Lymph Node Disease and Advanced Head and Neck Imaging: A Review of the 2013 Literature

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Abstract Detection and differentiation of lymph node disease in the head and neck can be very difficult but is of importance for staging and treating head and neck (H&N) tumors. This topic is therefore a source of much ongoing study. With constantly evolving imaging technology, there is an ongoing need for evaluation of both new and improved techniques, and potential new uses of current modalities. CT, MRI, and PET are examined in this article, with a focus on H&N disease processes and the technical aspects of imaging. The goal of this review article is to bring the reader up to date on pertinent articles in advanced imaging of H&N lymph node disease from the year 2013.

Keywords Lymph nodes · Head and Neck · Radiology · Advanced Imaging

Introduction

The presence of lymph node metastases is one of the most important prognostic indicators in head and neck squamous cell carcinoma (HNSCC). Five year survival is reduced by 50 % when a single metastatic cervical lymph node is present, and drops to 25 % in the setting of a contralateral metastatic cervical lymph node [1, 2]. In addition, nodal metastatic disease not only increases the risk of local recurrence but also increases the risk of distant metastases

[3, 4]. Accurate lymph node classification and staging is therefore a vital component of tumor imaging and previous work has been done to unify both in the clinical and radiological spheres [5, 6].

Two excellent review articles in 2013 describe a systematic approach to the evaluation of cervical lymph nodes and the imaging pitfalls in staging nodes in head and neck (H&N) cancer for routine CT, MR, PET and ultrasound neck evaluation [7, 8]. They also quote key original articles on the use of these modalities in solving complex clinical problems in patients with H&N cancer [9–14]. The purpose of this review article is to update the reader with the literature in 2013 on MR, CT and PET techniques and their clinical applications. We will first review CT imaging of extracapsular spread of tumor (ECS) and the detection of residual nodal metastases in the treated neck. Next we will review advances in MRI and specifically look at techniques for differentiating tumor, infection and normal nodes with diffusion, perfusion and high-resolution rapid imaging. Finally we will review advances in PET imaging and PET/CT and PET/MR.

CT of Lymph Nodes: The Dilemmas of ECS & Baseline Treatment Scans

Extracapsular Spread of Tumor (ECS)

Nodal ECS is an important topic that was investigated in multiple articles in 2013. The presence of ECS in patients with HNSCC is associated with a significant decrease in overall survival and increased rates of both regional recurrence and distant metastases [15–21]. De Juan et al. [22•] proposed a new classification system incorporating ECS to staging, noting that it is not included in the existing TNM classification system. They demonstrated a

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significant difference in five-year survival between patients without nodal metastases on neck dissection (pN0) and patients with nodal metastases without ECS (pN +/ECS-), as well as between these patients and patients with nodal metastases with ECS (pN +/ECS +). The proposed classification considered both pN stage and ECS, and this classification system achieved a better prognostic discrimination than the currently used pTNM classification system. This is a pathology study, however imaging studies were also published in 2013 evaluating the ability of imaging to detect ECS. Url et al. [23] retrospectively looked at the detection of ECS in cervical lymph node metastases in a small series of patients with HNSCC. Using the single criterion of infiltration of perinodal tissues in radiologically N + necks they found a sensitivity of 73 % and specificity of 91 %, which is similar to prior studies (Fig. 1). Chai et al. [24] retrospectively evaluated contrast enhanced neck CT scans in 100 patients with HNSCC for the presence of ECS. They concluded that CT is not reliable in determining the presence of ECS, since they found poor detection. They concluded that CT findings suggestive of ECS should not be relied upon for treatment planning in HNSCC patients. Kann et al. [25] retrospectively assessed ECS as an independent prognosticator in 111 patients with stage III and stage IV oropharyngeal carcinoma. Such an independent factor could help to guide therapy in patients who have primary concurrent chemoradiation and no pathological proof of ECS. Their study found a significantly worse overall survival, worse progression free survival, and worse distant control in the group with radiographic evidence of ECS. They did note that due to the small number of cases that included surgery, they could not reliably address the accuracy in which radiographic ECS predicted pathologic ECS. Randall et al. [26] performed a retrospective case-control study to examine central nodal necrosis in predicting ECS among oral cavity squamous cell carcinoma patients, 17 of whom had pathological proven ECS and 23 of which were pathologically proven negative for ECS. They found that central node necrosis was a significant and strong predictor of ECS, with an odds ratio of 12.1 on multivariate analysis.

It should be noted that there is a wide variation between pathologists evaluating nodal ECS, with interobserver variability kappa values ranging from 0.14 to 0.75 [27]. In addition, there are no standard pathologic ECS grading criteria at this time [28]. In light of this it is not clear whether surgical pathology or pre-operative imaging should be the gold standard for the detection of ECS, or perhaps an alternative imaging feature such as central nodal necrosis should be used to predict overall survival in place of pathological ECS [26].

Maxwell et al. [29] retrospectively looked at ECS in HNSCC and the impact of cancer site (oropharynx versus oral cavity) and human papillomavirus (HPV) status,

Fig. 1 Extracapsular spread of tumor on CT. Axial (a) contrast enhanced CT scan shows a right level 5 lymph node that has a shaggy, irregular border. Coronal (b) and sagittal (c) CT images in the same patients show that there are multiple nodal conglomerates, noting that the same one as in the axial plane in (a) again demonstrates an irregular border

noting that a reevaluation of ECS in oropharyngeal cancer is important given the increasingly used minimally invasive surgical techniques such of trans-oral robotic surgery (TORS) and laser microsurgery instead of chemoradiation.

Fig. 2 HPV positive metastatic oropharyngeal HNSCC. Axial CT image shows predominantly cystic bilateral level 2 nodes in a 64 year old patient with HPV positive base of tongue squamous cell carcinoma

They found that ECS was a significant, independent adverse factor on 3 year disease specific survival in patients with oral cavity cancer but not in patients with oropharyngeal cancer. Cantrell et al. [30] performed a retrospective blinded matched-pair analysis evaluating the imaging characteristics of HPV-positive and HPV-negative oropharyngeal cancers and metastatic lymph nodes. They found that cystic nodal metastases were more likely to be found in HPV-positive cancers (Fig. 2) than in HPV-negative cancers, but found no significant difference in ECS in nodal metastases.

Baseline Post-Treatment Nodal Evaluation

Following definitive chemoradiation for oropharyngeal HNSCC, baseline imaging is obtained at 6–8 weeks to determine whether there is residual disease that warrants surgical resection. Hamilton et al. [31] retrospectively evaluated contrast-enhanced neck CT scans in order to create a multiparametric scoring system that might better predict persistent nodal metastases. The study compared pre and post treatment scans in 138 patients with oropharyngeal HNSCC, assigning two points for new necrosis and 1 point each for residual necrosis/cyst, new calcification, ring enhancement, extranodal disease, and ≤ 50 % diameter decrease in nodal size (if the node was initially more than 1.5 cm). A score of 0–1 found 29 patients without disease and zero patients with positive disease. Patients with a score of 5–6 had five patients with positive disease and zero patients without disease. The authors suggest that the remaining intermediate scores allow for stratification of nodal positivity [31].

Fig. 3 Patient with a large hypopharyngeal HNSCC and nodal metastases. A. Note the central necrosis within the metastatic node on the DWI image (a) that appears as increased ADC (b). The same patient has a metastatic level 1 node on DWI (c) that shows more diffusely low ADC (d). Images courtesy of Ashok Srinivasan, University of Michigan

MR of Lymph Nodes: Diffusion, Perfusion & Rapid Imaging Sequences

MR Diffusion & ADC Values

MR diffusion weighted imaging (DWI) shows promise for more detailed evaluation of lymph nodes and specifically determining the presence of metastatic disease. Driessen et al. [32] performed a systematic literature review looking at DWI in the detection of nodal metastatic disease and in the evaluation of primary HNSCC and local recurrence. They reviewed three nodal metastatic disease articles of patients with previously untreated HNSCC that went on to surgery. These studies found the accuracy of DWI to range from 85 to 91 % with negative predictive values higher than 91 %, but acknowledged that literature is sparse and varying ADC thresholds were reported. They also noted that when measuring nodal ADC values, the inclusion of necrotic and cystic areas will elevate values, and one of the three studies included such areas during their nodal evaluation. This is demonstrated in Fig. 3.

Lee et al. [33] evaluated ADC values at 3T to predict cervical nodal metastases in head and neck cancer in a group of 22 untreated patients. Prior studies performed at 1.5T provided cutoff ADC values ranging from 0.94 to $1.38 \times 10^{-3} \text{ mm}^2/\text{s}$. Lee's study at 3T determined an ADC

Fig. 4 Extracapsular spread of tumor on CT and MRI. Contrast enhanced CT scan shows a left level 3 lymph node that lacks a fat plane between the node and the sternocleidomastoid muscle (**a**). Axial

T2 MR images (**b, c**) shows that the node has an irregular border and that there is soft tissue infiltration of the muscle

cutoff value of $0.851 \times 10^{-3} \text{ mm}^2/\text{s}$ to best differentiate malignant from benign lymph nodes, with an overall sensitivity of 91.3 % and specificity of 91.1 %. When only considering lymph nodes over one centimeter in size, they determined even higher values with sensitivity of 100 % and specificity of 91.8 %. They noted that their ADC cutoff may be higher due to their selection of a lower b2 value of 800 whereas the other studies had selected a b2 value of 1,000.

Other papers have evaluated ADC values to help distinguish metastatic lymph nodes from infectious nodes. Zhang et al. [34] studied ADC values of both the solid and necrotic portions of cervical lymph nodes, finding that both components could help in differentiating the causes of lymphadenopathy within a study group of metastatic, lymphomatous, and tuberculous nodes. Differentiation of lymphomatous from non-lymphomatous lymphadenopathy was much more effective than differentiating metastasis from tuberculosis. Furthermore, they found that the ADC value of the necrotic nodal portion was especially helpful in distinguishing metastases from tuberculosis. The optimal ADC threshold was found to be $1.59 \times 10^{-3} \text{ mm}^2/\text{s}$ with a sensitivity and specificity of 88 and 100 % respectively. Kato et al. [35] also looked at necrotic areas in cervical lymph nodes in a study group that included nodes with suppurative lymphadenitis, lymphoma, thyroid and squamous cell carcinoma metastases. They found that ADC values in necrotic areas were lower in suppurative lymphadenitis ($0.89 \times 10^{-3} \text{ mm}^2/\text{s}$) compared to that in nodal metastases ($1.46 \times 10^{-3} \text{ mm}^2/\text{s}$). They also calculated a ratio of DWI signal intensity of necrosis relative to the spinal cord at the level of the lymph node in question, and found that the ratio was higher in suppurative lymph nodes (2.50) when compared to malignant nodes (1.29). Finally, they also found that the same ratio applied to T1 post contrast values yielded a higher result in thyroid cancer (1.95) compared to suppurative lymphadenitis

(0.87), lymphoma (0.95), and squamous cell carcinoma metastases (0.92), which was felt to be due to the T1 bright signal intensity inherently associated with the intranodal presence of thyroglobulin.

Extracapsular Spread of Tumor (ECS)

Lodder et al. [36] retrospectively studied the ability of MRI to detect ECS in 39 patients who had HNSCC that had been evaluated pre-operatively and subsequently underwent neck dissection. Using nodal measurements in conjunction with radiological and surgical designated neck nodal levels, a retrospective topographical correlation was performed. Sixty lymph nodes were selected for radiographic study by two radiologists with twenty felt to represent ECS by overall MR characteristics. The overall radiologist impression had a sensitivity of 60 % and specificity of 93 %. However, since this overall impression in not a generalizable criterion, the authors noted the need to depend on well trained H&N radiologists. The sole finding of infiltration of adjacent planes however did have a sensitivity of 50 % and a specificity of 100 % (Fig. 4), which the authors suggest may be high enough to direct treatment planning. Aside from the retrospective nature of the study, the authors noted limitations of the lack of clinically N0 necks, and the inherent limitation of MRI in that it cannot assess microscopic ECS.

Rapid MRI Techniques for Detecting Nodal Disease

A study by Finkenzeller et al. [37] evaluated post-contrast T1 BLADE (Siemens propriety name for periodically rotated overlapping parallel lines with enhanced reconstruction [PROPELLER]) versus turbo-spin echo (TSE) T1 post-contrast, both with fat-saturation, in the MRI of the neck, using two versions of the technique, BLADE and BLADE-IR (with inversion recovery). BLADE has

previously shown improvement in image quality by reducing patient motion artifacts [38] and pulsation artifacts related to vascular flow [39, 40] and bowel peristalsis [41, 42]. Although the study found that pulsation artifacts were reduced and upper thoracic structures were thereby better delineated, the TSE T1 technique showed better contrast between lymph nodes and fat. There were a small number of cases (40) but they noted a trend toward the TSE technique for the overall detection of lymph nodes. They postulated that the longer TE inherent in the BLADE technique ($TE = 10/23/56$ for TSE/BLADE/BLADE-IR respectively) and resultant loss of T1 contrast may have been the reason for decreased lymph node conspicuity, while also noting that they performed both BLADE techniques after the standard TSE T1 sequence which may have resulted in contrast washout leading to decreased lesion detection.

DCE Perfusion MRI

Dynamic contrast-enhanced (DCE) Perfusion MRI is a relatively new technique that in the H&N is still mostly used in the realm of research, but it may have future use as an imaging biomarker. Chawla et al. [43•] studied the utility of DWI and DCE-MRI in predicting response to chemoradiation therapy in patients with HNSCC, evaluating both the primary tumor and metastatic lymphadenopathy. After statistical analysis, they found that ADC and DCE-MRI parameters for the primary tumor and metastatic cervical lymphadenopathy did not show statistical significance in differentiating those patients that would go on to respond to treatment versus those that did not when considering the tumor and lymphadenopathy separately. However, when the data for both was combined into multivariate logistic regression analyses, there was a significant difference in differentiating responders from non-responders. The authors noted that such evaluation may aid in the response to chemoradiation therapy in the future, noting that studies with larger cohorts may be necessary to validate their findings, and that more robust acquisition and post-processing tools will be needed in the future.

PET of Lymph Nodes: Including PET/MR & PET/CT Perfusion

H&N PET: The N0 Neck, Unknown Primary and Post-Treatment Neck

Treatment of the clinical N0 neck in HNSCC patients remains somewhat controversial and the decision of when to operate depends on the probability of nodal metastases in such patients. The sensitivity and specificity of PET/CT

Fig. 5 Clinically unknown primary, in a 62 year old patient with palpable right sided neck lymphadenopathy. Axial fused PET/CT image (**a**) shows an FDG avid lesion more anteriorly in the parotid (*arrow*) with more posterior FDG avid lymphadenopathy. PET rotational maximum intensity projection (MIP) image (**b**) shows extensive cervical lymphadenopathy throughout the right neck, with the primary parotid lesion (*arrow*). This was proven to be a primary parotid mucoepidermoid carcinoma with cervical nodal metastases

for the detection of nodal metastases have been reported to range between 70–90 and 80–95 % respectively, with a negative predictive value around 90 % [44]. Cetin et al. [45] retrospectively studied the role of PET/CT in nodal staging of clinical and radiographical N0 HNSCC, in 36 patients who later had neck dissection. CT and/or MRI was negative prior to the PET/CT which utilized low dose, non-contrast CT. Using their optimal cutoff maximum standardized uptake value (SUV_{max}) of 2.95, and histopathological comparison, they determined an 84.2 % sensitivity and a 76.5 % specificity for nodal-level staging, in addition to an accuracy of 75 %. They noted that their sensitivity seemed high which may have been in part due to their routine histopathological work-up of the neck dissection, which has been shown to miss up to 28 % of micrometastases [46]. Roh et al. [47] studied PET/CT in HNSCC prospectively in 91 patients with negative findings on neck palpation. They found that PET/CT had a significantly higher sensitivity than CT or MRI on a per-level nodal basis, 69–39 % respectively, as well as on a per-patient basis, 71–50 % respectively, with micrometastases responsible for most occult nodal metastases. They concluded that PET/CT is better than CT or MRI to detect occult nodal metastases in the neck, but that the relatively low sensitivity may not lessen the need for elective neck treatment.

McDermott et al. [48••] studied the negative predictive value of surveillance PET/CT in HNSCC retrospectively in

Fig. 6 CT Perfusion of nodal metastasis in a 55 year old with a supraglottic HNSCC. Perfusion images show increased blood volume (a) and increased permeability (b) in an otherwise normal size left

level 2 lymph node (c) which was positive for metastasis. Images courtesy of Ashok Srinivasan, University of Michigan

Fig. 7 PET/MRI depicting nodal metastases in a 66 year old with a supraglottic HNSCC. T2 MR image (a) shows bilateral level 2A nodes which are normal appearing. PET image (b) and fused PET/MR

image (c) show that both nodes are FDG avid, and both nodes were proven to be metastatic. Images courtesy of Matthew Parsons, Mallinckrodt Institute of Radiology

512 patients. A contrast-enhanced diagnostic CT was part of the PET/CT protocol. They determined a 91 % negative predictive value based on a single negative PET/CT scan in 214 patients and a 98 % negative predictive value based on two consecutive negative PET/CT scans within six months of each other in 114 patients. They concluded that after a second negative PET/CT scan, radiologic surveillance can be suspended in asymptomatic patients.

A frequent use of PET/CT in HNSCC is for determination of the primary tumor site when a patient presents with nodal metastatic disease and no known site on clinical examination. Prowse et al. [49] retrospectively studied 32 such patients with PET/CT. PET/CT found 50 % of the unknown primaries, with a sensitivity of 94 % and specificity of 67 %. When the data was pooled with ten prior studies from the literature, for a total of 329 patients, the primary tumor detection rate was only 37 %. While this is

low, the authors underscored the value of PET/CT noting that this modality still has the highest detection rate in such cases (Fig. 5).

PET/CT Perfusion & PET/CT Detection of ECS

Veit-Haibach et al. [50] prospectively studied combined PET/CT-perfusion in 41 patients with HNSCC. The PET component of the study included a low dose CT for attenuation correction, followed by a split bolus of intravenous contrast for CT-perfusion followed by conventional diagnostic CT. They did not find any significant correlation between PET and CT-perfusion parameters, and thus offered that the CTP provides additional information not otherwise inherent in the PET/CT portion of the study. They did find that CT-perfusion values were significantly different between primary tumors and nodal metastases, in

addition to significant differences between primary tumors and inflammatory lesions. See Fig. 6 for an example of increased perfusion in a metastatic lymph node.

Extracapsular spread and PET/CT were also evaluated retrospectively in 80 patients with oral squamous cell carcinoma [51]. ECS was found in 39 of 71 pathologically proven metastatic nodal levels. They found a significant difference in SUV_{max} values in cervical lymph node metastases with ECS and those without. Through receiver operating characteristic curve analysis, an optimum SUV_{max} cut-off value of 2.25 was found, with a sensitivity of 85 % and a specificity of 88 %. Several limitations of the study other than its retrospective nature included a small sample size, and a single reader for PET/CT scans.

PET/MRI

PET/MRI is a relatively new technique that may improve the yield of diagnostic imaging through the increased soft tissue contrast afforded with MRI (Fig. 7). Early research was performed with the fusion of separately acquired PET and MR images, while PET/MR scanners are now being produced and marketed, although they are still predominantly being used in large academic centers. A number of studies were published in 2013 evaluating PET/MR as hybrid machines or as separately acquired scans, and comparing PET/MR image quality and diagnostic utility to PET/CT.

Platzek et al. [52] wrote about their initial experience with PET/MRI in head and neck cancer, and compared a stand-alone PET scanner to a hybrid PET/MRI system in twenty patients with HNSCC. Scans performed with the hybrid PET/MRI identified 17/20 primary tumors, compared to 16/20 for the PET alone, and 14/20 for the MRI alone. More lymph nodes were identified by PET/MRI than PET alone, although it was noted that the PET images from the hybrid PET/MR were technically superior to the PET alone. Additionally the PET/MRI was performed after the stand alone PET which may have led to increased FDG uptake in tumors and decrease in background activity with the PET/MRI scans (i.e. increased conspicuity of areas of uptake). It was found to be feasible to do a PET/MRI of the H&N with a hybrid system without PET-induced MRI artifacts nor MRI-induced PET artifacts.

A study by Varoquaux et al. [53] compared PET/MR and PET/CT for the detection and quantification of focal uptake in H&N tumors. They found no significant difference in qualitative results regarding image quality, fusion quality, lesion conspicuity, and anatomic location of focal uptake. They did however find a significant underestimation of SUVs measured on PET/MR compared to PET/CT. They attributed this in part to the time delay between the completion of the PET/MR and the PET/CT, noting that the SUVs of malignant tumors may increase over time

while those of inflammatory lesions tend to remain stable or decrease [54, 55]. They also found an underestimation of SUVs in benign lesions and organ tissue, which is less readily explained by timing alone.

Kanda et al. [56] looked at retrospective fusion of separately obtained PET/CT and contrast enhanced MRI images of the neck, in 30 patients with HNSCC being preoperatively staged. PET and MRI images were generated from different scanners and then fused. The authors found that for T-staging, the accuracy of both fused PET/MR (87 %) and MRI alone (90 %) were significantly better than that of PET/CT (67 %). Regarding N-staging, accuracy for fused PET/MR and PET/CT (both 77 %) was superior to that of MRI alone (63 %), but this was not found to be significant. M-staging could not be compared as the MRI only included the head and neck. Aside from the retrospective nature of the study, a notable limitation of the PET/CT was the use of a low-dose CT scan (40mAs) without intravenous contrast.

Heusch et al. [57] compared the diagnostic accuracy of ultrasound, PET/CT, and fused PET/MRI including DWI, for the detection of cervical lymph node metastases in 18 patients with oral cavity HNSCC [50]. Ultrasound was found to be significantly more accurate (95 %) than either PET/CT (90 %), PET/MR 91 % or PET/MRI with DWI (92 %). The sensitivity for the detection of cervical lymph node metastases was poor for all modalities: PET/MRI 52 %, PET/MRI with DWI 53 %, ultrasound 63 %, and PET/CT 30 %. They felt that this underscored the presence of micrometastases that are not readily apparent on any type of imaging study. They concluded that fused PET/MRI with or without DWI did not increase diagnostic performance for N-staging compared to US and PET/CT.

Conclusion

After this review article, the reader should be more familiar with important advances in the imaging of nodal disease in the H&N in 2013. As technology further evolves, more studies will continue to evaluate nodal disease for the most accurate detection of primary or residual cancer and differentiation from benign lymph node disease.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Rihan Khan declares no potential conflicts of interest

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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