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Review

Multidisciplinary management of head and neck cancer: First expert consensus using Delphi methodology from the Spanish Society for Head and Neck Cancer (part 2)

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ABSTRACT

Head and neck cancer is one of the most frequent malignances worldwide. Despite the site-specific multimodality therapy, up to half of the patients will develop recurrence. Treatment selection based on a multidisciplinary tumor board represents the cornerstone of head and neck cancer, as it is essential for achieving the best results, not only in terms of outcome, but also in terms of organ-function preservation and quality of life. Evidence-based international and national clinical practice guidelines for head and neck cancer not always provide answers in terms of decision-making that specialists have to deal with in their daily practice. This is the first Expert Consensus on the Multidisciplinary Approach for Head and Neck Squamous Cell Carcinoma (HNSCC) elaborated by the Spanish Society for Head and Neck Cancer and based on a Delphi methodology. It offers a number of specific recommendations based on the available evidence and the expertise of our specialists to facilitate decision-making of all health-care specialists involved.

Introduction and methods

Introduction and Methodology has been described in the first part of this article.

(QUOTE first article* Ref. [1])

This second article focuses on recurrent/metastatic disease, second primary tumors and squamous cell carcinoma metastatic to cervical nodes with an unknown primary site including categories (C) 3, 4, 5 and 6.

Results and discussion

C3. Evaluation of response after CRT (see Table 1)

Evaluation of response in head and neck after an organ-preservation approach is crucial. Its complexity is based on three main questions. The first question is when exactly we should

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Table 1
Summary of Recommendations on the evaluation of response after non-surgical treatment.

Recommendation	Phase	Accepted consensus (% of agreement)
Evaluation of response should be performed after the resolution of the inflammatory effect caused by concurrent chemo or bioradiotherapy to avoid doubtful residual disease that could hinder decision-making and lead to unnecessary salvage surgery	1	YES (100)
Evaluation of response should be assessed at least 12 weeks (1 week variation is accepted) after completion of radiotherapy	1	YES (88)
Authors do not recommend the evaluation of response at 8 weeks		
Evaluation of response should first be based on clinical assessment, followed by an imaging test (CT or MRI) according to each center protocol, but always considering the initial imaging test (basal)	1	YES (88)
In case of suspected residual disease by CT/MRI, a PET/CT should be performed	2	YES
– Primary Tumor		(76)
– Residual neck disease		(71)
After conservative treatment, salvage surgery of the primary tumor is recommended if it was considered resectable at the initial staging. In the absence of residual neck disease, neck dissection is not recommended	1	YES (72)
Planned neck dissection is not recommended in patients with N-positive disease (including N3) when complete response is achieved after conservative treatment	2	YES (96)
If a complete response of the primary tumor is achieved, but there is evidence of residual neck disease, an elective neck dissection based on the initial N stage is recommended. Radical neck dissection should be avoided	1	YES (90)

assess the response. Classically, the choice of a time frame depended on the optimal timing for neck dissection (ND) in case of residual neck disease (RND), which is considered between 4 and 12 weeks after CRT to allow for resolution of acute effects while preceding late fibrosis [2,3]. For many years, 8 weeks has been taken as the optimal time to perform it, however, since de introduction of PET/CT for the evaluation of response, most authors and international guidelines recommend 12 weeks, to minimize the rate of false positives caused by radiation-induced delayed inflammatory changes [4]. In this regard, the experts agree that response assessment should be performed after the resolution of the inflammatory effect caused by radiation to avoid doubtful residual disease that could lead to unnecessary salvage surgery. The optimal recommended time is 12 weeks (1 week variation is accepted) after completion of CRT. The second question is how to assess the response after CRT. Although clinical assessment might be unreliable, it is essential to evaluate symptoms and signs that might indicate progression. Many studies have documented the accuracy and high sensitivity of CT and MRI [2,3], however, their specificity is low, especially to evaluate neck response, as not all patients who undergo salvage surgery when RND is suspected by CT evidence disease on pathologic examination [5]. In the last decade, retrospective studies evaluating the role of PET/CT have reported high negative predictive values of 94.5–96.0% in patients who have received CRT and bioradiotherapy, leading to a lower number of NDs [6–8]. A recently published phase III trial evaluating the role of PET/CT confirmed these results [9]. In the light of this evidence, NCCN guidelines recommend PET/CT at 12 weeks as the new standard of care for the evaluation of response after an organ-preserving approach [4]. However, CT and MRI are still considered valid imaging techniques and are still the standard of care in many institutions. In this regard, the authors of this consensus agree that evaluation of response should first be based on clinical assessment, followed by an imaging test (CT or MRI), according to each center protocol, but always considering the initial imaging test (basal). The authors did not reach consensus on whether PET/CT should be the initial imaging test, however, they recommend its use upfront of a FNA or ND when RND is suspected by CT.

The third question is what to do once having assessed the response. Planned ND after an organ-preservation approach is still debated. When nodal CR is achieved, no differences in recurrence rates have been reported between planned ND and observation [10–13]. ND entails considerable comorbidity, with a complication rate of up to 35% [14,15]. Balancing the benefit with the increased morbidity of post-CRT surgery, current evidence suggests that ND should be limited to patients with RND after an organ-preservation protocol [9]. International guidelines recommend observation of patients who achieve CR after CRT. In case of confirmed RND, selective neck dissection (SND) has become widely accepted and is currently the procedure most frequently used by head and neck surgeons. The authors reached consensus in this regard, whereas after conservative treatment, salvage surgery of the primary tumor is recommended if it was considered resectable at initial staging and they do not recommend planned ND in patients with N-positive disease (including N3) when CR is achieved. In case of partial response of the primary tumor but no evidence of RND, ND is not recommended either. Conversely, in case of CR of the primary tumor but RND, an elective ND based on the initial N stage is recommended. Radical ND should be avoided, as it entails comorbidity without improvement of survival.

C4. Recurrent/metastatic disease (see Table 2)

Most patients with HNSCC are diagnosed with locally advanced disease whereas initial metastatic disease is rare [16]. Despite multimodality therapy, 60% will develop locoregional or distant recurrence [17]. Most patients with recurrence and ineligible for salvage therapy with radical intent, palliative systemic therapies remain the only treatment option. However, some patients, especially those with locoregional recurrence, might benefit from a radical approach, as some series have reported prolonged survival in patients amenable for salvage surgery or reirradiation [18–20]. In oligometastatic disease, prolonged survival has also been reported for patients with resected metachronous pulmonary metastases [21]. Sacco et al. suggested that an aggressive approach removing all known sites of disease might be beneficial for selected patients. When surgery is not feasible, stereotactic radiotherapy (SBRT) might be an alternative, although due to the lack of prospective trials, this approach cannot be routinely recommended and should be weighed against treatment-related toxicity [22]. Incomplete resections with positive margins are at high risk of recurrence, and reirradiation could entail high toxicity that must be balanced within the potential clinical benefit [19]. Some authors have suggested clinical factors that might predict the benefit of local therapies [23]. The panel of experts suggests that all patients diagnosed with HNSCC presenting local, regional or distant recurrence should be evaluated by a multidisciplinary tumor board to decide the best therapeutic approach, either radical or palliative. In the decision-making process for patients with locoregional recurrence, patients' general condition and comorbidities, localization and disease burden, resectability (odds of achieving a R0/1 resection), time to

Table 2
Summary of recommendations for recurrent/metastatic disease.

Recommendation	Phase	Accepted consensus (% of agreement)
All patients diagnosed with HNSCC presenting local, regional or distant recurrence should be evaluated by a multidisciplinary tumor board to decide the best therapeutic approach, either radical or palliative	1	YES (100)
To select the best therapeutic approach for patients with locoregional recurrence, the following factors should be considered:	1	YES
• Performance status (ECOG)		(100)
• Comorbidities		(92)
• Localization		(96)
• Disease burden		(84)
• Resectability (odds of achieving a R0/1 resection)		(96)
• Time to progression/recurrence		(92)
• Previous radiation field involving the actual recurrence		(88)
To select the best therapeutic approach for patients with oligometastatic disease (including oligorecurrence), the following factors should be considered:	2	YES
• Performance status (ECOG)		(92)
• Comorbidities		(84)
• Age		(81)
• Status of locoregional disease in terms of response/remission,		(100)
• Size and number of metastatic lesions		(88)
• Localization (lung/other sites)		(92)
• Previous treatments		(88)
• Time to progression/recurrence.		(88)
In patients diagnosed with oligometastatic disease amenable to radical treatment, all metastases should be treated either with surgery or SBRT	1	YES (96)
In patients with recurrent/metastatic (R/M) disease who are candidates for palliative systemic therapy, the following factors must be considered:	1	YES
• Performance status (ECOG)		(96)
• Comorbidities		(96)
• Age		(71)
• Weight loss		(76)
• Previous systemic therapies for R/M or locoregional disease		(84)(76)
Systemic therapies for patients with R/M disease:	1	YES
• In patients with ECOG 0–1 and no significant comorbidities, first-line chemotherapy should be based on the EXTREME regimen: platinum plus FU in combination with cetuximab, followed by cetuximab until disease progression or unacceptable toxicity		(84)
• In patients who are platinum-refractory (recurrence or progression within the first 6-months after receiving cisplatin for locally-advanced disease) weekly paclitaxel plus cetuximab followed by cetuximab until disease progression or unacceptable toxicity is the regimen of choice		(68)
• In patients with ECOG 0–1 and no significant comorbidities that have progressed to a first-line platinum based chemotherapy, weekly paclitaxel plus cetuximab followed by cetuximab until disease progression or unacceptable toxicity is the regimen of choice		(68)
• In patients with ECOG 2 or with significant comorbidities, best supportive care (which could include palliative radiation) is recommended. Systemic chemotherapy is not recommended		(72)
* It should be noted that at the time this consensus was performed, data from Nivolumab had not yet been published and was therefore not included as a treatment option to discuss in the study		
All patients progressing to first-line cisplatin-based chemotherapy (regardless DFS and response to treatment) that preserve good performance status, should be offered to participate in a clinical trial	1	(88)

recurrence, previous radiation involving the actual recurrence are the main factors to be considered. Additionally, for oligometastatic disease, status of locoregional disease in terms of response, size/number of the metastatic lesions, localization (lung/other sites) and previous treatments should also be considered.

Systemic therapy should be offered to patients who are not amenable for a radical approach. Although survival outcomes are poor, with a median progression-free survival (PFS) between 4 and 7 months and overall survival (OS) between 7 and 10 months [24,25], selected patients might achieve long-term disease free survival (DFS) with palliative chemotherapy (CT). In this regard, several clinical factors regarding patient status and disease burden can be strong pretreatment predictors of outcome [26]. Elderly patients can obtain the same benefit from systemic treatments compared to younger patients, however at the expense of higher toxicity rates [27,28]. Weight loss, malnutrition and comorbidities are well-known negative prognostic factors in HNSCC [29,30]. Consequently, the experts suggest that for patients with recurrent/metastatic (R/M) disease, candidates for palliative systemic therapy, performance status (ECOG), comorbidities, age, weight loss and previous CT for R/M or locoregional disease should be considered.

Platinum is the most active agent in terms of response rates (RR) and survival outcome. Palliative CT consists of a platinum doublet, using 5-FU or taxanes. The addition of both agents improves RR but not survival compared to monotherapy [31–33]. Cetuximab, a monoclonal antibody (MAb) directed against the epidermal growth factor receptor, is the only targeted therapy to date that has improved OS in combination with platinum/5FU in first-line R/M HNSCC [25]. This regimen (EXTREME) is now the standard of care for fit patients. It should be noted that in the subgroup analysis of the EXTREME trial, the survival advantage fell short of statistical significance in the elderly cohort (>65 years) compared to younger adults and the entire intention-to-treat population [28]. In 2011, a non-randomized phase II trial evaluating paclitaxel in combination with cetuximab in first-line treatment for R/M patients unfit for cisplatin therapy showed a RR of 54% and an improved OS, with a safe toxicity profile [34] whereas it might be an alternative for patients unfit for a triplet. To date, agents used in second-line therapy for R/M HNSCC, including methotrexate, taxanes or cetuximab, have a low RR and none have shown survival benefit. Nivolumab, an anti–programmed death 1 (PD-1) monoclonal antibody, is the first drug that has recently shown improved OS compared with single-agent chemotherapy or cetuximab in a phase III randomized trial for platinum-refractory R/M SCCHN [35].

The experts recommend the EXTREME regimen as first-line CT for fit patients, without significant comorbidities and ECOG 0–1.

Patients who are platinum-refractory (recurrence or progression within the first 6-months after receiving cisplatin for locally-advanced disease) or have progressed to a first-line platinum-based CT, weekly paclitaxel plus cetuximab until disease progression or unacceptable toxicity is recommended. Patients with significant comorbidities or ECOG2 should be offered best supportive care (which might include palliative radiation). In the light of recent results, nivolumab should be the treatment of choice in patients progressing to a platinum-based CT, when clinically available. Cetuximab as single agent is an acceptable alternative for patients who are neither amenable to receive paclitaxel nor nivolumab. All patients progressing to first-line CT with ECOG 0–1 should be offered to participate in a clinical trial.

It should be noted that at the time this consensus was performed, data on nivolumab had not yet been published and was therefore not included as a treatment option in the first 2 phases of the study.

C5. Management of second primary tumors (see Table 3)

Patients with HNSCC are at high risk of developing second primary tumors (SPT). SPT are defined as metachronous invasive solid cancer developing ≥6 months after an index HNSCC, under the criteria of Warren and Gates and modified by the National Cancer Institute (NCI) [36,37]. Their incidence is high, from 5% to 12% at 5 years, representing the leading long-term cause of death in patients with HNSCC, tripling the number of deaths caused by distant metastases [38,39]. In addition, patients with a SPT have an increased risk for developing subsequent primary tumors: this risk remains constant through follow-up, and survival decreases progressively with the development of every new head and neck tumor [38,40,41]. Most common sites of SPT are the head and neck region, lung and esophagus. The risk and distribution of SPT differ significantly according to the subsite of the index cancer [42]: hypopharynx and oropharynx carried the highest excess risk of SPT, but during the HPV era, risk associated with oropharynx cancer declined; the head and neck region is the most common site when the index tumor is in the oral cavity or oropharynx, while hypopharynx and larynx tumors are frequently associated to SPT in the lung [42]. Therefore, the panel recommends the definition of SPT according to Warren and Gates Criteria and agrees that patients should be followed up for a minimum of 10 years, which could be extended in patients with a history of alcohol and smoking abuse.

SPT located in the head and neck can be detected during follow-up by fiberoptic endoscopy, CT or MRI imaging, which are the routinely recommended tests. However, there is no consensus in the literature regarding which imaging technique is the most appropriate for the detection of second primary malignances in the lung. The NCCN guidelines for HNSCC based on Lung Cancer NCCN guidelines recommend the use of low-dose computed tomography (LDCT) of the chest to screen selected patients at high risk of lung cancer, since chest X-rays are not recommended for lung cancer screening [43–45]. The authors agree that chest X-rays are insufficient for the detection of SPT in the lung. However, as LDCT has not been approved by the Spanish National Public Health System, no consensus was reached on its recommendation. As reported by Hearle and col. [46], when a SPT has been diagnosed, PET/CT might to be useful to detect other synchronous tumors and to rule out metastasis. Therefore, the experts recommend a PET/CT as part of the initial staging.

No level 1 evidence exists regarding the best treatment approach for patients with a previously treated HNSCC diagnosed with a SPT. Treatment options usually include surgery, CT and reirradiation with the aim of improving local control, quality of life and survival. It is important to select patients that could benefit from a treatment, either radical or palliative. Age, general condition and comorbidities, as well as late toxicity from previous treatments are to be considered, as these patients might be at risk of developing complications. SPT localization and previous treatment are crucial to decide whether they are eligible for radical or palliative therapy. The authors recommend considering these factors to select the best therapeutic approach in this scenario.

As mentioned, whenever possible, surgery and reirradiation are both treatments to be considered upfront. When feasible, surgery in early stage SPT is also recommended, with studies indicating a 5-year survival rate of 35% in radically resected SPTs (11% for lung metastases) [47,48]. It should also be noted that some patients could benefit from limited resections, as some authors have suggested that early-stage SPT in head and neck without nodal involvement could avoid ND [49]. Reirradiation might achieve favorable outcomes, but must be well balanced against toxicity [50,51], however, as mentioned, the treatment approach could change depending on the location. In non-radiated patients, RT or

Table 3
Summary of recommendations on second primary tumors (SPT).

Recommendation	Phase	Accepted consensus (% of agreement)
The definition of SPT must be based on Warren and Gates Criteria:	2	YES (76)
Due to the high incidence of SPT, patients should be followed-up for a minimum of 10 years	1	YES (71)
Chest X-rays are considered insufficient to detect and diagnose a SPT in the lung during follow-up	2	YES (84)
PET/CT is recommended as part of the initial study for all patients with a treated index HNSCC and diagnosed with a SPT located in the head and neck, lung or esophagus.	1	YES (84)
To select the best therapeutic approach for patients diagnosed with a SPT, the following factors should be considered: • Patient's general condition and comorbidities. • Previous treatments received • Localization of the second primary	1	YES (100)
Treatment recommendations for SPT:	2	YES
• CRT is the recommended treatment for patients with high burden SPT (60 mm3 or greater) that have not been previously irradiated		(76)
• Neck dissection and/or neck radiation of areas previously treated within the index tumor should be avoided in patients diagnosed with N0 SPT		(84)
• Reirradiation must always be considered in all patients presenting SPT of head and neck		(72)
• CRT is recommended over bioradiotherapy in patients diagnosed with non-surgical SPT		(71)
• CRT is recommended over surgery for SPT located in the oropharynx		(72)
• Total glossectomy plus total laryngectomy is not recommended in patients with locally advanced recurrent oropharyngeal cancer		(72)

CRT is preferred for SPT in the oropharynx, as resection might entail loss of organ function and high comorbidity. The same should apply in patients with high burden disease that imply mutilating surgeries. Surgery might represent the only option in previously radiated patients, but it should be balanced with the risk of surgical complications. The experts suggest several specific recommendations for the treatment of SPT that are shown in Table 3.

C6. Squamous cell carcinoma of unknown primary of the head and neck (SCCUP) (see Table 4)

SCCUP is defined as metastatic disease in the cervical lymph nodes without any evidence of a primary tumor in the upper aerodigestive tract after appropriate investigation [4,52]. It represents approximately 1–4% of all cancers of the head and neck [53] and must be a diagnosis of exclusion, as increasingly imaging and biopsy techniques have limited the number of patients in whom SCCUP is diagnosed. Tissue confirmation is mandatory. Cytology obtained by a FNA is preferred over an open biopsy, as the latter could cause disruption of fascial planes that act as a natural barrier to tumoral spread [54]. Cross-sectional imaging of the neck such as contrast-enhanced CT and/or MRI and the availability of fiberoptic endoscopy has changed the detection of small primary cancers, and have shown to increase the rates of detection of tumors not found by physical examination, but with suggestive anatomic images [55]. The panel agree to define SCCUP as the presence of SCC metastasis in any cervical lymph node confirmed by FNA or core needle biopsy, with or without concomitant supraclavicular metastatic nodes, without any evidence of a primary tumor of the upper aerodigestive tract, after an appropriate investigation that must include a thorough physical examination, a proper imaging test (CT or MRI) and a fiberoptic endoscopy performed by a qualified specialist. Excisional biopsy of the metastatic lymph nodes before having carried out a complete diagnosis is not recommended.

In patients diagnosed with SCCUP, PET or PET/CT has proven useful to detect up to 30% of primary mucosal tumors that had not previously been detected by CT/MRI [56] and to rule out distant metastases. However, due to a 10% to 20% rate of false positives, findings should be confirmed by biopsy, by direct panendoscopy under general anesthesia. In the event preprocedural findings do not suggest potential biopsy targets, direct panendoscopy should explore the following locations: nasopharynx, oropharynx, larynx, hypopharynx and upper esophagus; Directed biopsy of the suspected mucosal areas is recommended in all head and neck guidelines. As nasopharyngeal and oropharyngeal carcinoma might be caused by EBV and HPV infection respectively, their determination from FNA samples is recommended in all patients diagnosed with SCCUP. Recent studies suggest that an increasing proportion of SCCUP are associated with HPV at a rate similar to that of primary oropharyngeal cancer [57,58]. Directed biopsies might also be driven by node levels involved. Ipsilateral tonsillectomy rather than deep tonsil biopsy is frequently performed in the initial evaluation of a patient with SCCUP, as tonsils and base of the tongue are the most common sites for small primary tumors initially thought to represent SCCUP [55,59]. Moreover, p16 or

Table 4
Summary of recommendations for squamous cell carcinoma of unknown primary of the head and neck (SCCUP).

Recommendation	Phase	Accepted consensus (% of agreement)
Squamous cell carcinoma (SCC) of unknown primary of the head and neck (SCCUP) is defined as the presence of SCC metastases in any cervical lymph node confirmed by cytology or core needle biopsy, with or without concomitant supraclavicular metastatic nodes, without any evidence of a primary tumor of the upper aerodigestive tract, after an appropriate investigation that must include a thorough physical examination (particularly of the oral cavity and skin), a proper imaging test (CT or MRI) and a fiberoptic endoscopy performed by a qualified specialist	1	YES (84)
The authors do not recommend performing an excisional biopsy of metastatic lymph nodes before having carried out a complete diagnosis	1	YES (88)
Complete diagnosis of SCCUP should include:	1	YES
• PET/CT		(100)
• Direct laryngoscopy under general anesthesia (exploring nasopharynx, oropharynx, larynx, hypopharynx and upper esophagus)		(84)
• HPV determination detected from a FNA specimen using IHC or PCR		(84)
• EBV determination detected from a FNA specimen using IHC or PCR		(72)
Regarding direct laryngoscopy:	1	YES
• Directed biopsy of the suspected mucosal areas is recommended		(90)
• Routinely lingual tonsillectomy is not recommended		(72)
• There was no consensus on whether randomized base of tongue biopsies, unilateral or bilateral palatine tonsillectomy should be recommended		NO CONSENSUS
• In case of p16 or DNA-HPV positive lymph nodes, the approach should be discussed in a multidisciplinary tumor board		YES
The primary goals of SCCUP treatment are to achieve control of the neck disease burden and prevent mucosal emergence	1	YES (96)
Regarding the treatment of N1-N2b disease;	1	YES
• Surgery (Ipsilateral neck dissection) is recommended		(88)
• Adjuvant RT is indicated when:		(96)
• pN2b		
• Perineural invasion and/or perivascular invasion		
• Adjuvant CRT is indicated when:		(92)
• Extranodal spread		
• Soft tissue infiltration		
• Recommended regimen for Concurrent CT is cisplatin at a dose of 100 mg/m2 on days 1, 22, 43 during RT		
• Adjuvant RT should involve suspected mucosal subsets based on initial diagnosis		(93)
Treatment of N2c-N3 disease;	2	YES
• Concurrent CRT is recommended as treatment of choice. Salvage ND should be offered in patients with residual neck disease at the evaluation of response		(80)
• ICT followed by concurrent CRT is recommended as an alternative option to CRT. Salvage ND should be offered in patients with residual neck disease at the evaluation of response		(76)
• ICT followed by surgery and adjuvant RT is not recommended		NO
• Recommended CT regimen for ICT is cisplatin-5-fluoracil-Docetaxel		(80)
• Evaluation of response should be assessed 8–12 weeks after CRT		(84)

DNA-HPV positive lymph nodes suggests the oropharynx as the most common site for a primary tumor, although other primary tumors with involved lymph nodes above the clavicles may also stain for the p16 protein [60]. Conversely, contralateral tonsillectomy is widely discussed: some authors justify this procedure as there are studies reporting the contralateral spread of occult tonsil cancer and the presentation of synchronous bilateral tonsil cancer [61,62], however rates are low and evidence of contralateral progression rare after surgery for known primary T1 tonsil cancer [63]. Diagnostic tonsillectomy is not considered a standard procedure in some institutions: most data comes from the US, where HPV-related tumors are more frequent, but in areas like Europe, most tumors are caused by smoking and alcohol abuse. Consequently, and because PET/CT might rule out tumors in that area, some authors considered tonsillectomy unnecessary in the absence of suspected mucosal findings. The panel of experts agree that complete diagnosis of SCCUP should include a PET/CT, a direct pan-endoscopy under general anesthesia (exploring nasopharynx, oropharynx, larynx, hypopharynx and upper esophagus) and HPV and EBV determination (detected from a FNA specimen using IHC or PCR) [58]. During direct pan-endoscopy, a direct biopsy of the suspected mucosal areas is recommended. Routinely lingual tonsillectomy is not recommended, and there was no consensus on whether randomized base of tongue biopsies, unilateral or bilateral palatine tonsillectomy should be recommended. However, in case of p16 or DNA-HPV positive lymph nodes, this approach should be discussed in a multidisciplinary tumor board.

Treatment of SCCUP often requires multimodality therapy. Due to its low prevalence, prospective randomized trials are lacking and treatment recommendations are based on large retrospective series and extrapolated data from studies including HNSCC with a known primary. The experts agree that the primary goals of the treatment are achieving control of the neck disease burden and preventing mucosal emergence. Treatment will depend on nodal stage. N1 is rare and usually has good prognosis, so generally single-modality therapy is acceptable, as patients do well either with RT or with surgery alone, and ipsilateral neck recurrence and mucosal progression rates range between 10% and 20% [60,64]. N2a and N2b are common presentations of SCCUP, which are usually managed with surgery followed by RT or CRT. N2a treatment can vary depending on patients' risk factors and the presence of adverse pathological factors. p16 positive patients with no smoking history could be treated with either surgery or RT alone, assuming that the oropharynx would be the most common primary site and that they might have better prognosis compared to p16-negative patients. [65,66]. N2a and N2b disease with extranodal spread usually receive adjuvant CRT as extrapolated from prospective studies, although it must be considered that these did not include patients with SCCUP and only a few presented oropharyngeal cancer [67,68]. The same rule applies when adjuvant RT is given in presence of minor adverse features (perivascular and perineural invasion) [68]. Some authors recommend concurrent CRT in patients with clinical or radiological extranodal spread to save ND, assuming they would further receive adjuvant CRT [52]. N2c-N3 disease has higher rates of regional and distant recurrence when treated with surgery alone [53,63]. Surgery followed by postoperative RT/CRT has similar results to radical CRT, although its use has been extrapolated from trials in locally-advanced HNSCC [69–74]. CRT is generally preferred to leave surgery as a salvage therapy. Regarding RT treatment, IMRT is the modality of choice as it allows tissue-sparing and preserves salivary glands. Radiation of mucosal subsets and the contralateral neck is the standard of care at most institutions as it reduces mucosal emergence and contralateral failure, although its use has reported increased toxicity [71,75–78]. Most common mucosal targets include oropharynx and nasopharynx, as up to 80% of SCCUP usually present level 2 and 3 neck disease [52]. The absence of level 2 nodes indicates a higher probability of a supraglottic or hypopharyngeal primary tumor. Recommendations from the panel of experts regarding treatment of SCCUP are exhibited in Table 4.

Conclusions

HNSCC treatment is complex and its management challenging. It requires the work and expertise of all specialists involved. This consensus using the Delphi methodology has been developed as an educational tool to be used by all head and neck professionals in their daily practice to achieve the best outcome and care for head and neck cancer patients.

Disclosures

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References

[1] Maños M, Girald J, Rueda A, Mesía R. Comprehensive treatment of the head and neck squamous cell carcinoma: first expert consensus from the Spanish society for head and neck cancer (part 1).
[2] Clavel S, Charron MP, Despres P. The role of computed tomography in the management of the neck after chemoradiotherapy in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2012;82:567–73.
[3] Liauw SL, Mancuso AA, Amdur RJ. Postradiotherapy neck dissection for lymph node-positive head and neck cancer: the use of computed tomography to manage the neck. J Clin Oncol 2006;24:1421–7.
[4] National Comprehensive Cancer Network: Head and Neck Cancer. V2.2016. <http://oralcancerfoundation.org/treatment/pdf/head-and-neck.pdf>.
[5] Montal R, Oliva, Mesia R. Residual neck disease management in squamous-cell carcinoma of the head and neck treated with radiotherapy plus cetuximab. Clin Transl Oncol 2016;18(11):1140–6.
[6] Yao MMDP, Luo PMDP, Hoffman HT. Pathology and FDG PET correlation of residual lymph nodes in head and neck cancer after radiation treatment. Am J Clini Oncol 2007;30:264–70.
[7] Brkovich VS, Miller FR, Karnad AB. The role of positron emission tomography scans in the management of the N-positive neck in head and neck squamous cell carcinoma after chemoradiotherapy. Laryngoscope 2006;116:855–8.
[8] Ong SC, Schoder H, Lee NY. Clinical utility of 18F-FDG PET/CT in assessing the neck after concurrent chemoradiotherapy for locoregional advanced head and neck cancer. J Nucl Med 2008;49:532–40.
[9] Mehanna H, Wong WL, Dunn J. PET-NECK trial management group. PET-CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med 2016;374(15):1444–54.
[10] Lango MN, Myers JN, Garden AS. Controversies in surgical management of the node-positive neck after chemoradiation. Semin Radiat Oncol 2009;19:24–8.
[11] Lau H, Phan T, Mackinnon J, Matthews TW. Absence of planned neck dissection for the N2–N3 neck after chemoradiation for locally advanced squamous cell carcinoma of the head and neck. Arch Otolaryngol Heard Neck Surg 2008;134:257–61.

[12] Corry J, Peters L, Fisher R. N2–N3 neck nodal control without planned neck dissection for clinical/radiologic complete responders: Results of Trans Tasman Radiation Oncology Group Study 98.02. Head Neck 2008;30:737–42.
[13] Wee JT, Anderson BO, Corry J. Management of the neck after chemoradiotherapy for head and neck cancers in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009;10:1086–92.
[14] Lavertu P, Bonafede JP, Adelstein DJ. Comparison of surgical complications after organ-preservation therapy in patients with stage III or IV squamous cell head and neck cancer. Arch Otolaryngol Head Neck Surg 1998;124:401–6.
[15] Christopoulos A, Nguyen-Tan PF, Tabet JC. Neck dissection following concurrent chemoradiation for advanced head and neck carcinoma: pathologic findings and complications. J Otolaryngol Head Neck Surg 2008;37:452–6.
[16] Argiris A, Kramouzis MV, Ferris RL. Head and neck cancer. Lancet 2008;371:1695–709.
[17] Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis and treatment. Mayo Clin Proc 2008;83:489–501.
[18] Goodwin WJ. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 2000;110(3 Pt 2 Suppl. 93):1–18.
[19] Janot F, de Raucort D, Bourhis J. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol 2008;26:5518–23.
[20] De Crevoisier R, Bourhis J, Eschwege F. Full-dose reirradiation for unresectable head and neck carcinoma: experience at the Gustave-Roussy Institute in a series of 169 patients. J Clin Oncol 1998;16:3556–62.
[21] Sacco AG, Cohen EE. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. J Clin Oncol 2015 Oct 10;33 (29):3305–13.
[22] Young ER, Diakos E, Khalid-Raja M. Resection of subsequent pulmonary metastases from treated head and neck squamous cell carcinoma: systematic review and meta-analysis. Clin Otolaryngol 2005;40:208–18.
[23] Buglione M, Maddalo M, Bruni A. Reirradiation in head and neck recurrent or second primary tumor: efficacy, safety, and prognostic factors. Tumori 2015;101:585–92.
[24] Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2006;24:2644–52.
[25] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.
[26] Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. Cancer 2004;101:2222–9.
[27] Argiris A, Li Y, Murphy BA. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. J Clin Oncol 2004;22:262–8.
[28] Szturz P, Vermorken JB. Treatment of elderly patients with squamous cell carcinoma of the head and neck. Front Oncol 2016:1–14.
[29] Paleri V, Wight RG, Bradley PJ. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. Oral Oncol 2010;46:712–9.
[30] Locher JL, Bonner JA, Carroll WR. Prophylactic percutaneous endoscopic gastrostomy tube placement in treatment of head and neck cancer: a comprehensive review and call for evidence-based medicine. JPEN J Parenter Enteral Nutr 2011;35:365–74.
[31] Clavel M, Vermorken JB, Cognetti F. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994;5(6):521–6.
[32] Forastiere AA, Metch B, Schuller DE. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10(8):1245–51.
[33] Jacobs C, Lyman G, Velez-García E. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10 (2):257–63.
[34] Hitt R, Irigoyen A, Cortes-Funes H. Spanish Head and Neck Cancer Cooperative Group (TTCC). Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Ann Oncol 2012;23 (4):1016–22.
[35] Ferris RL, Blumenschein G, Gillison ML. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375(19):1856–67.
[36] Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. Am J Cancer 1932;16:1358–414.
[37] Curtis RE, Freedman DM, Ron E. New malignancies among cancer survivors: SEER cancer registries, 1973–2000. Bethesda, MD: National Cancer Institute; 2006. p. 9–14.
[38] León X, Quer M, Burgués J. Second neoplasm in patients with head and neck cancer. Head Neck 1999;21(3):204–10.
[39] Garavello W, Ciardo A, Gaini RM. Risk factors for distant metastases in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2006;132(7):762–6.
[40] León X, Martínez V, Quer M. Second, third, and fourth head and neck tumors. A progressive decrease in survival. Head Neck 2012;34(12):1716–9.
[41] León X, Martínez V, Quer M. Risk of third and fourth tumors in patients with head and neck cancer. Head Neck 2010;32(11):1467–72.
[42] Morris LG, Sikora AG, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol 2011;20; 29(6):739–46.
[43] National Lung Screening Trial Research T, Aberle DR, Adams AM. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.
[44] National Comprehensive Cancer Network: Lung Cancer. V1.2017 <http://oralcancerfoundation.org/treatment/pdf/head-and-neck.pdf>.
[45] Midthun DE. Screening for lung cancer. Clin Chest Med 2011;32:659–68.
[46] Haerle SK, Strobel K, Stoeckli SJ. F-FDG-PET/CT versus panendoscopy for the detection of synchronous second primary tumors in patients with head and neck squamous cell carcinoma. Head Neck 2010;32(3):319–25.
[47] Schwartz LH, Ozsahin M, Zhang GN. Synchronous and metachronous head and neck carcinomas. Cancer 1994;74(7):1933–8.
[48] Wong LY, Wei WI, Yuen AP. Salvage of recurrent head and neck squamous cell carcinoma after primary curative surgery. Head Neck 2003;25(11):953–9.
[49] León X, Pedemonte G, Quer M. Elective treatment of the neck for second primary tumors of the head and neck. Eur Arch Otorhinolaryngol 2014;271 (5):1187–90.
[50] Goldstein DP, Karnell LH, Funk GF. Outcomes following reirradiation of patients with head and neck cancer. Head Neck 2008;30:765–70.
[51] Stevens KR, Britsch A, Moss WT. High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys 1994;29:687–98.
[52] Galloway TJ, Ridge JA. Management of squamous cancer metastatic to cervical nodes with an unknown primary site. J Clin Oncol 2015;33(29):3328–37.
[53] Grau C, Johansen LV, Jakobsen J. Cervical lymph node metastases from unknown primary tumours: results from a national survey by the Danish Society for Head and Neck Oncology. Radiother Oncol 2000;55:121–9.
[54] Jones AS, Cook JA, Phillips DE, et al. Squamous carcinoma presenting as an enlarged cervical lymph node. Cancer 1993;72:1756–61.
[55] Cianchetti M, Mancuso AA, Amdur RJ. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 2009;119:2348–54.
[56] Johansen J, Buus S, Loft A. Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumor: results from the DAHANCA-13 study. Head Neck 2008;30:471–8.
[57] Motz K, Qualliotine JR, Fakhry C. Changes in unknown primary squamous cell carcinoma of the head and neck at initial presentation in the era of human papillomavirus. JAMA Otolaryngol–Head Neck Surg 2016;142(3):223–8.
[58] Keller LM, Galloway TJ, Holdbrook T. P16 status, pathologic and clinical characteristics, biomolecular signature, and long term outcomes in unknown primary carcinomas of the head and neck. Head Neck 2014;36:1677–84.
[59] Lee WY, Hsiao JR, Jin YT. Epstein-Barr virus detection in neck metastases by in-situ hybridization in fine-needle aspiration cytologic studies: an aid for differentiating the primary site. Head Neck 2000;22:336–40.
[60] Koch WM, Bhatti N, Williams MF, et al. Oncologic rationale for bilateral tonsillectomy in head and neck squamous cell carcinoma of unknown primary source. Otolaryngol Head Neck Surg 2001;124:331–3.
[61] Cosmidis A, Rame JP, Dassonville O. T1–T2 NO oropharyngeal cancers treated with surgery alone: a GETTEC study. Eur Arch Otorhinolaryngol 2004;261:276–81.
[62] Waltonen JD, Ozer E, Schuller DE, et al. Tonsillectomy vs. deep tonsil biopsies in detecting occult tonsil tumors. Laryngoscope 2009;119:102–6.
[63] Waltonen JD, Ozer E, Hall NC. Metastatic carcinoma of the neck of unknown primary origin: evolution and efficacy of the modern workup. Arch Otolaryngol Head Neck Surg 2009;135:1024–9.
[64] Kim SH, Koo BS, Kang S. HPV integration begins in the tonsillar crypt and leads to the alteration of p16, EGFR and c-myc during tumor formation. Int J Cancer 2007;120:1418–25.
[65] Iganej S, Kagan R, Anderson P. Metastatic squamous cell carcinoma of the neck from an unknown primary: management options and patterns of relapse. Head Neck 2002;24:236–46.
[66] Coster JR, Foote RL, Olsen KD. Cervical nodal metastasis of squamous cell carcinoma of unknown origin: indications for withholding radiation therapy. Int J Radiat Oncol Biol Phys 1999;23:743–9.
[67] Fakhry C, Westra WH, Li S. Improved survival of patients with human papillomavirus positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261–9.
[68] Chung CH, Zhang Q, Kong CS. P16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol 2014;32(35):3930–8.
[69] Cooper JS, Pajak TF, Forastiere AA. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
[70] Bernier J, Cooper JS, Lefèbvre JL. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck 2005;27(10):843–50.
[71] Chen AM, Farwell DG, Lau DH. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? Int J Radiat Oncol Biol Phys 2001;81:346–52.

[72] Aroisio AD, Pignataro L, Garavello W. Neck Lymph node metastases from unknown primary. Cancer Treat Rev 2016;53:1–9.
[73] Lou J, Wang S, Guo L. Squamous cell carcinoma of cervical lymph nodes from an unknown primary site: The impact of neck dissection. J Cancer Res Ther 2015;11(Suppl. 2):C161–7.
[74] Strojan P1, Ferlito A, Barnes L. Contemporary management of lymph node metastases from an unknown primary to the neck: II. A review of therapeutic options. Head Neck 2013;35(2):286–93.
[75] Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. Int J Radiat Oncol Biol Phys 1997;37:797–802.
[76] Sher DJ, Balboni TA, Haddad RI. Efficacy and toxicity of chemoradiotherapy using intensity modulated radiotherapy for unknown primary of head and neck. Int J Radiat Oncol Biol Phys 2011;80:1405–11.
[77] Marcial-Vega VA, Cardenes H, Perez CA. Cervical metastases from unknown primaries: radiotherapeutic management and appearance of subsequent primaries. Int J Radiat Oncol Biol Phys 1990;19:919–28.
[78] Sinnathamby K, Peters LJ, Laidlaw C, et al. The occult head and neck primary: to treat or not to treat? Clin Oncol (R Coll Radiol) 1997;9:322–9.