REVIEW ARTICLE

Recent Advances in the Management of Metastatic Neck Cancer

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ABSTRACT

One of the most important prognostic factors in head and neck cancer is the presence or absence, level, and size of metastatic neck disease.

Controversies in neck management still exist due to the paucity of quality clinical trials with most evidence extrapolated from retrospective studies. However, recent evidence has emerged to address some of these areas including the ideal management of the N0 neck, the role of sentinel node biopsy in occult neck disease, posttreatment surveillance with positron emission tomography and computed tomography (PET-CT) and incorporation of P16 status and extranodal extension (ENE) in the recent 8th edition of AJCC in nodal staging.

This paper provides an update on the current management of metastatic neck disease in the setting of squamous cancers arising from the upper aerodigestive tract.

Keywords: Chemotherapy, Computed tomography, Head and neck squamous cell cancer recurrent, Metastatic, Neck, Positron emission tomography, Radiotherapy.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the 8th most common cancer worldwide within the male population, with an increasing trend also noted amongst females.[1] Tumors of the head and neck have a great propensity to metastasize to cervical nodes. The presence of neck nodes, coupled with their size and site play a crucial factor in the overall prognosis of HNSCC.[2] Until recently, much controversy existed regarding the treatment of HNSCC due to the scant quantity of high-level data available to clinicians. The recent publication of randomized control trials (RCTs), as well as systematic reviews, has moved some way towards addressing some of the controversies in the management of metastatic neck disease.

ASSESSMENT AND STAGING

Approximately 150 lymph nodes are present on either side of the neck, with normal sizes ranging from 3 mm–3 cm, although most are <1 cm. The largest node, often referred to as the jugulodigastric node (JDN), is found in level II situated within a triangle formed by the IJV, facial vein and posterior belly of the digastric muscle. The JDN receives lymph from a large region of the neck including the submandibular region, oropharynx and oral cavity. It is crucial for clinicians to appreciate that contralateral nodal spread may occur early in tumours that either lie in or adjacent to the midline. The Memorial Sloan-Kettering group first published the widely adopted levels within the neck, containing lymph node groups, which represented the primary sites for metastases from HNSCC. A total of 6 neck levels were described, with level VII describing a chain of paratracheal nodes from the level of the suprasternal notch to the innominate artery. Further revisions included subdivisions of levels I, II and V (Table 1). Nodal staging should be radiologically confirmed and documented according to the TNM classification, prior to any medical or surgical intervention. Whilst imaging remains a key modality in the initial diagnosis, up to 33% of patients presenting with SCC of the oral cavity have occult cervical disease undetectable by conventional techniques (computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).[3] Liao et al. undertook a meta-analysis, comparing the diagnostic accuracy of various imaging modalities, including CT, MRI, PET and US, when evaluating N0 HNSCC patients. Of the 168 relevant articles which were identified, 7 studies fulfilled the inclusion criteria for CT, 6 for MRI, 11 for PET and 8 studies for USS respectively. The study reported no variation in sensitivity and specificity among the imaging modalities, with the exception of CT, which had a superior specificity compared to USS.[4]

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Table 1: Anatomical levels of the neck and boundaries

Level I
☐ Below mylohyoid muscle and above lower margin of the hyoid bone/carotid bifurcation
☐ Anterior to the posterior border of the submandibular glands (SMG)
○ Level Ia: Submental nodes, (between the anterior bellies of the digastric muscles)
○ Level Ib: Submandibular nodes (posterolateral to the anterior belly of the digastric muscles and anterior to the posterior border of the submandibular glands)
Level I I
☐ Internal jugular/deep cervical chain
☐ The base of the skull to the inferior border of the hyoid bone/carotid bifurcation
☐ Anterior to the posterior border of the sternocleidomastoid muscle (SCM)
☐ Posterior to the posterior border of the SMG
Level III
☐ Internal jugular/deep cervical chain
☐ Lower margin of hyoid to lower margin of the cricoid cartilage
☐ Anterior to the posterior border of SCM
☐ Lateral to the medial margin of the common carotid artery (CCA)/internal carotid artery (ICA)
Level IV
☐ Internal jugular/deep cervical chain
☐ Lower margin of the cricoid cartilage to a level of the clavicle
☐ Anterior and medial to an oblique line drawn through the posterior edge of SCM and the posterolateral edge of the anterior scalene muscle
☐ Lateral to the medial margin of the CCA
Level V
☐ Posterior triangle nodes
☐ Posterior to the back of the SCM and anterior to the trapezius muscle
☐ Va and Vb separated by accessory nerve
Level VI
☐ Prelaryngeal (Delphian node)/pretracheal
☐ Anterior to visceral space
☐ From the inferior margin of hyoid bone to the manubrium
☐ Anterior to levels III and IV
Level VII
☐ Superior mediastinal nodes
☐ Between CCAs, the below superior aspect of manubrium to a level of the brachiocephalic vein

Clinical Palpation

Clinical palpation is an entirely operator dependent first-line method for assessment and follows an experiential learning curve. With sensitivity and specificity of 70–80%, palpation is regarded as an inaccurate method of detecting cervical metastases, due in part to a variety of factors including; operator variability, the variability of overlying and surrounding soft tissue (such as post-radiotherapy changes), and size of nodal metastasis.[2,5] Furthermore, in particular reference to the retropharynx, some areas are inaccessible and therefore cannot be clinically assessed.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) as a modality in detecting cervical metastasis, has been routinely used since the early 1980s.[6] CT boasts a higher diagnostic accuracy in detecting metastatic neck disease when compared to clinical examination. A meta-analysis comparing CT versus clinical examination following 647 neck dissections, elicited a sensitivity of 83% and specificity and overall accuracy of 83% in CT.[7] Furthermore, positron emission tomography (PET), combined with CT can change the initial disease staging in up to 30% of patients,[2] with a far superior sensitivity in detecting occult primaries, synchronous primaries and distant disease progression.[2]

Magnetic resonance imaging (MRI) protocols include; T1/2 sequences, STIR, TIRM, DWI, perfusion +/– contrast, enabling detection of small lesions, whilst simultaneously permitting assessment of local tumor infiltration, and aiding operative planning. MRI demonstrates sensitivities of 82% and a specificity of 66.7% in determining soft tissue and bone/ marrow infiltration. MRI is comparable to CT in terms of sensitivity and specificity, although MRI demonstrates a higher sensitivity with respect to soft tissue assessment.[8]

Ultrasound Scan (USS) and Fine Needle Aspiration Cytology (FNAC) or Core Biopsy (CB)

A high spatial resolution, ease of multi-planar scanning, power Doppler, and the ability to undertake guided FNAC give USS a significant advantage over other imaging modalities when assessing for nodal disease in HNSCC.[9] Ultrasound has demonstrated sensitivities of 87% in the diagnosis of metastatic neck cancer. The modality does, however, require both expertise and experience, and when these criteria have been achieved, high specificities of 98% have been reported.[2] The disadvantages include, operator dependency, and an inability to visualize structures beyond bony and air interfaces due to the inability of sound waves to transmit through such mediums.[10] Despite its widespread use in clinical practice, USS is yet to provide conclusive differentiation between benign and malignant disease. FNAC remains particularly useful in the assessment of palpable lymphadenopathy in the carcinoma of unknown primary (CUP) setting. A core biopsy provides the additional benefit over FNAC of providing tissue which can be subjected to immunohistochemical analysis, including isolation of HPV or Epstein-Barr virus (EBV) transcripts, raising the suspicion of a primary site within the oropharynx or nasopharynx respectively. Accuracy rates of FNAC are reported to be as high as 90%.[11]

Sonoelastography is a relatively novel modality, which has demonstrated some promise in the evaluation of neck nodes.[12] Low-amplitude and frequency shear waves are propagated through tissue, with real-time Doppler used to image the resulting vibration pattern. The reduction in the amplitude of vibration as a result of tumor inhomogeneity is subsequently measured.

Positron Emission Tomography and Computed Tomography

This modality combines 18 F-fluorodeoxyglucose PET (18F-FDG PET) and CT to highlight both structural and metabolic changes within tumors and is a reliable modality in assessing response to treatment.[8] Unfortunately, PET-CT is relatively nonspecific, with tracer uptake also demonstrated within inflammatory pathology.[10] Negative predictive values of 94.5% and 96% have been demonstrated through meta-analyses

of predominantly small cohort single-center studies in patients with HNSCC.[13,14] Kyzas et al. aimed to assess the diagnostic accuracy of 18F-FDG PET in detecting lymph node metastases in patients with HNSCC through a meta-analysis, whilst also providing comparisons against conventional modalities. Across 32 studies [(n = 1236), 18F-FDG PET sensitivity was 79% (95% confidence interval CI = 72–85%), with a specificity of 86% (95% CI = 83–89%). In the case of cN0 patients, the sensitivity of 18F-FDG PET was remarkably low at 50% (95% CI = 37–63%), although the specificity was 87% (95% CI = 76–93%). Where both 18F-FDG PET and conventional modalities were utilized, the sensitivity and specificity of 18F-FDG PET was 80 and 86%, and 75% and 79%, respectively for the conventional modalities.[15] Calls to implement PET-CT in routine practice are not only to aid in staging and planning, but to also exclude distant metastatic disease, which would otherwise be missed on conventional imaging, and invariably advocate a palliative approach.

Open Biopsy

Open biopsies are generally avoided as an initial diagnostic tool and only adopted in certain situations, such as unavailability of FNAC or core biopsy, equivocal/nondiagnostic results, or when the clinical or radiological findings are consistent with a diagnosis of either lymphoma or anaplastic carcinoma. When all avenues have been exhausted in the assessment of a suspicious neck node, an open biopsy can be undertaken, namely a selective neck dissection, as there is no body of evidence to suggest that this alters the overall prognosis, should the correct treatment be instigated <6 weeks.[16]

Treatment Options

Surgery

Neck dissection has historically been the surgical treatment of choice in metastatic neck disease. The readily accepted neck dissection terminology produced by the American Academy of Otolaryngology and Head and Neck Surgery (1991), has been updated by the committee for Neck Dissection Classification of the American Head and Neck Society (Table 2).[17] A trend now exists to categorize neck dissections into two distinct subdivisions; comprehensive (removal of levels I–V) and selective (<5 levels).[2,17] In an era

Table 2: Neck dissection classification

(1) Radical neck dissection (RND)	Removal of levels I–V, accessory nerve, IJV and SCM
(2) Modified radical neck dissection	Removal of levels I–V dissected; preservation of one or more of the accessory nerve, IJV or SCM (types I, II, III respectively)
(3) Selective neck dissection	Preservation of ≥ 1 level of lymph nodes
(4) Extended radical neck dissection	Removal of ≥1 additional lymphatic and/or non-lymphatic structures(s) relative to an RND (level VII, retropharyngeal lymph nodes, hypoglossal nerve)

of increased chemoradiotherapy (CRT) use, with the need for less extensive surgery, there have been increased calls for further revisions due to some dissections not falling within distinct categories.[18] There is conclusive evidence to suggest low long-term morbidity in selective compared to radical neck dissections (RND).[19] Any surgical intervention must be validated by an accredited multidisciplinary team (MDT), comprising of members routinely involved in the delivery of care for head and neck cancer patients.

Radiotherapy and Concurrent Chemotherapy

Accredited departments are responsible for the delivery of megavoltage photons, with similar principles adopted as described for surgery. As the T stage increases, the likelihood of microscopic spread to other nodal groups also increases. As a result, a larger volume of tissue irradiation is required.[2] Coventional radiotherapy (RT) consists of a once-daily treatment (fraction) over a 3–7 weeks period, with cumulative doses ranging from 50–70 Gy.[20] Whilst the morbidity associated with surgery is confined to the neck; RT has a multitude of side effects due to the field of irradiation, and often includes salivary glands and some viscera, resulting in debilitating mucositis and xerostomia. Conventional treatment techniques have now been replaced by intensity modulated radiotherapy (IMRT), and in particular for bilateral irradiation where the side effect profile is more significant. IMRT produces an even distribution of radiation dose within a target volume with irregular contours, subsequently sparing normal tissue in close proximity to a tumor. This provides scope for escalating radiation dose if required,[20] as well as improving the QOL, at least in the early stages of treatment.[21]

Following the publication of level 1 studies, there has been an upward trend in the use of primary and concomitant chemotherapy (CCT).[22] Studies have demonstrated that both overall and progression-free survival in advanced head and neck cancers is improved, both in a primary and post-operative scenario, although morbidity is higher in patients who have previously undergone RND.[2]

Management Strategies for Various Neck Nodal Stages

Nodal treatment can either be elective, or therapeutic, in a clinically negative or positive neck respectively. The recent 8th edition of the AJCC has updated staging for non–p16+, non–EBER+, cancers of the head and neck nodal staging (Table 3) with the addition of extranodal extension (ENE) as a prognostic variable, in addition to number and size of metastatic lymph nodes. Determining unambiguous ENE will be challenging with current imaging modalities but should support clinical ENE defined by the invasion of skin, infiltration of musculature/dense tethering to the adjacent structure, dysfunction of cranial nerve, the brachial plexus, the sympathetic trunk or phrenic nerve. Pathological ENE has been defined as the extension of metastatic carcinoma from within the lymph node through the fibrous capsule and into surrounding connective tissue, regardless of the presence of stromal reaction.[23]

Clinical Node Negative (N0) Neck (New Primary)

The assessment and management of the N0 neck with regards to elective dissection versus watchful waiting continue to remain an area of debate. Detection rates of micrometastasis (metastasis <2 mm in size) in lymph nodes through clinical and radiological correlation is poor.[24] The rationale for elective treatment is due to the relatively high incidence of subclinical disease in elective RND specimens. Several retrospective series have demonstrated the presence of micrometastasis in up to 25% of patients[25] based on histological evaluation of neck dissection specimens in patients deemed to be node negative (N0), guiding a risk-based approach in the adoption of prophylactic treatment of the neck (Flow chart 1).
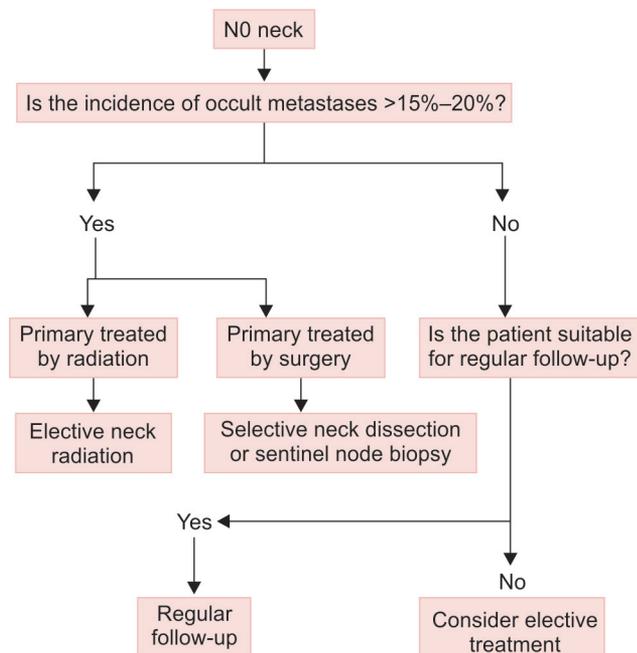
During the 1990s, a period where RND was widely accepted as the only procedure for elective neck treatment, the risk-benefit analysis was undertaken through retrospective studies. These suggested prophylactic treatment of the neck in instances where risk of occult nodal metastasis

Table 3: N staging for cervical metastasis

N category	Criteria
Nx	Unable to assess regional nodes
N0	No regional metastasis
N1	Metastasis in a single ipsilateral node ≤3 cm in greatest dimension, ENE-negative
N2a	Metastasis in a single ipsilateral lymph ≥3 and ≤6 cm in greatest dimension, ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, ENE-negative
N2c	Metastasis in bilateral/contralateral lymph nodes, ≤6cm in greatest dimension, ENE-negative
N3a	Metastasis in a lymph node ≥6cm in greatest dimension, ENE-negative
N3b	Metastasis in any node(s), ENE-positive

ENE = extra-nodal extension

Flow chart 1: Algorithm for management of the N0 neck (Paleri V, Urbano TG, Mehanna H, Repanos C, Lancaster J, Roques T, et al. Management of neck metastases in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S161-S92)

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                    ┌─────────┐
                    │ N0 neck │
                    └────┬────┘
                         │
      ┌──────────────────────────────────────┐
      │ Is the incidence of occult metastases │
      │              >15%–20%?                 │
      └──────────────────────────────────────┘
            │                          │
           Yes                         No
      ┌─────┴──────┐                   │
      │            │                   │
┌──────────┐ ┌──────────┐   ┌──────────────────┐
│ Primary  │ │ Primary  │   │ Is the patient   │
│ treated  │ │ treated  │   │ suitable for     │
│by radiation│ │by surgery│   │ regular follow-up?│
└────┬─────┘ └────┬─────┘   └────────┬─────────┘
     │            │                   │
┌──────────┐ ┌──────────────┐    Yes      No
│ Elective │ │ Selective neck│     │        │
│   neck   │ │ dissection    │     │        │
│ radiation│ │ or sentinel   │     │        │
└────┬─────┘ │ node biopsy   │     │        │
     │       └───────┬───────┘     │        │
     │               │             │        │
     └──────── Yes ◄──────────────┘         │
                  │                          │
            ┌──────────┐              ┌──────────────┐
            │ Regular  │              │ Consider     │
            │ follow-up│              │ elective     │
            └──────────┘              │ treatment    │
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was >20%, although there has also been advocacy in those with a risk of 5–15% given the low morbidity associated with both treatment modalities.[2] All SCC's of the upper aerodigestive tract, with the exception of T1–2 carcinomas of the glottis and select T1 cancers of the oropharynx would fall within the aforementioned category of an occult metastatic risk of >15%.

Protagonists of elective neck dissection cited lower relapse rates and better overall survival,[26] whilst others considered the evidence to be non-definitive.[27,28] Data from prospective trials further added to the conflicting evidence.[29] An observational approach would have served to reduce an additional surgical procedure in 70% of patients who were deemed to be node-negative on histopathological evaluation, whilst providing simultaneous cost-benefit and reduced overall morbidity.[30] Additionally, early nodal metastasis could be detected with the use of USS during the observational period, in the absence of compromised outcomes.[29]

Two recent major studies have attempted to address concerns in regards to the ideal management of the N0 neck in oral cavity SCC. D'Cruz et al., recently published the largest single-center RCT to date, comparing elective neck dissection (END) versus therapeutic neck dissection (TND) in 500 patients with T1/T2 N0 SCC of the oral cavity. At 3 years, END reported improved rate of overall survival compared to the TND group (80% vs. 67.5%, $p = 0.01$) and disease-specific survival in the END than the TND group (45.9% vs 69.5%, $p < 0.001$), with relapse within the TND presenting at a more advanced stage,

with higher incidences of extracapsular spread.[30] The transferability of the study findings have been questioned, as it only utilized ultrasound scan in the evaluation of the N0 neck where often now CT is preferred and the disproportionate use of adjuvant radiotherapy between the two groups (49% END *vs.* 34% TND) not included in the multivariate analysis.

Sentinel node biopsy (SNB) is not widely recognised as standard care in early oral and oropharyngeal cancer but does possess the ability to detect occult metastases in HNSCC,[31,32] through typical drainage patterns to echelon nodal basins depending upon the primary site. Particular promise has been seen in reducing unnecessary neck dissection (with consequent improved function, reduced morbidity[33,34] and significantly reduced inpatient stay)[35] allowing for comprehensive salvage surgery in a minimally disturbed surgical bed and identifying the need for unilateral versus bilateral neck dissection in midline tumours.[3]

The Sentinel European Node (SENT) trial, the largest observational prospective study to date incorporating fourteen European centres, recruited 415 patients with radiologically staged T1–T2 oral SCC. A sentinel node (SN) was detected in 99.5% and positive SNs were found in 23%. False-negative result occurred in 14% (7% were amenable to a salvage procedure) with recurrence in 22 patients following a positive SNB and SND. Disease – specific survival was 94% (at 3-years) with sensitivity of SNB of 86% and negative predictive value of 95%. The low rate of regional recurrence within the study, counters the historical concerns of dissemination of tumour within the neck when biopsying suspected neck metastasis[36,37] Of the 47 patients with midline tumors who would have otherwise undergone a bilateral neck dissection, 16 patients based on a positive SN went onto have a neck dissection of which only 8 required a bilateral neck dissection. The study suggests SNB to be both reliable and safe for staging the clinically N0 neck in T1/T2 oral cancers. However, as the study authors highlight, further evaluation through prospective RCTs is needed and refinement of the SNB technique will improve both ease and accuracy of sampling through future incorporation of intraoperative 3D navigation,[38] new tracers[39] and fluorescent markers.[40]

Currently, the choice of treatment at present for the N0 neck lies between modified radical neck dissection (MRND) and selective neck dissection (SND), with prospective studies demonstrating equal effectiveness of the SND compared to MRND, with reduced morbidity rates.[2] There is no further role for the historically accepted RND in the treatment of the clinically N0 neck.[41] SND of levels I–III should be undertaken in the case of oral tumors and levels II–IV in cases of oropharyngeal, laryngeal and hypopharyngeal SCCs. Level IIb dissection is seldom necessary for most

patients with N0 disease, as metastasis to this subsite is <2%.[2] Clearance of this level during SND involves operating through a significantly narrow field, with marked retraction of the SCM. This will invariably result in traction injury of the accessory nerve, and a subsequent neuropraxia resulting in shoulder dysfunction for very little oncological benefit in laryngeal cancer (although slightly higher metastatic rates of 3.4% are reported in the case of SCCs of the oral.[42] There also remains a consensus in addressing level IV in oral SCCs due to the presence of skip lesions, in tongue base tumors,[43] with reported rates of 2%.[44]

Elective neck irradiation is as effective as elective neck dissection in the control of subclinical disease, with reported rates of 90%.[2] When irradiating the primary site, nodes deemed highest risk of harboring occult disease (the echelon lymph nodes), are also incorporated within the treatment field. Literature comparing elective ND and neck irradiation in tumors of the oral cavity, oropharynx, and larynx demonstrated no statistical difference in local control at 60 months. Local control was also statistically better in patients with hypopharyngeal cancer, treated with RT.[2]

In the case of a unilateral primary with ipsilateral nodal disease, historical data suggest a significantly high incidence of occult metastases within the contralateral neck, ranging between 30% and 70%, especially in supraglottic,[45,46] hypopharyngeal[47,48] and oropharyngeal tumors.[49] In advanced primaries, with a high risk of occult spread, contralateral neck treatment should be considered.

Large retrospective series data has also reported the risk of contralateral nodal involvement from a primary site, with contralateral neck treatment advocated in instances where the occult metastatic risk exceeds 20%. This includes tumors encroaching or passing the midline. In instances where treatment of the bilateral neck is indicated, nodal irradiation may be preferred due to the reduced associated morbidity.[2]

The untreated N0 neck requires long-term surveillance, with early detection and treatment essential prior to disease becoming clinically detectable. Consideration should as such be directed to routine USS and FNAC.[29] Despite routine surveillance, clinicians should be aware that patients within this cohort will present clinically with overt disease and require a therapeutic ND.

Disease Recurrence at the Primary Site

If the neck has been incorporated within the treatment field, occult metastatic rates remain as low as 5%.[2] Salvage ND is associated with greater rates of morbidity. As such, elective ND in the salvage setting may not be required if primary resection or reconstruction does not require access to major vessels.

Node-positive Neck

Active treatment is required in the instance of either clinical or radiologically positive nodal disease, with level 1 studies formulating algorithms to guide clinicians in the treatment of metastatic disease based on the treatment to the primary site,[50] There is a high risk of occult metastasis to clinically uninvolved levels, and depending on the primary site, treatment to these regions may also be warranted. Level V is least likely to be involved, with studies showing positive nodes in up to 7% of patients undergoing a RND.[2]

N1 Disease

Data suggest that single modality therapy in ipsilateral solitary nodal disease (where nodes are <3 cm in size) is adequate. In the instances where surgery is the modality of choice, SND may be adequate.[2] Most patients will require postoperative RT given half of all N1 patients will have their nodal status upstaged following pathological evaluation. In the absence of bulky disease, SND with postoperative RT achieves local rates equivalent to comprehensive ND.[41] An adequate response is demonstrated in patients with nodes <3 cm, with regional control rates following RT, improved in patients with nodes <2 cm. Concurrent CRT offers excellent control rates,[51] with no further treatment warranted for complete responders, and an ND advocated in partial responders.

N2a/b Disease

A wide array of practice is associated with advanced nodal disease due to the lack of prospective RCTs.[52] The treatment for this subset of patients is dependent on the management of the primary, and if deemed operable, a comprehensive neck dissection should be offered. If macroscopically clear of disease, an MRND with sparing of the accessory nerve achieves comparable control to an RND.[53,54] Postoperative adjuvant treatment is recommended in larger nodes, given the risk of extranodal extension is higher.

With the increasing use of chemoradiotherapy in the primary, there was wide variation in practice in the management of advanced nodal disease (N2 or N3) as retrospective studies had shown persistent nodal disease in 40% of patients post chemoradiotherapy.[55] As a result, the practice of planned neck dissection either before or after chemoradiation continued.[52] The need for a neck dissection post chemoradiation has been addressed with the recent publication of the prospective PET-Neck RCT.

The PET-neck phase III RCT[22] compared PET-CT guided surveillance versus a planned ND for ≥N2 disease, where the primary treatment modality was CRT. This prospective trial, recruiting 282 patients to each treatment arm, demonstrated comparable survival outcomes in both p16 positive and negative patients, with a minimum follow-up period of 2 years. An active surveillance strategy with PET-CT led to fewer ND procedures in 80% of patients, and a subsequent reduction in morbidity, and a per patient cost saving of £1415. There were an additional 0.07 additional quality-adjusted life years (QALY) in contrast to elective ND. Hence, the current standard of care is a PET-CT scan 8 to 12 weeks following completion of CRT (due to false positive rates at an earlier stage), and elective neck dissection in those who demonstrate an incomplete response. Complete response on PET-CT requires no further treatment.[13] The extent of salvage procedures is usually based on local guidance, although a trend is developing where limited clearance of involved levels or adjacent levels is undertaken. In instances of unresectable disease, RT or CRT is the sole modality available, and one must recognize the low likelihood of a curative outcome.[2] In cases of small but inaccessible tumors, with advanced neck disease, resection of any nodal disease can be followed by RT +/– CT to a primary tumor and RT to the contralateral neck. There must be an appreciation that such a treatment strategy may result in a delay in treating the primary disease, and thus result in potential disease progression.[2,13,56]

N3 Disease

It is essential to accept that patients presenting with nodes >6 cm will have some form of fixation to skin or underlying structures. Any decision to intervene surgically will be dependent on a multitude of factors including; the site of primary disease, presence/absence of fixation, structures involved in fixation, operator experience, and patient factors. Patients with N3 disease tend to present with distant metastatic disease, and PET-CT imaging is recommended to evaluate the extent of the disease fully.

Caution is advised in extrapolating the findings of PET-Neck trial to N3 (stage IVb), as this group formed a very small cohort (n = 17) within the study. Surgery in the N3 neck should always be in conjunction with CRT or RT alone, either pre- or postoperatively.

Adjuvant Radiation for the Postoperative Neck

Literature has quoted post-concurrent CRT complication rates in neck dissections to be as high as 28%.[57] In the instance where the primary treatment modality is surgery (N2/3) neck disease, a RND is traditionally adopted. Disease control rates are comparable when RND or MRND is undertaken within a select group of patients.[41]

Controversies exist regarding carotid artery resection, particularly given extension into the adventitia occurs in 42% of patients, with luminal involvement rarely reported.[58]

Literature advocates the addition of RT postoperatively, to increase local control, and in particular, where adverse features are present (extracapsular spread, positive margins, ≥T3 disease, multiple nodes, level IV/V involvement, perineural invasion, vascular embolism).[59] Randomized trials undertaken by the European Organisation for Treatment of Cancer (EORTC) and the Radiotherapy Oncology Group (RTOG), have demonstrated improved postoperative control with CCT in groups where margins are positive, or extracapsular spread has been detected.[60] In patients with ≥2 lymph nodes as their only risk factor, in the absence of extra-capsular spread, did not benefit from the addition of chemotherapy. If the primary site is amenable to non-surgical intervention, the neck should be treated simultaneously. In the instances of ≥N2 disease, this will involve CRT.

Human Papilloma Virus-associated Neck Disease

A substantial amount of research has been undertaken in this distinct subset of head and neck cancer, which continues to increase in incidence within many parts of the world.[61] The overwhelming majority of HPV associated cancer is observed within the oropharynx, and these patients tend to present with advanced disease, and extra-nodal extension. At present, no consensus exists as to whether HPV associated oropharyngeal squamous cell carcinoma (OPSCC) should be treated any differently to non-HPV HNSCC with nodal metastasis, despite better survival outcomes and results of de-escalation trials are eagerly awaited. The recent 8th edition of AJCC has now updated nodal staging in HPV associated OPSCC into both clinical and pathological stages (Table 4) reflecting that number rather than size and site of node impacted on survival.

Table 4: Clinical (c) and pathological (p) nodal staging in HPV associated OPSCC

N category (c)	Criteria
Nx	Unable to assess regional nodes
N0	No regional
N1	One or more ipsilateral nodes ≤6 cm in greatest dimension
N2	Contralateralal or bilateral nodes ≤6 cm in greatest dimension
N3	Lymph node >6 cm

N category (p)	Criteria
Nx	Unable to assess regional nodes
N0	No regional
N1	Metastasis in ≤4 lymph nodes
N2	Metastasis in >4 lymph nodes

Assessing Adequacy of Treatment

Following RT, neck node size and fixity are good predictors of response rate and local control. In the case of N2 or N3 disease, there is a poor correlation between clinical and pathological response post-CRT. Owing to advances in cross-sectional imaging, recurrence rates as low as 10% have been found amongst the 30–45% of patients, who were deemed to have demonstrated a complete response following CRT.[62,63] As a result, image-guided response-based approaches have gained prominence, without high-level evidence. Studies comparing CT with PET-CT demonstrated a higher efficacy of PET-CT in instances of advanced HNSCC and in particular those within a high-risk category with; a significant history of smoking, alcohol excess, or p16 -ve nonoropharyngeal malignancies.[64] PET-CT has also been shown to be more costeffective[65] and accurate in identifying complete nodal response, particularly in p16 +ve patients (93% *vs.* 50% in standard CT). A planned PET-CT scan 10 to 12 weeks post CRT is now the accepted standard of care, with a negative scan indicative of an adequate response. High standardized uptake values (SUVs) are associated with residual disease and can be used as a decision-making tool for salvage surgery.[13,14,56]

Management of Recurrent Disease of the Neck

Any salvage surgery should be preceded by a thorough assessment to exclude distant metastasis. In the instances where recurrence has occurred following CRT and is deemed resectable, then surgical intervention through an oncologically adequate SND, with the understanding that associated morbidity is higher, is recommended. Where the disease is unresectable, re-irradiation may be considered, especially if the patient is >2 years after primary treatment. The introduction of IMRT and proton therapy results in significant sparing of critical neurological and vascular structures and means such treatment is more realistic when compared to previous regimes and modalities. Where recurrence follows primary surgical resection, re-resection combined with RT or primary RT +/− chemotherapy remain viable.[2]

Palliative Care

Patients with incurable nodal disease in the absence of distant metastasis present a significant clinical conundrum, given survival can extend for months and occasionally longer. Early involvement of the palliative care team plays a pivotal role in controlling the sequelae of advanced HNSCC,[20] particularly before the development of associated complications. Fungating nodes can have a detrimental impact on psychosocial function, and implications on speech and swallowing require early

speech and language therapy (SALT) and dietetic input to discuss the benefits and risks of overmedicalizing through enteral feeding. A role for palliative surgery, CCT (untreated HNSCC is usually chemosensitive, with response rates lower in recurrent disease), or RT, in improving patient quality of life exists in certain circumstances but should be used judiciously to avoid painful mucositis and subsequent distress with modest therapeutic gain. Overall prognosis, patient goals, morbidity, and likely benefits must be discussed so that expectations are realistic.

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