exposure the optimal management is poorly defined and no clear recommendation can be derived from the international guidelines.

However, recent retrospective data indicate promising activity with taxanes in combination with cetuximab after CPI failure [28].

### Conclusion

HNSCC is a heterogenous disease affecting mainly elderly patients, who frequently suffer from significant comorbidities. Due to the aggressive tumour biology and high recurrence rates after curative treatment it is essential to follow the evidence-based treatment recommendations outlined in the international guidelines, although it has to be emphasized that relevant data gaps and controversies exist as outlined above. Interdisciplinary management is key for the optimal management of HNSCC patients at all disease stages.

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