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REVIEW ARTICLE

Neck management in head and neck squamous cell carcinomas: where do we stand?

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Abstract

Head and neck squamous-cell carcinomas (HNSCCs) have a significant lymph node tropism. This varies considerably depending on the primary tumor site and the Human Papillomavirus (HPV) status of the disease. The best therapeutic option, between up-front lymph node dissection and chemoradiotherapy (CRT) +/− followed by lymph node dissection in case of persistent lymphadenopathy or regional relapse, remains unclear. The purpose of this review is to discuss the pros and cons related to the different approaches of the neck management in HNSCC. A narrative review of the management of the cervical lymph nodes was undertaken. Searches of PubMed database were performed using the terms 'neck management' OR 'cervical lymphadenopathies' AND 'head and neck neoplasms'. Recent advances in imaging, pathological analysis, surgery and radiotherapy let to personalize the type of lymph node dissection and, the volumes of radiation therapy. Excluding inoperable patients and unresectable diseases, N3 lymphadenopathies, as well as bulky N2 stages, specifically HPV− or necrotic nodes, would be in favor of an up-front surgical approach, while HPV+ diseases, and lymphadenopathies of unknown primary would support CRT first. However, efficacy of such strategies is challenged by a significant morbidity in the medium and long terms. In the absence of higher level of evidence, the decision-making tools for the neck dissection before or after the CRT are based on the Mehanna's trial and retrospective studies with significant biases. Consequently, the approaches and the ensuing outcomes remain not homogenous depending on the centers' experience, in the context of limited data, especially for N2–3 HPV− HNSCC.

Keywords Head and neck neoplasms · Neck dissection · Radiotherapy · Disease management · Lymphadenopathy · Combined modality therapy

Introduction

Except for T1 glottic tumors, head and neck squamous cell carcinomas (HNSCCs) are prone to nodal metastases, with up to 75% of hypopharyngeal cancers and 90% of nasopharyngeal cancers presenting metastatic lymph nodes at diagnosis. The presence of metastatic neck nodes is associated with worse prognosis compared to equivalent T stage node-negative primaries [1]. Most large clinical trials have focused on the overall management and on the response of the primary tumor alone. However, radioresistance and relapse may occur in the nodes only as compared to the primary [2]. For this reason, neck dissection (ND) has long been performed as first treatment, regardless the primary features. Despite a paradigm shift with the integration of systemic treatment, leading to non-surgical organ preservation strategies [3] and better tumor response rates, there

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remains controversy regarding the best therapeutic attitude for node-positive HNSCC [4]. Several trials with a specific nodal endpoint have failed to complete accrual due to above mentioned reasons. Thus, selection of patients who benefit from treatment intensification in advanced nodal stages remains uncertain. However, a recent pivotal trial showed that functional imaging by computed tomography (PET–CT) can be used as therapy guidance in strategies based on chemoradiotherapy (CRT) in locoregionally advanced HNSCC [5]. Further, characteristics such as necrotic nodes, multiple cystic nodes and extra-nodal extension (ENE) are major prognostic factors extrapolated from some retrospective studies that have not been so far weighed in treatment decision making [6].

Neck-specific challenges with their level of evidence and unmet needs are reported here in the context of the overall HNSCC management.

Cervical lymph node staging

The 8th edition of the TNM/AJCC integrates substantial revisions to the 7th classification of HNSCC to further take into account the prognosis related to pathological and clinical features. One major change is the addition of p16 staining as a surrogate marker to identify Human Papillomavirus (HPV)+ oropharyngeal HNSCC. This entity has a better prognosis in the absence of classical risk factors such as tobacco and alcohol consumption [7]. Significant changes in the nodal clinical (cN) classification for p16+ oropharyngeal HNSCC relocate advanced stages in a better prognostic group. Namely, cN1, cN2a and cN2b stages of the 7th edition are classified as cN1 for p16+ oropharyngeal HNSCC in the 8th edition.

With the exception of p16+ oropharyngeal HNSCC, clinical and pathological ENE are factors associated with adverse prognosis [8–10]. Various studies have demonstrated that CT scan and/or magnetic resonance imaging (MRI) failed to reliably predict radiological ENE compared to histology [11, 12]. Consequently, clinical ENE in this 8th edition exclusively refers to unequivocal clinical or radiological reports. Lymphadenopathies with clinical ENE for oral cavity, hypopharynx, larynx and p16− oropharyngeal HNSCC are upstaged as cN3b, regardless of their size or laterality in this 8th edition.

Principles of neck dissection

ND can be radical, modified radical or selective. The choice of the procedure depends on initial cN stage, involved nodal level and involvement of adjacent structures based on radiological and perioperative findings. Radical ND, as described by Martin et al., updated by Robbins et al. [13, 14], consists of a resection of all the lymph nodes running from the lower border of the mandible to the supraclavicular virtual line; laterally, from the lateral border of the sterno-hyoid muscle, the hyoid bone, the anterior contralateral belly of the digastric muscle to the anterior border of the trapezius muscle. In other words, a radical ND removes all lymph nodes from levels I to V, including level VI for laryngeal or hypopharyngeal HNSCC, sacrificing the accessory spinal nerve, the internal jugular vein and the sternocleidomastoid muscle. Radical ND is no longer systematically performed because of its morbidity. In addition, neck nodes are infrequently all at risk of being involved. It may be indicated in case of clinical or radiological ENE and, in case of close contact with one of the sacrificed structures according to local institutional protocols. However, as ENE is a standard indication of postoperative CRT, other centers will prefer an up-front CRT without ND in this setting [15].

A modified radical ND, also called a *comprehensive* ND, removes all the lymph node groups routinely removed in a radical ND but preserves one or more non-lymphatic structures like the sternocleidomastoid muscle, the internal jugular vein and/or the spinal accessory nerve. Median lymph node dissection is usually indicated for laryngeal HNSCC with involvement of the Delphian node [15, 16].

A *selective* ND has been developed according to regional pathway for spread depending on the primary site. Specifically, for oral cavity carcinomas, a *selective* ND removes lymph nodes of levels I–III above the omohyoid muscle. For oropharyngeal and laryngeal carcinomas, a *selective* ND includes levels II–IV ± VI. A *selective* ND is considered as a diagnostic procedure, commonly used for cN0–1 disease because skip metastases of the first nodal relay is rare (2%) and, risk of isolated nodal recurrence below remains relatively low (10%) [17]. Downstaging of nodal stage following chemoradiation might allow less invasive NDs. Such question may be best investigated in clinical trials.

Bilateral or ipsilateral ND is performed based on tumor thickness, extent, site and cN stage according to institutional protocols. Specifically, bilateral ND is generally favored for tumors approaching the midline, ≥ N2b status, depth of invasion > 3 mm for oral cavity tumors and, for following sites: anterior tongue, base of tongue, floor of the mouth, palate, supraglottic larynx, posterior pharyngeal wall of the hypopharynx, nasopharynx, deep pre-epiglottic space involvement. However, several strategies should be discussed if a bilateral treatment is indicated. For instance, in case of a locally advanced tumor with cN0 contralateral that need bilateral neck treatment, three main options could be considered: a bilateral ND combined with a bilateral irradiation; a bilateral ND combined with an ipsilateral irradiation or an ipsilateral ND combined with a bilateral irradiation. Because no clinical trials have investigated these

approaches, the role of a dedicated multidisciplinary tumor board is critical in each institution.

Nodal resectability is usually defined as the absence of continuum between the primary and the lymph nodes, the absence of retropharyngeal positive lymph nodes, the absence of extension to the base of the skull or prevertebral fascia or muscles, the absence of peri-carotid artery extent over 270°, involvement of the common or internal carotid artery and involvement of the external skin.

A final point is the quality of the surgical procedure. As in other cancers (colon, stomach), the number of resected lymph nodes appears as a relevant prognostic factor of overall survival. Divi et al. reported the outcomes of more than 45,000 patients with at least 18 lymph nodes on the surgical piece of the ND, and almost 19,000 patients with fewer than 18 lymph nodes. A number of removed lymph nodes less than 18 was a risk factor for death (hazard ratio = 1.18; 95% CI 1.13–1.22) compared to a number of nodes greater than 18 [18]. A threshold of 18 for the number of resected lymph nodes seems to be a relevant metric correlated with the quality of ND, which has a direct impact on the overall survival whatever the N stage.

Principles of chemoradiotherapy

In the 1980s, chemotherapy and, later, targeted therapies were combined with radiation therapy and, integrated into a multi-modality surgical or non-surgical approach. The standard regimen of concurrent chemotherapy consists in cisplatin 100 mg/m^2, administrated every 3 weeks for three courses [19]. In case of contraindication, another regimen option is the association over 4 days of 5-fluorouracil 600 mg/m^2/day (continuous infusion) and carboplatin 70 mg/m^2/day, every 3 weeks for three courses [20].

Recent technical advances and development of intensity modulated radiation therapy (IMRT) have led to more favorable toxicity outcomes. IMRT allows a better coverage of the target volumes while minimizing the dose to healthy tissues [21].

In the absence of ND, the nodal gross target volume (GTV) is defined as the involved lymph node(s) on pretherapeutic staging. Morphological and functional characteristics of metastatic or suspicious lymphadenopathies are addressed in the "Primary site" and "Nodal stage" sections. In case of conflicting arguments between the CT and the FDG-PET, it is important to remember that FDG-PET may be a potential source of false positives (non-specific inflammatory lymph node), and its high negative predictive value (around 95%) may be mistaken by necrotic lymphadenopathies. The delineation of the high-risk clinical target volume (CTV) includes the GTV encompassed by an isotropic expansion margin of 5 to 10 mm to take into account microscopic disease spread. The CTV is adjusted to the anatomical barriers and skin except for muscle contact or infiltration (absence of fat tissue between the lymph node and the muscle), bone involvement, skin involvement which are included into a GTV isotropic expansion margin ranging from 10 to 20 mm [22]. A total dose of 70 Gy equivalent is delivered to the high-risk target volumes. An intermediate-risk CTV may be considered and includes the nodal level(s) of the involved lymphadenopathy(ies) and the adjacent levels along 3 cm [23]. This optional target volumes receives usually 59 Gy to 63 Gy (1.8–2 Gy/fraction).

In this postoperative setting, the ND pathology report specifies the number and the level(s) of involved lymph node(s) as well as the presence of ENE, or muscle/skin infiltration. The high-risk CTV is defined as the nodal level(s) with ENE on the surgical specimen, including muscle along the nodal level if a muscle is infiltrated. The total dose delivered to the postoperative target volumes at high-risk ranges from 60 to 66 Gy equivalent. The low-risk CTV is based on both the primary site and the nodal involvement, including nodal levels at risk of microscopic tumor cells. The low-risk target volumes receive 50 Gy to 54 Gy (1.6–2 Gy/fraction) with or without prior ND [23]. Historically, this irradiation with several dose prescription ranges was carried out using a sequential scheme. In the IMRT era, doses are commonly delivered using a simultaneous integrated boost technique.

Prognostic factors for locoregional control

Primary site

Relationship between primary site and probability of cervical nodal control remains unclear. In historical series, the primary site did not influence regional control, even in Bataini et al. 's study which included 1251 patients [24]. On the contrary, a large series of 938 HNSCC patients treated with definitive radiotherapy, prognostic factors for neck failure at 5 years were the site of the primary (laryngeal and hypopharyngeal HNSCC), irrespective of post-irradiation ND status [25]. Hypopharyngeal and laryngeal HNSCC are often considered together in the literature. Their cervical recurrence rate is estimated between 15 and 20%, predominantly in level VIb [26]. Laryngeal HNSCC have a rate of occult nodal metastases at diagnosis approaching 15% in case of locally advanced true glottic carcinomas, and up to 33% in case of supraglottic extension [26]. Hypopharyngeal HNSCC exhibit a rate of occult nodal metastases ranging from 45 to 55% at diagnosis. Risk of contralateral nodal metastasis approaches 50%, even in N0 stage, reflecting a strong lymphatic tropism [26]. In addition, they showed a half-fold lower response rate to radiotherapy on the primitive tumor as well as on the nodes, achieving an isolated

nodal control of 84% at 5 years [25, 26]. Grabenbauer et al. confirmed previous results with lower response rates and more regional nodal failure (around 20%) for hypopharyngeal carcinomas treated with definitive CRT [27]. However, these results, which have been found with radiotherapy alone or historical CRT regimens, are not confirmed using modern CRT protocols. In two recent studies using accelerated radiotherapy schedules, nodal failure approached 20% and, was not related to the primary site [28, 29].

Nodal stage

A single modality (surgery or radiotherapy) is currently favored for the management of early stage HNSCC, whereas a multi-modality approach is often required for locoregionally advanced stages. In N0 stages, prophylactic treatment of cervical lymph nodes can be either a selective ND or definitive radiotherapy in case of high probability of occult nodal metastases. In this setting, risk of neck failure is currently estimated inferior to 10% whatever treatment modality [30]. This is why in case of definitive radiation therapy to the primary site, ND should be omitted given high control rates [31].

Locoregionally advanced stages (stages III–IV) can be treated either with exclusive CRT or surgery to the primary with a comprehensive or selective ND. Surgery is followed by postoperative radiotherapy in case of risk factors for primary relapse (T stage and positive or close margins) and neck relapse: positive lymph nodes (≥ 3) and/or vascular, lymphatic or perineural invasion and/or pT3–T4 and is combined with concurrent chemotherapy in case of ENE and/or positive surgical margins. In N1 stages managed by definitive radiotherapy, neck node control rates are around 90% at 5 years [32]. Definitive CRT for N1 stages should not be combined with ND given high nodal response rates.

In N2–3 stages managed by ND, 5-year regional control rate is estimated between 70 and 85% [33]. In this setting, adjuvant radiotherapy or CRT improved cervical nodal control, and CRT improved overall survival in patients with risk factors of neck relapse [33]. In N2–3 stages treated by CRT, neck nodal control is estimated around 80% [34]. Recently, Van den Bosch et al. showed an increased risk of infield nodal recurrence with increasing lymphadenopathy volume at initial staging. Volume > 1.5 cm^3 or alternative volumetric parameters like summed short- and long-axis diameter ≥ 17 mm were highly predictive of neck relapse after radiotherapy [29]. In N2–3 stages, no consensus exists as regard the use of up-front ND before CRT. This issue is especially challenging as the approaches used vary, depending in large part on the primary site extent and resectability. For instance, locally advanced carcinomas of the oral cavity are managed by surgical resection of both the primary and neck followed by postoperative CRT on a case by case basis. Exclusive CRT is generally limited to inoperable patients or inextirpable diseases [25].

Nodal features

Conventional adverse prognostic factors, such as size > 3 cm, stage $\geq$ N2c, contralateral lymphadenopathies (N2c or bilateral N3), extent to levels IV and V, fixed lymphadenopathies and ENE are consistent across series [8]. Other criteria such as cystic and necrotic lymphadenopathies are not included in the 8th edition of the TNM/AJCC classification despite implications on radiosensitivity [35]. Cystic lymphadenopathies exhibit regular 2 mm capsula, homogenous content, and are either defined as $> 30\%$ of lymph node hypodensity on CT or any low signal intensities on contrast enhanced T1-MRI sequence [36]. They may be observed in vitro-induced oropharyngeal HNSCC and, harbor favorable profile response to radiation therapy [36]. Necrotic lymphadenopathies exhibit a heterogeneous content and are defined as non-enhancing areas circumscribed by enhancing nodal tissue on CT or MRI. They have been associated with radioresistance, through hypoxia in particular [37].

Assessment of the nodal response after definitive CRT

Morphological imaging

Since Peters et al., development of cross-sectional imaging using CT has significantly improved assessment of the nodal response after CRT [38]. Consequently, an image-guided approach has emerged based on CT assessment and follow-up. It allows detection of residual lymph nodes and characterization of their size, their density (necrotic or not) and their shape (well or poorly circumscribed). A lymph node is considered suspicious when its short axis is larger than 12 mm in the upper jugulo-carotid and submandibular regions, larger than 5–8 mm in the retropharyngeal level and, larger than 10 mm in the other regions. Nonetheless, a central necrotic lymph node, defined as a heterogeneous lymph node with central hypodensity and peripheral contrast enhancement, remains highly suspicious, regardless of their size. More than three lymph nodes grouped together, with a smallest diameter longer than 6 mm, are equally highly suspicious. Loss of the oval shape or round nodes and loss of fatty hilum are also common patterns of metastatic involvement. The ratio of major to minor axis of the lymph node < 1.5 has a pathological value and is assumed to be a better invasion criteria as in regards to size [39]. The first CT evaluation should be performed in millimetric sections, with intra-venous contrast fluid at 12 weeks after the treatment completion. However, there is currently no consensus tool

to determine whether a post-CRT lymph node is at risk of harboring residual viable tumor cells.

Further imaging modalities may be relevant in cases of equivocal CT. Cervical ultrasound practiced in expert centers provides information although it is highly operator-dependent. The characteristics of size, sphericity and density are used to confirm or invalidate the suspicious nature of a lymph node after CRT. An ultrasound or CT-guided nodal fine-needle aspiration could be carried out but has a positive value, exclusively, because of a sensitivity of 73% [40].

Functional imaging

Role of the functional imaging has been of major importance to enhance the radio-pathological correlation in this setting. FDG-PET has proven to be a key exam. Early studies on the impact of FDG-PET were not conclusive, perhaps because of initial limitations of the technique (sensitivity and spatial resolution), but also because of an inadequate time gap between the exam and radiotherapy completion [41, 42]. An interval of 3–4 months seems a reasonable compromise between the predictability of the response and the risk of ND morbidity [43]. Accurate discrimination between residual disease uptake and post-therapeutic changes may be challenging during follow-up. No consensus exists as regards a threshold of maximum standardized uptake value (SUV_{max}) to distinguish radiation-induced focal inflammatory reaction and residual nodal disease. Sjövall et al. reported that three methods (visual inspection, SUV_{max} and Likert scale) could predict regional control but not overall survival following radiotherapy. To identify accurately neck node responders and non-responders, the Likert scale, already commonly used for lymphoma assessment, was the most promising tool to minimize equivocal FDG-PET [44]. Most retrospective data show a sensitivity and a specificity around 90%, with a positive predictive value of approximately 70%. They underlined consistently a high negative predictive value ranging from 95 to 100% [45]. Thus, the excellent negative predictive value of FDG-PET might prevent unnecessary ND in many cases.

Mehanna et al. realized a randomized trial to compare efficacy and economic outcomes of planned ND versus FDG-PET-guided surveillance in 564 patients with N2–3 HNSCC managed by definitive CRT. FDG-PET was performed 12 weeks after completion of CRT. Planned ND was undertaken within 4 weeks before or within 4 to 8 weeks after the CRT. The rate of complete metabolic response in both the primary tumor and nodes was 69%. The rate of complete metabolic response in the primary and incomplete or equivocal in the nodes was 17%. At 2 years, FDG-PET follow-up was not inferior compared to planned ND in terms of overall survival and locoregional control. The rates of complications after ND were 42% in the surveillance group, 39% in the planned ND after CRT and 35% in the planned ND before CRT [5, 46]. In terms of health economy, this study confirmed previous publications that FDG-PET surveillance is more cost-effective than planned ND or CT-guided surveillance by avoiding unnecessary ND [46, 47]. Nonetheless, this study suffers from a few limits. The location of the primary tumor was uneven, with mostly oropharyngeal carcinomas (85%) predominantly induced by oncogenic HPV. Consequently, the population sample of interest had a favorable prognosis. Another shortcoming was that patients who had undergone planned ND were followed by CT and MRI without FDG-PET. To conclude, FDG-PET and CT should be combined to assess the nodal residual disease as part of the follow-up [48]. The first FDG-PET evaluation should be performed at least 12 weeks after completion of CRT. More recently, Schmitz et al. assessed prospectively the performance of FDG-PET in case of residual disease suspected on CT or MRI and negative FDG-PET. The presence of viable tumor cells was reported in 27/145 ND (19%). The negative predictive value of FDG-PET alone was 94.6%. They conclude that FDG-PET-guided surveillance alone would result in fewer ND and, less associated morbidity on shoulder and swallowing function without compromising regional control [49].

Performance of morphologic MRI turned out to be disappointing to predict nodal response or to detect residual disease in the neck after CRT [50, 51]. Functional MRI, like diffusion-weighted MRI (DW-MRI), quantifies the apparent diffusion motion of water molecules based on measurement of the apparent diffusion coefficient (ADC). Low ADC is indirectly the reflect of hypercellular tissue as a residual or recurrent tumor in contrast to high ADC associated with hypocellular tissue like necrosis. First, adding DW-MRI to FDG-PET-guided surveillance could improve FDG-PET specificity up to 95% and may avoid unnecessary ND [52]. Second, pretreatment and mid-treatment DW-MRI exhibited promising results to predict treatment response of cervical lymphadenopathies [53, 54]. A high initial perfusion fraction in the nodes and a high nodal ADC_{1000} might be predictive of poor response to CRT and locoregional recurrence [53, 54]. Perspectives in imaging are on one side development of PET–MRI. Early results for neck node staging indicated a sensitivity of 85% and a specificity of 92% [55]. A recent review did not support the superiority of PET–MRI over PET–CT in nodal staging in HNSCC [56].

Influence of oncogenic HPV

Cystic lymphadenopathies, as described previously, appear to be associated with HPV-induced HNSCC [57]. The incidence of HPV+ HNSCC has increased significantly over the past decade in industrialized countries

[58]. Among non-smoking patients with oropharyngeal HNSCC, oncogenic HPV infection is a prognostic factor associated with higher overall survival and locoregional control compared to HPV− oropharyngeal HNSCC [59]. Furthermore, HPV-related oropharyngeal HNSCC occurs usually in 50-year-old or less non-comorbid patients [13]. Prospective studies demonstrated that HPV infection is a predictive factor for chemo- and radiosensitivity in this setting, motivating the currently on-going therapeutic de-escalation trials [11, 60]. In HPV+ carcinomas of the oropharynx, de-escalation strategies are especially investigated owing to the medium- and long-term toxicities, impairing the quality of life in more than 50% of these patients with favorable outcomes [14]. The radiological response of HPV+ lymphadenopathies treated by CRT was compared the HPV− counterpart. HPV-related nodes have a relatively more rapid CT involution. However, complete response on imaging may be delayed and achieved later than 6 to 8 weeks after the completion of the CRT compared to HPV− nodes [6]. Thus, surveillance of nodal response on the first evaluation at 12 weeks should be extent up to 18 weeks in HPV-induced HNSCC. The study of Mehanna et al. included approximately 75% of p16+ HNSCC in each group. FDG-PET surveillance was not inferior to planned ND, irrespective of HPV status. However, in case of an equivocal response on FDG-PET at 3 months, HPV+ lymph nodes underwent ND. It is not excluded that these patients could have achieved a delayed complete response without ND. For HPV-induced HNSCC, FDG-PET appears more accurate than CT alone to assess nodal response after CRT. A complete metabolic nodal response at 3 months in HPV+ HNSCC is associated with an excellent negative prognostic value, averaging 96%, even in case of enlarged lymph nodes on CT [61]. To summarize, in HPV-related locoregionally advanced HNSCC, the first FDG-PET evaluation should be delayed up to 18 weeks after the completion of CRT. At 12 weeks, early complete metabolic response or an equivocal metabolic response associated with a nodal involution on CT support continuation of follow-up up to 18 weeks rather than ND. In HPV− carcinomas, any equivocal lymph node uptake on FDG-PET at 3–4 months would require ND.

To optimize these results and further predict treatment response, innovative techniques are being used to test for HPV–DNA circulating in peripheral blood at pretherapeutic screening and after radical treatment in HPV+ patients. Early prospective results indicated outstanding sensitivity (90–100%) and specificity (93–100%) at initial staging. During follow-up, circulating HPV–DNA revealed a correlation with the clinical response and, appeared as a promising predictive biomarker of tumor and nodal response [62].

Timing of neck dissection

Up-front neck dissection followed by definitive chemo-radiotherapy

Up-front ND prior to radiation therapy is performed by some specialized centers for N2–3 stages, notably for necrotic nodes, bulky N2–3 or hypopharyngeal HNSCC [63].

This approach is supported by several findings established with two-dimensional radiation therapy and/or without concurrent chemotherapy. First, response of the primary and lymph nodes are often dissociated, with a lower rate of nodal complete response [2]. Metastatic lymph nodes seem less radiosensitive than primitive tumor as mentioned in the veterans' essay [64, 65]. For instance, lymphadenopathies with high hypoxia volume or bulky tumor volume seem less responsive to CRT and could be removed by ND. Second, response assessment was historically challenging after radiation therapy. Before Mehanna's publication, correlation between the clinical–radiological and the pathological response was not demonstrated. This lack of correlation was especially true for lymph nodes > N1 [66]. Third, surgery does not compromise primary tumor control if postoperative radiotherapy could be started shortly after. The median delay between surgery and first day of radiotherapy across studies ranged from 21 to 29 days [63, 67–72]. Graboyes et al. demonstrated that CRT should be started within 6 weeks after ND, while a delay beyond 7 weeks was associated with decreased survival [73]. Furthermore, pathological staging as assessed on operative specimen could be used to modulate the dose of radiotherapy to the different lymph node areas, especially in case of ENE. Modesto et al. published outcomes of 63 patients with bulky and/or necrotic nodal metastasis treated by up-front ND followed by CRT. Doses delivered on the neck were ranging from 50 to 66 Gy based on surgical features. They reported only one isolated neck failure and a locoregional control of 88% at 3 years [74]. No prospective study addresses the question of a lower dose and a slightly smaller volume using up-front ND to achieve lower toxicity in the IMRT era. Finally, while up-front ND is relatively convenient for an experienced surgeon, this procedure after radiotherapy is associated with increased acute morbidity. Specifically, there are surgical issues with a risk of injury of noble structures and an increased risk of bleeding during the ND procedure. Delays in healing due to cutaneous and subcutaneous fibrosis may compromise definitive outcomes. Up-front ND followed by definitive CRT is associated with approximately 2.5% to 38% of minor acute toxicities and 15% of late toxicities [63, 68, 69, 71].

However, issues pointing against up-front ND are, first of all, that the large majority of lymphadenopathies < 3 cm

should be sterilized by CRT [75]. Because of a low probability of cervical failure, a systematic ND before CRT could represent an over-treatment in more than 50% of cases associated with increased morbidity [76, 77]. Consequently, N1 stages are generally managed with exclusive CRT rather than up-front ND [25, 78]. Second, a comprehensive or a selective ND is commonly used for the N2–3 stages, while a less morbid elective ND may be discussed in majority of cases after CRT in case of residual or recurrent nodal disease.

The timing of ND in locoregionally advanced HNSCC has been retrospectively compared between up-front ND followed by CRT versus CRT followed by ND (Table 1).

Published data include a limited number of patients, and the use of two or three-dimensional radiation therapy without concurrent chemotherapy [38, 79–83]. In this setting, some reports showed that ND followed by radiotherapy was superior to radiotherapy ± chemotherapy alone as regards overall survival, disease-free survival and cervical nodal control [79, 81, 83]. During the same period, conflicting results were published without superiority of up-front ND in terms of efficacy [38, 80, 82]. Toxicity suffers from a lack of accurate assessment. Two historical studies reported acute and late toxicity without any significant difference [79, 80]. Recent retrospective studies showed reduced surgical morbidity using up-front ND compared to ND after CRT. Elicin et al. found lower rates of mucositis and pain of grade ≥ 3 with up-front ND compared to post-CRT ND [82]. Liu et al. recorded 6.5% of acute toxicity with up-front ND and 47% with post-CRT ND, without any statistical comparative analysis [83]. The most recent retrospective study conducted by Nevens et al. compared up-front ND followed by CRT (114 patients) to definitive CRT (150 patients) in N2–3 HNSCC. They demonstrated no statistical difference regarding the 2-year local (91% vs. 86%, $p = 0.09$), regional (89% vs. 83%, $p = 0.12$) and distant control (77% vs. 75%, $p = 0.92$) in the groups with and without up-front ND, respectively. In terms of toxicity, they reported a significantly higher rate of grade ≥ 2 fibrosis at all time points up to 24 months ($p = 0.01$) in the ND group [84].

Elicin et al. conducted recently a systematic review to present treatment-related complications, toxicity rates and efficacy outcomes of up-front ND. They underlined heterogeneity of disease and patient features, with a large prevalence of two-dimensional radiotherapy without concurrent chemotherapy, and with a large majority of retrospective studies. They concluded that up-front ND might improve nodal control compared to radiotherapy alone and might reduce serious local complications compared to planned or salvage ND, with validation of this assumption requiring controlled randomized trials [85].

Neck dissection after definitive chemo-radiotherapy

Historically, two approaches coexisted regarding ND following definitive CRT in stage N2–3 HNSCC [65]. A first one was a systematic planned ND, regardless of response to CRT. It had been based on the absence of correlation between the clinical–radiological response and the histological one. Patients initially staged N2–3 were considered at high-risk of residual tumor (up to 40%) and neck recurrence [86]. This approach was progressively abandoned with a level Ib evidence following Mehanna's trial for patients in complete response after CRT, even in case of initial N3 stage. Survival among patients with FGD-PET-guided surveillance was not inferior to those who underwent a planned ND. This strategy was both more cost-effective and lead to fewer ND procedure. A planned ND is currently performed in case of residual nodal disease at the first physical and imaging evaluation. Imaging follow-up at 3 months includes a CT with intra-venous contrast and/or an MRI, and FDG-PET at 3–4 months.

A salvage ND is defined as recurrent nodal disease beyond 12–15 weeks following the completion of CRT in HPV− HNSCC [87]. This definition could be extended beyond 18 weeks in case of HPV+ HNSCC, as complete response is often delayed [6]. Historically, based on operative specimens from planned ND following CRT, > 70% were free from viable tumor cells in cases of > 70% of complete response. Also N3 stages in complete response exhibit regional control rates ≥ 85% [21, 25, 38, 42, 75, 88, 89]. Recently, Adams et al. showed a low rate of 6% of isolated neck failure after CRT and FDG-PET-guided surveillance for N3 stages [90]. The most critical issue for N3 stages is more likely to be distant-metastatic failure (around 30%) rather than neck recurrence [90].

Minor acute complications occurred among 28–33% of patients, major ones up to 16% and, severe late toxicities in up to 55% [65, 91, 92]. Machtay et al. looked for prognostic factors of late toxicities for 230 patients after CRT in locoregionally advanced HNSCC. The rate of severe late toxicity > 2 years after CRT was 43%. Among others, ND after CRT was correlated with development of severe late toxicity [92]. More recently, the most relevant predictive factor of toxicity appears to be the extent of surgery [93, 94]. For this reason, super-selective or elective ND modulated by the nodal recurrent disease has emerged and may be offered instead of a comprehensive ND. It consists of dissection of residual/recurrent nodal disease and two or fewer contiguous nodal levels [95, 96]. Elective ND enables to reduce both acute complications at 10% and long-term morbidity of the procedure [91, 97]. Efficacy of an elective ND after CRT in N2–3 stages has been showed in several series, with a low risk of local relapse, ranging from 1 to 5% [98, 99]. However, this approach has been evaluated in the most part

Table 1 Retrospective studies comparing up-front neck dissection to definitive (chemo)radiotherapy in head and neck squamous cell carcinoma

Author year	Arm	Patient per arm	Nodal stage	Primary site	RT modality	Concomitant chemotherapy (%)	Overall survival	Local control (%)	Neck control (%)	Distant control (%)	Recurrence	Severe toxicity
GETTEC [81] 1984–1987	Up-front RT	195	N1 19% N2a 32% N2b 17% N2c 8% N3 24%	Pharyngo-larynx 100%	2D	0	89% (at 5 years)	91	80	28	Persistent 21% Planned ND 20% Salvage ND 2%	–
	Up-front ND	118			2D	0		92	94		–	–
Peters et al. [38] 1984–1993	Up-front RT	75	N1 35% N2a 20% N2b 18% N2c 13% N3 14%	Oropharynx 100%	2D 100% 72 Gy 54 Gy	0	–	95	72	–	Persistent 17% Planned ND 17% Salvage ND 4%	Fibrosis 22% Surgical 12.5%
	Up-front ND	17			63 Gy	0	–	94	76	–	–	Fibrosis 27% Surgical 2%
Allal et al. [80] 1991–1996	Up-front RT	17	N1 0% N2a 29% N2b 24% N2c 29% N3 18%	Oropharynx 82% Hypopharynx 18%	2D 100% 69.9 Gy 50.4 Gy	47	50% (at 2 years)	75	55	–	Salvage ND 12%	5%
	Up-front ND	24	N1 0% N2a 38% N2b 29% N2c 0% N3 33%	Oropharynx 46% Hypopharynx 54%	2D 100% 69.9 Gy 50.4 Gy	25	37%	81	73	–	–	Surgical 37% Laryngeal edemas 8%
Liu et al. [83] 1999–2005	Up-front RT	39	N2a 26% N2b 37% N2c 11% N3 26%	Hypopharynx 33% Larynx 67%	2D 100% 70 Gy 60 Gy 50 Gy	51	35% (at 5 years)	–	62	–	Persistent 20%	Wound complications 47%
	Up-front ND	46	N2a 26% N2b 3% N2c 13% N3 20%	Hypopharynx 39% Larynx 61%	2D 100% 70–72 Gy 66–70 Gy 50 Gy	52	42.5% (at 5 years)	78	85	96	–	Fistula 2% Suture line dehiscence 4%
Al-Mamgani et al. [79] 1996–2010	Up-front RT	103	N1 25% N2– 3 75%	Hypopharynx 100%	3D 100% 70 Gy 46 Gy	77	42% (at 3 years)	72	87	–	–	Acute 72% Dysphagia 46% Late 13% Xerostomia 20%
	Up-front ND	32	N1 19% N2– 3 81%		3D 100% 66 Gy 46 Gy	28	66% (at 3 years)	84	92	–	–	Acute 50% Dysphagia 22% Late 12% Xerostomia 17%

Table 1 (continued)

Author year	Arm	Patient per arm	Nodal stage	Primary site	RT modality	Concomitant chemotherapy (%)	Overall survival	Local control (%)	Neck control (%)	Distant control (%)	Recurrence	Severe toxicity
Elicin et al. [82] 2001–2012	Up-front RT	95	N1 33% N2 64% N3 3%	Oropharynx 62% Hypopharynx 26% Larynx 12%	IMRT 89% 72 Gy 54 Gy	89	65% (at 5 years)	77	75	83	Persistent 9.5% Planned ND 5%	Pain 38% Dermatitis 30% Mucositis 59% Dysphagia 58% Xerostomia 23%
	Up-front ND	129	N1 12% N2 81% N3 7%	Oropharynx 71% Hypopharynx 20% Larynx 9%	IMRT 83% 66 Gy 54 Gy	83	59% (at 5 years)	83	86	86	–	Pain 25% Dermatitis 22% Mucositis 34% Dysphagia 47% Xerostomia 28%
Nevens et al. [84] 2002–2012	Up-front RT	150	N1 0% N2a 5% N2b 42% N2c 49% N3 4%	Oropharynx 44% Hypopharynx 35% Larynx 12% Oral cavity 9%	IMRT 57% 70 Gy 50 Gy	85	71% (at 2 years)	86	83	75	Persistent 3% Salvage ND 6%	–
	Up-front ND	114	N1 0% N2a 5% N2b 52% N2c 36% N3 7%	Oropharynx 40% Hypopharynx 43% Larynx 11% Oral cavity 5%	IMRT 63% 67.2 Gy 60.9 50 Gy	77	48% (at 2 years)	91	89	77	–	Fibrosis HR = 2.8 ($p = 0.01$)

RT radiotherapy, *ND* neck dissection, *2D* two-dimensional radiotherapy, *persistent* persistent nodal disease after (chemo)radiotherapy, *planned ND* ND within 12 weeks after (chemo)radiotherapy, *salvage ND* ND beyond 12 weeks after (chemo)radiotherapy completion, *3D* three-dimensional radiotherapy, *IMRT* intensity modulated radiation therapy, *HR* hazard ratio

for single-node level involvement, and the extension of ND remains controversial in regionally advanced HNSCC with several involved node-levels.

Cervical lymphadenopathies of unknown primary

In a recent review, Troussier et al. provided an update on diagnostic achievements and management of HNSCC lymphadenopathies of unknown primary [100, 101]. In France, up-front ND is generally performed in this context. It can be proposed as an exclusive treatment for low nodal volume (pN1) without pathological ENE, with no history of incisional biopsy and histologically healthy tonsillectomy. Postoperative CRT is recommended in cases of high-risk features (vascular, lymphatic or perineural invasion, ENE, positive surgical margins or advanced nodal involvement (pN2b ≥ 3 lymphadenopathies, pN2c–3). In the absence of these adverse prognostic factors, exclusive postoperative radiotherapy should be started within 6 weeks after surgery. As it is usually practiced in the USA, radiation therapy combined with concurrent chemotherapy without surgery is also available. Nevertheless, up-front ND has been retrospectively associated with higher local recurrence-free survival compared to CRT alone [102]. No trial has statistically proven with a strong level of evidence a significant difference in overall survival according to treatment modality, in other words between up-front ND followed by postoperative radiotherapy or CRT compared to definitive and exclusive CRT.

Conclusion

The ongoing randomized, phase III UP-FRONT NECK trial compares definitive CRT for locally advanced HNSCC with or without up-front ND in the IMRT era (NCT02918955). The study is now recruiting, and the results will not be available until 2022. In the absence of a higher level of evidence, the decision-making tools for ND before or after CRT are based on Mehanna's trial and retrospective studies with significant biases. Furthermore, overall survival and infield cervical recurrence data for HPV− HNSCC are still limited, especially for N3 stages. Institutional trends are leading to a sequential treatment or, on the opposite, to CRT on the tumor and lymphadenopathies followed by FDG-PET-guided surveillance of the response. Excluding inoperable patients and unresectable diseases, N3 lymphadenopathies, as well as bulky N2 stages, specifically HPV− or necrotic nodes, would be in favor of an up-front surgical approach, while HPV+ diseases, and lymphadenopathies of unknown primary would rather support CRT. Nonetheless, the approaches and the ensuing outcomes remain not homogenous depending on the centers' experience. For instance, the management of hypopharyngeal HNSCC remains controversial without prospective investigation, since recent retrospective data have not suggested any relevant difference between the two strategies. However, the critical issue for locally advanced HNSCC now appears to be the rate of distant metastasis, which is in the range of 25–36% for these stages compared to 10–15% for all stages confounded of HNSCC. Systematic ND on its own does not seem enough to prevent metastatic escapes. Future therapeutic advances will definitely come from novel and innovative systemic therapies combined with effective local treatment.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. Chung E-J, Kim G-W, Cho B-K, Park HS, Rho Y-S. Pattern of lymph node metastasis in hypopharyngeal squamous cell carcinoma and indications for level VI lymph node dissection: Level VI lymph node metastasis in hypopharyngeal squamous cell carcinoma. Head Neck. 2016;38:E1969–73.
2. Bataini JP, Bernier J, Jaulerry C, Brunin F, Pontvert D, Lave C. Impact of neck node radio responsiveness on the regional control probability in patients with oropharynx and pharyngolarynx cancers managed by definitive radiotherapy. Int J Radiat Oncol Biol Phys. 1987;13:817–24.
3. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet Lond Engl. 2000;355:949–55.
4. Lango MN, Myers JN, Garden AS. Controversies in surgical management of the node-positive neck after chemoradiation. Semin Radiat Oncol. 2009;19:24–8.
5. Mehanna H, Wong W-L, McConkey CC, Rahman JK, Robinson M, Hartley AGJ, et al. PET–CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med. 2016;374:1444–54.
6. Huang SH, O'Sullivan B, Xu W, Zhao H, Chen D, Ringash J, et al. Temporal nodal regression and regional control after primary radiation therapy for N2–N3 head-and-neck cancer stratified by HPV status. Int J Radiat Oncol Biol Phys. 2013;87:1078–85.
7. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363:24–35.

8. Kharytaniuk N, Molony P, Boyle S, O'Leary G, Werner R, Heffron C, et al. Association of extracapsular spread with survival according to human papillomavirus status in oropharynx squamous cell carcinoma and carcinoma of unknown primary site. JAMA Otolaryngol-Head Neck Surg. 2016;142:683–90.
9. Maxwell JH, Ferris RL, Gooding W, Cunningham D, Mehta V, Kim S, et al. Extracapsular spread in head and neck carcinoma: impact of site and human papillomavirus status. Cancer. 2013;119:3302–8.
10. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. 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;27:843–50.
11. Chai RL, Rath TJ, Johnson JT, Ferris RL, Kubicek GJ, Duvvuri U, et al. Accuracy of computed tomography in the prediction of extracapsular spread of lymph node metastases in squamous cell carcinoma of the head and neck. JAMA Otolaryngol-Head Neck Surg. 2013;139:1187–94.
12. Ghadjar P, Schreiber-Facklam H, Gräter R, Evers C, Simcock M, Geretschläger A, et al. Quantitative analysis of extracapsular extension of metastatic lymph nodes and its significance in radiotherapy planning in head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2010;76:1127–32.
13. Martin H, Del Valle B, Ehrlich H, Cahan WG. Neck dissection. Cancer. 1951;4:441–99.
14. Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg. 2002;128:751–8.
15. Hamoir M, Silver CE, Schmitz S, Takes RP, Rinaldo A, Rodrigo JP, et al. Radical neck dissection: is it still indicated? Eur Arch Oto–Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol-Head Neck Surg. 2013;270:1–4.
16. Ferlito A, Rinaldo A. Is radical neck dissection a current option for neck disease? Laryngoscope. 2008;118:1717–8.
17. Moya-Plana A, Aupérin A, Guerlain J, Gorphe P, Casiraghi O, Mamelle G, et al. Sentinel node biopsy in early oral squamous cell carcinomas: long-term follow-up and nodal failure analysis. Oral Oncol. 2018;82:187–94.
18. Divi V, Chen MM, Nussenbaum B, Rhoads KF, Sirjani DB, Holsinger FC, et al. Lymph node count from neck dissection predicts mortality in head and neck cancer. J Clin Oncol. 2016;34:3892–7.
19. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol Off J Am Soc Clin Oncol. 1998;16:1310–7.
20. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst. 1999;91:2081–6.
21. Yao M, Hoffman HT, Chang K, Funk GF, Smith RB, Tan H, et al. Is planned neck dissection necessary for head and neck cancer after intensity-modulated radiotherapy? Int J Radiat Oncol Biol Phys. 2007;68:707–13.
22. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2014;110:172–81.
23. Lapeyre M, Toledano I, Bourry N, Bailly C, Cachin F. Délinéation des volumes cibles des cancers des voies aérodigestives supérieures en radiothérapie conformationnelle avec modulation d'intensité. Cancer/Radiothér. 2011;15:466–72.
24. Bataini JP, Bernier J, Brugere J, Jaulerry C, Picco C, Brunin F. Natural history of neck disease in patients with squamous cell carcinoma of oropharynx and pharyngolarynx. Radiother Oncol J Eur Soc Ther Radiol Oncol. 1985;3:245–55.
25. Thariat J, Ang KK, Allen PK, Ahamad A, Williams MD, Myers JN, et al. Prediction of neck dissection requirement after definitive radiotherapy for head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2012;82:e367–74.
26. Rivière D, Mancini J, Santini L, Giovanni A, Dessi P, Fakhry N. Lymph-node metastasis following total laryngectomy and total pharyngolaryngectomy for laryngeal and hypopharyngeal squamous cell carcinoma: frequency, distribution and risk factors. Eur Ann Otorhinolaryngol Head Neck Dis. 2018;135:163–6.
27. Grabenbauer GG, Rödel C, Ernst-Stecken A, Brunner T, Hornung J, Kittel K, et al. Neck dissection following radiochemotherapy of advanced head and neck cancer—for selected cases only? Radiother Oncol J Eur Soc Ther Radiol Oncol. 2003;66:57–63.
28. Kjems J, Gothelf AB, Håkansson K, Specht L, Kristensen CA, Friborg J. Elective nodal irradiation and patterns of failure in head and neck cancer after primary radiation therapy. Int J Radiat Oncol. 2016;94:775–82.
29. van den Bosch S, Dijkema T, Verhoef LCG, Zwijnenburg EM, Janssens GO, Kaanders JHAM. Patterns of recurrence in electively irradiated lymph node regions after definitive accelerated intensity modulated radiation therapy for head and neck squamous cell carcinoma. Int J Radiat Oncol. 2016;94:766–74.
30. Schmitz S, Machiels J-P, Weynand B, Gregoire V, Hamoir M. Results of selective neck dissection in the primary management of head and neck squamous cell carcinoma. Eur Arch Oto–Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol-Head Neck Surg. 2009;266:437–43.
31. NCCN guidelines v2. 2018. https://www.nccn.org/professionals/physician_gls/default.aspx#head-and-neck.
32. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC Cooperative Group of Radiotherapy. Radiother Oncol J Eur Soc Ther Radiol Oncol. 1992;25:231–41.
33. Clark J, Li W, Smith G, Shannon K, Clifford A, McNeil E, et al. Outcome of treatment for advanced cervical metastatic squamous cell carcinoma. Head Neck. 2005;27:87–94.
34. Adelstein DJ, Lavertu P, Saxton JP, Secic M, Wood BG, Wanamaker JR, et al. Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. Cancer. 2000;88:876–83.
35. Vergeer MR, Doornaert P, Leemans CR, Buter J, Slotman BJ, Langendijk JA. Control of nodal metastases in squamous cell head and neck cancer treated by radiation therapy or chemoradiation. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2006;79:39–44.
36. Li W-F, Sun Y, Mao Y-P, Chen L, Chen Y-Y, Chen M, et al. Proposed lymph node staging system using the International Consensus Guidelines for lymph node levels is predictive for nasopharyngeal carcinoma patients from endemic areas treated with intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2013;86:249–56.
37. Chua DT, Sham JS, Kwong DL, Choy DT, Leong L, Chan FL. Evaluation of cervical nodal necrosis in nasopharyngeal carcinoma by computed tomography: incidence and prognostic significance. Head Neck. 1997;19:266–75.

38. Peters LJ, Weber RS, Morrison WH, Byers RM, Garden AS, Goepfert H. Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. Head Neck. 1996;18:552–9.
39. Steinkamp HJ, Hosten N, Richter C, Schedel H, Felix R. Enlarged cervical lymph nodes at helical CT. Radiology. 1994;191:795–8.
40. van den Brekel MW. Lymph node metastases: CT and MRI. Eur J Radiol. 2000;33:230–8.
41. Schwartz DL, Rajendran J, Yueh B, Coltrera MD, Leblanc M, Eary J, et al. FDG-PET prediction of head and neck squamous cell cancer outcomes. Arch Otolaryngol Head Neck Surg. 2004;130:1361–7.
42. Yao M, Buatti JM, Dornfeld KJ, Graham MM, Smith RB, Funk GF, et al. Can post-RT FDG PET accurately predict the pathologic status in neck dissection after radiation for locally advanced head and neck cancer? In regard to Rogers et al. (Int J Radiat Oncol Biol Phys 2004;58:694–697). Int J Radiat Oncol Biol Phys. 2005;61:306–7; author reply 307.
43. Greven KM, Williams DW, Browne JD, McGuirt WF, White DR, D'Agostino RB. Radiographic complete response on post treatment CT imaging eliminates the need for adjuvant neck dissection after treatment for node positive head and neck cancer. Am J Clin Oncol. 2008;31:169–72.
44. Sjövall J, Bitzén U, Kjellén E, Nilsson P, Wahlberg P, Brun E. Qualitative interpretation of PET scans using a Likert scale to assess neck node response to radiotherapy in head and neck cancer. Eur J Nucl Med Mol Imaging. 2016;43:609–16.
45. Nayak JV, Walvekar RR, Andrade RS, Daamen N, Lai SY, Argiris A, et al. Deferring planned neck dissection following chemoradiation for stage IV head and neck cancer: the utility of PET–CT. Laryngoscope. 2007;117:2129–34.
46. Mehanna H, McConkey CC, Rahman JK, Wong W-L, Smith AF, Nutting C, et al. PET-NECK: a multicentre randomised Phase III non-inferiority trial comparing a positron emission tomography–computerised tomography-guided watch-and-wait policy with planned neck dissection in the management of locally advanced (N2/N3) nodal metastases in patients with squamous cell head and neck cancer. Health Technol Assess Winch Engl. 2017;21:1–122.
47. Smith AF, Hall PS, Hulme CT, Dunn JA, McConkey CC, Rahman JK, et al. Cost-effectiveness analysis of PET–CT-guided management for locally advanced head and neck cancer. Eur J Cancer Oxf Engl. 1990;2017(85):6–14.
48. Hoffmann TK, Schuler PJ, Laban S, Grässlin R, Beer M, Beer AJ, et al. Response evaluation in head and neck oncology: definition and prediction. ORL J Oto–Rhino-Laryngol Relat Spec. 2017;79:14–23.
49. Schmitz S, Van Maanen A, Rousseaux L, Andry G, Temam S, Dequanter D, et al. The role of PET for predicting nodal response in locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) treated with chemoradiotherapy (CRT): results of a prospective multicenter trial. J Clin Oncol. 2017;35:6013–6013.
50. King AD, Yu K-H, Mo FKF, Law BKH, Yuen TWC, Bhatia KS, et al. Cervical nodal metastases from head and neck squamous cell carcinoma: MRI criteria for treatment assessment. Head Neck. 2016;38(Suppl 1):E1598–604.
51. Quon H, Brizel DM. Predictive and prognostic role of functional imaging of head and neck squamous cell carcinomas. Semin Radiat Oncol. 2012;22:220–32.
52. Schouten CS, de Graaf P, Alberts FM, Hoekstra OS, Comans EFI, Bloemena E, et al. Response evaluation after chemoradiotherapy for advanced nodal disease in head and neck cancer using diffusion-weighted MRI and 18F-FDG-PET–CT. Oral Oncol. 2015;51:541–7.
53. Hauser T, Essig M, Jensen A, Laun FB, Münter M, Maier-Hein KH, et al. Prediction of treatment response in head and neck carcinomas using IVIM-DWI: evaluation of lymph node metastasis. Eur J Radiol. 2014;83:783–7.
54. Noij DP, Pouwels PJW, Ljumanovic R, Knol DL, Doornaert P, de Bree R, et al. Predictive value of diffusion-weighted imaging without and with including contrast-enhanced magnetic resonance imaging in image analysis of head and neck squamous cell carcinoma. Eur J Radiol. 2015;84:108–16.
55. Nakamoto Y, Tamai K, Saga T, Higashi T, Hara T, Suga T, et al. Clinical value of image fusion from MR and PET in patients with head and neck cancer. Mol Imaging Biol MIB Off Publ Acad Mol Imaging. 2009;11:46–53.
56. Platzek I, Beuthien-Baumann B, Schneider M, Gudziol V, Langner J, Schramm G, et al. PET/MRI in head and neck cancer: initial experience. Eur J Nucl Med Mol Imaging. 2013;40:6–11.
57. Cantrell SC, Peck BW, Li G, Wei Q, Sturgis EM, Ginsberg LE. Differences in imaging characteristics of HPV-positive and HPV-negative oropharyngeal cancers: a blinded matched-pair analysis. Am J Neuroradiol. 2013;34:2005–9.
58. Boscolo-Rizzo P, Schroeder L, Romeo S, Pawlita M. The prevalence of human papillomavirus in squamous cell carcinoma of unknown primary site metastatic to neck lymph nodes: a systematic review. Clin Exp Metastasis. 2015;32:835–45.
59. Mermod M, Tolstonog G, Simon C, Monnier Y. Extracapsular spread in head and neck squamous cell carcinoma: a systematic review and meta-analysis. Oral Oncol. 2016;62:60–71.
60. Liu JT, Kann BH, De B, Buckstein M, Bakst RL, Genden EM, et al. Prognostic value of radiographic extracapsular extension in locally advanced head and neck squamous cell cancers. Oral Oncol. 2016;52:52–7.
61. Mak D, Hicks RJ, Rischin D, Solomon B, Peters L, Bressel M, et al. Treatment response in the neck: p16+ versus p16− oropharyngeal cancer. J Med Imaging Radiat Oncol. 2013;57:364–72.
62. Lee JY, Garcia-Murillas I, Cutts RJ, De Castro DG, Grove L, Hurley T, et al. Predicting response to radical (chemo)radiotherapy with circulating HPV DNA in locally advanced head and neck squamous carcinoma. Br J Cancer. 2017;117:876–83.
63. Prades JM, Timoshenko AP, Schmitt TH, Delolme MP, Francoz M, Martin C, et al. Planned neck dissection before combined chemoradiation for pyriform sinus carcinoma. Acta Otolaryngol (Stockh). 2008;128:324–8.
64. Strasser MD, Gleich LL, Miller MA, Saavedra HI, Gluckman JL. Management implications of evaluating the N2 and N3 neck after organ preservation therapy. Laryngoscope. 1999;109:1776–80.
65. Wolf GT, Fisher SG. Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation. Laryngoscope. 1992;102:934–9.
66. Brizel DM, Prosnitz RG, Hunter S, Fisher SR, Clough RL, Downey MA, et al. Necessity for adjuvant neck dissection in setting of concurrent chemoradiation for advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2004;58:1418–23.
67. Byers RM, Clayman GL, Guillamondequi OM, Peters LJ, Goepfert H. Resection of advanced cervical metastasis prior to definitive radiotherapy for primary squamous carcinomas of the upper aerodigestive tract. Head Neck. 1992;14:133–8.
68. Paximadis PA, Christensen ME, Dyson G, Kamdar DP, Sukari A, Lin H-S, et al. Up-front neck dissection followed by concurrent chemoradiation in patients with regionally advanced head and neck cancer. Head Neck. 2012;34:1798–803.
69. Cupino A, Axelrod R, Anne PR, Sidhu K, Lavarino J, Kung B, et al. Neck dissection followed by chemoradiotherapy for stage IV (N+) oropharynx cancer. Otolaryngol-Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2007;137:416–21.
70. D'cruz AK, Pantvaidya GH, Agarwal JP, Chaukar DA, Pathak KA, Deshpande MS, et al. Split therapy: planned neck dissection

followed by definitive radiotherapy for a T1, T2 pharyngolaryngeal primary cancer with operable N2, N3 nodal metastases—a prospective study. J Surg Oncol. 2006;93:56–61.
71. Shenoy AM, Shiva Kumar T, Prashanth V, Chavan P, Halkud R, Jacob L, et al. Neck dissection followed by definitive radiotherapy for small upper aerodigestive tract squamous cell carcinoma, with advanced neck disease: an alternative treatment strategy. Indian J Otolaryngol Head Neck Surg. 2013;65:48–52.
72. Verschuur HP, Keus RB, Hilgers FJ, Balm AJ, Gregor RT. Preservation of function by radiotherapy of small primary carcinomas preceded by neck dissection for extensive nodal metastases of the head and neck. Head Neck. 1996;18:277–82.
73. Graboyes EM, Garrett-Mayer E, Ellis MA, Sharma AK, Wahlquist AE, Lentsch EJ, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer. 2017;123:4841–50.
74. Modesto A, Sarini J, Benlyazid A, Ouali M, Laprie A, Graff P, et al. Place du curage ganglionnaire avant radiothérapie exclusive dans la prise en charge des carcinomes épidermoïdes localement évolués des voies aérodigestives supérieures. Cancer/Radiothér. 2016;20:18–23.
75. Rengan R, Pfister DG, Lee NY, Kraus DH, Shah JP, Shaha AR, et al. Long-term neck control rates after complete response to chemoradiation in patients with advanced head and neck cancer. Am J Clin Oncol. 2008;31:465–9.
76. Frank DK, Hu KS, Culliney BE, Persky MS, Nussbaum M, Schantz SP, et al. Planned neck dissection after concomitant radiochemotherapy for advanced head and neck cancer. Laryngoscope. 2005;115:1015–20.
77. Gane EM, McPhail SM, Hatton AL, Panizza BJ, O'Leary SP. Predictors of health-related quality of life in patients treated with neck dissection for head and neck cancer. Eur Arch Oto–Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol-Head Neck Surg. 2017;274:4183–93.
78. Brown KM, Lango M, Ridge JA. The role of neck dissection in the combined modality therapy setting. Semin Oncol. 2008;35:229–35.
79. Al-Mamgani A, Meeuwis CA, van Rooij PH, Mehilal R, Basdew H, Sewnaik A, et al. Node-positive hypopharyngeal cancer treated by (chemo)radiotherapy: impact of up-front neck dissection on outcome, toxicity, and quality of life. Head Neck. 2012;35:1278–86.
80. Allal AS, Dulguerov P, Bieri S, Lehmann W, Kurtz JM. A conservation approach to pharyngeal carcinoma with advanced neck disease: optimizing neck management. Head Neck. 1999;21:217–22.
81. Early pharyngolaryngeal carcinomas with palpable nodes. French Head and Neck Study Group (GETTEC). Am J Surg. 1991;162:377–80.
82. Elicin O, Albrecht T, Haynes AG, Bojaxhiu B, Nisa L, Caversaccio M, et al. Outcomes in advanced head and neck cancer treated with up-front neck dissection prior to (chemo)radiotherapy. Otolaryngol-Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2016;154:300–8.
83. Liu X-K, Li Q, Zhang Q, Su Y, Shi Y-X, Li H, et al. Planned neck dissection before combined chemoradiation in organ preservation protocol for N2–N3 of supraglottic or hypopharyngeal carcinoma. ORL J Oto–Rhino-Laryngol Relat Spec. 2012;74:64–9.
84. Nevens D, Duprez F, Bonte K, Deron P, Huvenne W, Laenen A, et al. Upfront vs. no upfront neck dissection in primary head and neck cancer radio(chemo)therapy: tumor control and late toxicity. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2017;124:220–4.
85. Elicin O, Nisa L, Dal Pra A, Bojaxhiu B, Caversaccio M, Schmücking M, et al. Up-front neck dissection followed by definitive (chemo)-radiotherapy in head and neck squamous cell carcinoma: rationale, complications, toxicity rates, and oncological outcomes—a systematic review. Radiother Oncol. 2016;119:185–93.
86. Ohara K, Tatsuzaki H, Kurosaki Y, Fuji H, Myo-Min, Itai Y, et al. Metastatic lymph-node clearance from head and neck epidermoid carcinomas following radiotherapy. Acta Oncol. 1999;38:261–6.
87. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, et al. Randomized Phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 Trial: long-term report of efficacy and toxicity. J Clin Oncol. 2014;32:3858–67.
88. Johnson CR, Silverman LN, Clay LB, Schmidt-Ullrich R. Radiotherapeutic management of bulky cervical lymphadenopathy in squamous cell carcinoma of the head and neck: is postradiotherapy neck dissection necessary? Radiat Oncol Investig. 1998;6:52–7.
89. Vedrine P-O, Thariat J, Hitier M, Janot F, Kaminsky M-C, Makeieff M, et al. Need for neck dissection after radiochemotherapy? A study of the French GETTEC Group. Laryngoscope. 2008;118:1775–80.
90. Adams G, Porceddu SV, Pryor DI, Panizza B, Foote M, Rowan A, et al. Outcomes after primary chemoradiotherapy for N3 (> 6 cm) head and neck squamous cell carcinoma after an FDG-PET-guided neck management policy. Head Neck. 2014;36:1200–6.
91. Malone J, Robbins KT. Neck dissection after chemoradiation for carcinoma of the upper aerodigestive tract: indications and complications. Curr Opin Otolaryngol Head Neck Surg. 2010;18:89–94.
92. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol Off J Am Soc Clin Oncol. 2008;26:3582–9.
93. Peters TTA, van Dijk BAC, Roodenburg JLN, van der Laan BFAM, Halmos GB. Relation between age, comorbidity, and complications in patients undergoing major surgery for head and neck cancer. Ann Surg Oncol. 2014;21:963–70.
94. van den Bovenkamp K, Noordhuis MG, Oosting SF, van der Laan BFAM, Roodenburg JL, Bijl HP, et al. Clinical outcome of salvage neck dissections in head and neck cancer in relation to initial treatment, extent of surgery and patient factors. Clin Otolaryngol. 2017;42:693–700.
95. Robbins KT, Wong FS, Kumar P, Hartsell WF, Vieira F, Mullins B, et al. Efficacy of targeted chemoradiation and planned selective neck dissection to control bulky nodal disease in advanced head and neck cancer. Arch Otolaryngol Head Neck Surg. 1999;125:670–5.
96. Hamoir M, Ferlito A, Schmitz S, Hanin F-X, Thariat J, Weynand B, et al. The role of neck dissection in the setting of chemoradiation therapy for head and neck squamous cell carcinoma with advanced neck disease. Oral Oncol. 2012;48:203–10.
97. Christopoulos A, Nguyen-Tan PF, Tabet J-C, Fortin B, Soulières D, Charpentier D, et al. Neck dissection following concurrent chemoradiation for advanced head and neck carcinoma: pathologic findings and complications. J Otolaryngol-Head Neck Surg J Oto–Rhino-Laryngol Chir Cerv.-Fac. 2008;37:452–6.
98. Chung E-J, Lee S-H, Baek S-H, Bae W-J, Chang Y-J, Rho Y-S. Clinical outcome and prognostic factors after salvage surgery for isolated regional squamous cell carcinoma recurrences. Head Neck. 2015;37:1612–7.
99. Robbins KT, Ferlito A, Shah JP, Hamoir M, Takes RP, Strojan P, et al. The evolving role of selective neck dissection for head and neck squamous cell carcinoma. Eur Arch Oto–Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol-Head Neck Surg. 2013;270:1195–202.

100. Troussier I, Klausner G, Blais E, Giraud P, Lahmi L, Pflumio C, et al. Advances in the management of cervical lymphadenopathies of unknown primary with intensity modulated radiotherapy: doses and target volumes. Cancer Radiother J Soc Fr Radiother Oncol. 2018. https://doi.org/10.1016/j.canrad.2017.10.008.
101. Troussier I, Klausner G, Morinière S, Blais E, Faivre J-C, Champion A, et al. Advances in the management of cervical lymphadenopathies of unknown primary: advances in diagnostic imaging and surgical modalities and new international staging system. Bull Cancer (Paris). 2018;105:181–92.
102. Amsbaugh MJ, Yusuf M, Gaskins J, Silverman C, Potts K, Bumpous J, et al. Neck dissection for unknown cancer of the head and neck in the era of chemoradiation. Am J Otolaryngol. 2017;38:588–92.