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Potential Role of PET/MRI for Imaging Metastatic Lymph Nodes in Head and Neck Cancer

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Abstract

OBJECTIVE—This article explores recent developments in PET and MRI, separately or combined, for assessing metastatic lymph nodes in patients with head and neck cancer.

CONCLUSION—The synergistic role of PET and MRI for imaging metastatic lymph nodes has not been fully explored. To facilitate the understanding of the areas that need further investigation, we discuss potential mechanisms and evidence reported so far, as well as future directions and challenges for continued development and clinical research.

Keywords

head and neck cancer; lymph nodes; metastasis; MRI; PET

Head and neck cancers predominantly originate from mutations within squamous epithelial cells of the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx [1, 2]. Approximately two-thirds of patients with head and neck cancer present with locally advanced disease at the primary site and/or spread to regional lymph nodes [2–4]. The 5-year survival rate of patients with these cancers ranges between 40% and 70%, depending on the primary site and stage [1]. Standard therapeutic options at initial presentation include surgical resection of the primary tumor, lymph node dissection, and/or chemoradiation therapy [4, 5].

Accurate identification and characterization of lymph node metastases by imaging has important therapeutic and prognostic significance for patients with newly diagnosed head and neck cancers and is also critical when evaluating therapy response. Regional lymphatic metastasis is one of the important factors for poor prognosis, such that the decision to treat the lymph nodes in the neck has to be considered for most patients, even if metastases are not apparent clinically [6]. Accurate information about the extent of nodal metastases can also be helpful in planning neck dissection and potentially reduces the duration of the surgical operation.

Although the need for an accurate imaging method to assess lymph nodes is paramount, this need is not adequately met by currently available diagnostic imaging methods. Most commonly used cross-sectional imaging modalities, such as ultrasound, CT, and MRI, rely on size and morphologic criteria and lack the accuracy necessary for characterizing lymph nodes [6–8]. Metastases can be present in nonenlarged lymph nodes, and not all enlarged nodes are malignant [9]. The identification of lymph node necrosis on conventional imaging is a reliable sign for nodal metastasis, but it has a limited negative predictive value (NPV) with smaller nodes.

PET with ^{18}F -FDG and advanced MRI methods, such as dynamic contrast-enhanced (DCE) MRI and DWI, have emerged as promising imaging methods for the detection of lymph node metastasis [8, 10–12]. FDG PET is the modality of choice to assess abnormally high rates of aerobic glycolysis in cancer cells [13–16]. DCE-MRI and DWI can be used to measure the vascular and cellular properties of the cancer, respectively [17–20]. These imaging methods have been used for imaging metastatic lymph nodes, separately or combined. However, they have yet to realize the unique potential in probing lymph node microenvironmental changes. In addition, the synergistic potential of FDG PET and MRI for metastatic lymph node detection has not been fully investigated [21].

The aims of this article are to review the recent development of PET and MRI for assessing metastatic lymph nodes in head and neck cancer, to assess the role of these two modalities combined together in recently reported studies, and to discuss the potential of these imaging methods for future research and applications. We limit our discussion to the use of FDG PET and DCE-DWI for detecting metastatic lymph nodes, monitoring and predicting treatment response, and assessing persistent or recurrent tumor in patients with head and neck cancer.

Detection of Metastatic Lymph Nodes

Regional metastasis to the lymph nodes is one of the most important predictors of poor prognosis in head and neck cancer [22]. Precise definition of metastatic involvement is required for planning surgical strategy in patients with resectable cancers or individualized radiation therapy in patients with non-resectable disease. However, detecting small nodes with micrometastases remains challenging for the currently available diagnostic imaging methods, including PET and MRI. Elective neck dissection is often considered essential even for early oral tongue cancer because there is no imaging method that can reliably identify patients without occult metastasis [23]. The decision analysis by Weiss et al. [24] recommended that stage N0 neck cancer with a less than 20% probability of occult metastasis could be observed without elective neck dissection. A recent meta-analysis by Liao et al. [25] found that current diagnostic imaging methods, including MRI and PET, may have NPVs higher than 80%, such that they could be used to select patients for a watchful waiting policy. These promising results call for larger and prospective studies to further establish the role of current imaging methods for optimal management of patients with head and neck cancer. It is also timely to consider whether there is any synergistic role of PET and MRI in the accurate determination of nodal metastasis.

PET

PET, or primarily PET/CT in recent years, has been widely used for initial staging and is reported to have high sensitivity (92–100%) but mixed specificity (77–93%) for detecting metastatic lymph nodes [12, 15, 26, 27]. Many of the PET studies for the detection of metastatic nodes have typically included patients with different degrees of regional lymph node involvement. Liao et al. [25] conducted a meta-analysis of 11 PET studies of head and neck cancer that included only patients with clinically negative neck examinations and found that the pooled estimates of sensitivity and specificity of PET were 66% and 87%, respectively. The accuracy of PET for detecting cervical metastatic nodes can vary depending on the study time dedicated for the neck and the uptake time after the tracer injection. Yamamoto et al. [27] found that higher quality images from a dedicated study with 8 minutes, compared with 2 minutes, in their whole-body protocol improved the detectability of small nodes (mean diameter, 7.1 mm). Rodrigues et al. [28] showed that their 15-minute study after a 150-minute postinjection delay detected small nodes (< 15 mm) about four times more often than did a 6-minute study after a 90-minute postinjection delay. These studies suggest that a delayed dedicated high-resolution neck PET scan may be useful after the whole-body study when the presence of small metastatic lymph nodes will affect the treatment plan.

MRI

Contrast-enhanced MRI with a gadolinium-based contrast agent is an increasingly used method for staging head and neck cancers and assessing nodal metastases. A meta-analysis of 32 studies by Klerkx et al. [29] found that contrast-enhanced MRI had specificity of 87% and sensitivity of 72% for detecting metastatic lymph nodes. For N0 neck cancers, Liao et al. [25] identified six contrast-enhanced MRI studies with pooled estimates of 65% sensitivity and 81% specificity, which are quite close to those of PET. Most studies were based on contrast-enhanced images and did not use dynamic imaging to capture the time-intensity curves of contrast agent wash-in and washout in the lesion. Noworolski et al. [30] showed how quantitative metrics derived from DCE-MRI data can be used to assess the cervical nodes and also showed a multivariate logistic regression model, based on short-axis length, peak enhancement, and peak time, for the detection of metastatic lymph nodes. Using the similar DCE-MRI method, Fischbein et al. [31] reported that tumor nodes have significantly longer time to peak, lower enhancement, lower maximum slope, and slower washout slope in metastatic nodes compared with normal nodes. However, the diagnostic accuracy of DCE-MRI with quantitative contrast kinetic analysis for the detection of metastatic nodes in clinically N0 neck cancer has not been reported to date.

DWI is another promising imaging method to probe tissue microenvironment changes due to tumor growth [32]. Vandecaveye et al. [33] showed that, in 301 lymph nodes of 33 patients, apparent diffusion coefficient (ADC) had 84% sensitivity and 94% specificity on a 1.5-T system. Another study by Barchetti et al. [34] used a 3-T system with 80 patients and showed that the ADC values in the pathology-proven metastatic ($n = 239$) and benign ($n = 412$) lymph nodes were $0.90 \mu\text{m}^2/\text{ms}$ (range, $0.40\text{--}1.00 \mu\text{m}^2/\text{ms}$) and $1.65 \mu\text{m}^2/\text{ms}$ (range, $0.95\text{--}2.4 \mu\text{m}^2/\text{ms}$), respectively, which resulted in 97% sensitivity and 93% specificity. These studies suggest that higher cell densities in metastatic nodes result in lower ADC

values relative to benign lymph nodes. The diagnostic accuracy of DWI can be affected substantially by imaging resolution. Park et al. [35] developed a high-resolution DWI method allowing 1-mm² in-plane resolution and 2-mm slice thickness, albeit with a smaller FOV, with which they successfully identified the hilar structure of cervical lymph nodes. With this kind of technical development, DWI promises to be a promising tool to detect clinically occult metastatic lymph nodes.

PET/MRI

A limited number of studies have assessed the advantage of combining PET and MRI in head and neck cancer [11, 36–38]. For detecting metastatic lymph nodes, Yoon et al. [37] compared the diagnostic values of PET and MRI as well as those of ultrasound and CT separately and combined. They found that these modalities showed no statistically significant difference, but the combination of all modalities improved sensitivity to about 86%, although it also did not reach statistical significance. Nakamoto et al. [38] reported that the use of MRI and PET with software fusion had sensitivity and specificity of 85% and 92%, respectively. They also showed an adenoid cystic case in which a histologically proven metastatic node was read as positive on MRI but was considered negative on the fused image because of low FDG uptake (Fig. 1). This raises an important question of how to interpret PET and MRI together to maximize their combined diagnostic strengths to detect occult metastatic lymph nodes.

The recent introduction of hybrid PET/MRI scanners provides new opportunities for investigating the synergistic effect of these two modalities without the challenge of image coregistration [39]. It has been shown that the PET system integrated with the MRI scanner performs the same as the PET portion of a PET/CT for various cancers [40, 41]. For lymphoma, Heacock et al. [42] found a strong correlation ($r = 0.98$; $p < 0.001$) between the maximum standardized uptake value (SUV) measured on a hybrid PET/MRI scanner and those measured on PET/CT. Platzek et al. [43] performed PET/MRI in the head and neck for initial staging after the clinical PET/CT without additional FDG injection and found that PET/MRI was able to detect 64% more metastatic lymph nodes, partly because of the increased uptake time. Hybrid PET/MRI is still at its early stage of development, especially for assessment of metastatic nodes. Figure 2 shows example PET/MR images of a head and neck cancer from our on-going study that show high-resolution PET images overlaid on highly detailed contrast-enhanced MR images. In addition to the anatomic detail of the soft tissues provided by MRI, the multiparametric MRI methods for assessment of tumor vascular and cellular properties may be useful to interpret glucose metabolic rate measured by FDG PET in future studies.

Treatment Response Monitoring and Prediction

Treatment of head and neck cancer is challenging because the patient's quality of life can be severely affected by possible functional losses, such as impaired swallowing and speech deficit, as well as cosmetic deformity from surgery. Organ-preserving definitive radiation therapy, typically with concurrent chemotherapy, is often considered a viable option for patients with metastatic cervical nodes [44–49]. Despite these rigorous treatment methods,

the overall survival rate of these patients has not improved significantly; the 5-year survival rate of these patients remains below 50% [44, 48, 49]. The treatment outcome may be improved by using an optimized treatment strategy personalized for an individual patient on the basis of imaging biomarkers [50]. If the outcome can be predicted before or at an early stage of treatment, the patient could also be spared from ineffective and unnecessary toxicity.

PET

Malignant tumors have high rates of aerobic glycolysis, as first observed by Warburg [13]. Previous studies have shown that high uptake of FDG in primary tumors is associated with poor survival [51–54]. SUV of primary tumors greater than 10 [52] or 7 [53, 54] predicted significantly worse outcomes in terms of long-term local control and disease-free survival after treatment, including neoadjuvant radiation therapy. On the other hand, Schinagl et al. [55] reported that the prognostic value of pretreatment PET depended on the primary tumor location; prediction of treatment response was possible in oral cavity and oropharynx tumors but not in hypopharyngeal and laryngeal cancers. The prognostic value of FDG PET for the nodes has not been reported as extensively as that for the primary tumors and may be an interesting subject for future studies.

Hoang et al. [56] showed that PET could be used to measure early metabolic rate changes induced by chemoradiation therapy. The intrinsic variability of SUV was lower in nodes (mean $\pm$ SD, 7.6% $\pm$ 5.2%) than in primary tumor (12.6% $\pm$ 9.2%), such that it was recommended to measure the early treatment response in nodal disease rather than that in the primary tumors. The optimal time for assessing metabolic response is yet to be determined.

PET is more commonly used for response assessment after the completion of treatment and to identify viable tumor within an area of residual soft-tissue abnormality [57, 58]. The best time for posttherapy PET has been suggested to be 3–6 months after therapy [59], to decrease the false-positive rate due to post-treatment inflammation. Previous studies have shown that posttreatment PET assessment can be used to avoid unnecessary planned neck dissection even in the presence of nodal abnormalities on CT if they become negative on PET [60, 61]. Keski-Säntti et al. [62] reported that PET/CT conducted about 3 months after therapy has sensitivity, specificity, positive predictive value (PPV), and NPV of 59%, 94%, 71%, and 91% for detecting residual disease in the primary sites, and 95%, 100%, 100%, and 93% in the nodes, respectively. Recently, Anderson et al. [63] used SUV measurements at 60, 90, and 120 minutes and found that change of maximum SUV slope after 90 minutes more accurately identified non-recurrence in positive or equivocal sites than using SUV at one point. This finding suggests that quantitative measures from pharmacokinetic analysis of PET data may provide more reliable and accurate imaging markers to identify residual tumor after therapy.

MRI

DCE-MRI has been used for prediction of treatment response [64] by measuring blood flow–related parameters such as perfusion, permeability, or vascular volume [65–67].

Because the efficacy of chemoradiation therapy relies on effective delivery of therapeutic agents and oxygen to the tumor, the information on tumor vessels and related tumor microenvironment measured by DCE-MRI can provide critical information on selection of the most effective treatment strategy [50, 68, 69]. Quantitative kinetic model parameters, such as forward volume transfer constant (K^{trans}) and reverse volume transfer constant (k_{ep}), represent a combination of vascular permeability and perfusion of the tumor and can be used to detect hypoxic nodes with poor perfusion [70]. Previous studies have shown that a higher K^{trans} in the metastatic nodes at the pretreatment study is associated with favorable short-term response to chemoradiation therapy [71] and prolonged disease-free survival [72]. Heterogeneity of K^{trans} in the nodes was also reported as a promising predictor of chemoradiation therapy response [73]. However, it remains challenging to perform DCE-MRI studies for contrast kinetic model analyses because it requires separate measurement of the longitudinal relaxation time of the tissue (T1) and the coil sensitivity map (B1) to convert MRI signal intensity to contrast agent concentration. Measurement of T1 and B1 is particularly important for application of DCE-MRI in longitudinal monitoring of treatment response because tissue T1 can change during the treatment, and the patient position in the MRI coil is also variable, which affects the estimated contrast agent concentration in lesions of interest. This technical limitation might be one of the reasons why DCE-MRI has not yet become widely used for head and neck cancer.

DWI has also been used for prediction and monitoring of treatment response in head and neck cancer. Kim et al. [19] reported that the pretreatment ADC value of patients with a complete response ($1.04 \pm 0.19 \mu\text{m}^2/\text{ms}$) was significantly lower than that of patients with a partial response ($1.35 \pm 0.30 \mu\text{m}^2/\text{ms}$), and a significant increase in ADC within 1 week of treatment was observed in those with a complete response (Fig. 3). A similar observation was made in a recent study with 541 cases of nasopharyngeal carcinoma, showing that a high pretreatment ADC in the primary lesion predicted worse local relapse-free survival and disease-free survival [74]. Hoang et al. [75] showed that the treatment-induced early change in ADC ($32\% \pm 31\%$) of metastatic nodes is significantly different from the baseline variability ($8\% \pm 7\%$) in the same nodes. These studies showed the feasibility of using DWI as a noninvasive imaging method to monitor treatment response.

PET/MRI

PET and MRI have been used together to predict and assess treatment response in a limited number of studies. Jansen et al. [76] observed that the SD of K^{trans} and maximum SUV on pretreatment studies were significant predictors of short-term response. A recent study by Subesinghe et al. [77] found that PET and MRI could be used together to monitor treatment response of eight patients with head and neck cancer receiving 70 Gy of radiotherapy delivered in 35 daily fractions. All patients showed decreased maximum SUV and increased ADC and plasma flow when measured after eleven fractions. These studies show that PET and MRI are potentially complementary because they measure functional and structural changes induced by treatment. The use of PET and MRI together for treatment response monitoring and prediction is still at the early stage. It is often not practical to perform both PET and MRI multiple times during treatment. This is an area where hybrid PET/MRI systems can make a significant contribution. Given the active research in PET and MRI

individually to find prognostic markers of treatment response in recent years, it is expected that hybrid PET/MRI systems will be used more frequently in future studies.

Detection of Recurrence

Despite aggressive therapeutic approaches, head and neck cancers may recur at the primary site, in the regional lymph nodes, or both [78, 79]. Continuous surveillance of these patients after treatment is crucial. In patients treated with radiation therapy, differentiating between radiation-induced inflammation and recurrent tumors remains a diagnostic dilemma.

PET

PET/CT has been used as a modality of choice for posttherapy surveillance imaging. A meta-analysis of 27 studies of PET for detecting persistent or recurrent head and neck cancers after radio- or chemoradiotherapy found that the pooled sensitivity, specificity, PPV, and NPV were 94%, 82%, 75%, and 95%, respectively [80]. These results are in line with more recent studies that showed 86–100% sensitivity, 43–97% specificity, 42–71% PPV, and 98–100% NPV [59, 81, 82]. The PPV is low in all these studies because of high false-positive findings from posttreatment inflammation [59, 80].

MRI

A DCE-MRI study by Ishiyama et al. [83] found that benign posttreatment changes had significantly higher vascular permeability surface area product than did recurrent or newly diagnosed cancers. In distinction, King et al. [84] observed that the posttherapy residual masses with persistent tumors had higher permeability or perfusion measures, including higher k_{ep} and area under the contrast curve, than those with complete response. These studies show the feasibility of using DCE-MRI for surveillance imaging. They also show that there is a need for consensus on DCE-MRI data acquisition and analysis methods for detection of persistent or recurrent tumor, such that future studies can be easily combined. DWI has also been used for differentiating persistent or recurrent squamous cell carcinomas of the head and neck from nontumoral tissue changes after chemotherapy, with reported high specificity (90–96%) [85, 86] and high PPV (94%) [86]. DWI may be used to complement the poor PPV of PET for surveillance imaging. However, further studies with a large cohort are warranted.

PET/MRI

A recent study by Loeffelbein et al. [10] found no significant difference among PET, MRI, and PET/MRI fusion studies in the identification of recurrent tumor in the treated neck. However, the authors noted that analyzing both PET and MRI side by side or using fusion images was helpful for detecting recurrence. Nakamoto et al. [38] reported that some of the recurrent lesions were accurately diagnosed by use of image fusion only. In thyroid cancer, Seiboth et al. [87] reported that, in 34 patients with prior treatment, reading PET/MRI fusion images provided additional information that altered the treatment plan in 46% of cases, on average, according to the results from four independent reviewers. Nevertheless, the synergistic potential of PET and MRI in the management of recurrent or persistent head and neck cancer remains unknown and needs to be investigated further.

Future Directions

The combined use of PET and MRI by using either software fusion or a hybrid system appears to have potential synergy for assessment of metastatic lymph nodes in head and neck cancer. There have been a number of studies using PET and MRI together for detecting metastatic lymph nodes and initial staging, as discussed already in this article. However, its application in treatment response prediction and assessment has been limited. PET/MRI can be a viable alternative to PET/CT for posttherapy surveillance studies. Simultaneous acquisition of PET and MRI by a hybrid system makes it easier to investigate these two modalities in the time of only one examination. Extending the role of PET/MRI to these underutilized areas may help to establish the role of PET/MRI in management of head and neck cancer.

Most clinical PET studies are conducted 45–90 minutes after the tracer injection and use SUV measured at one time point as a standard measure. In contrast, dynamic PET can provide more information about the lesion, such as flow and metabolic rate [88]. It remains largely unknown whether quantitative measures from dynamic PET with pharmacokinetic model analysis are associated with multiparametric MRI measures of various tumor vascular and cellular properties. Joint analysis of dynamic PET and multiparametric MRI may provide new insight into tumor progression and treatment response. For instance, dynamic FDG PET measures kinetic parameters reflecting FDG delivery, uptake into the intracellular space, and phosphorylation, whereas DCE-MRI measures contrast agent delivery into the extracellular space. This fundamental difference in the tracer properties can be used to investigate the FDG cellular uptake rate reflecting glucose metabolism independently from the vascular delivery of tracer to the extracellular space by increased blood flow.

ADC values from DWI may also be used to estimate the cellular density, which can be useful to interpret the FDG metabolic rate. Heacock et al. [42] showed that ADC is not correlated with SUV in lymphoma, supporting the idea that ADC represents additional independent information. Recently, Rakheja et al. [89] reported that patients with progressive metastatic cancers have a higher ratio of SUV to ADC than do those with a partial treatment response. These new unique approaches afforded by PET/MRI need to be further investigated for cancer imaging applications, including metastatic lymph nodes in head and neck cancer.

Technical challenges of each modality also need to be addressed to support the combined use of PET/MRI for clinical applications. One common issue is motion artifact by involuntary motion, such as swallowing and breathing. MRI data can be used for PET data motion correction, as shown in the brain [90] and the chest [91]. However, whether a similar approach can also be used for motion correction in the complex anatomy of the head and neck region remains unclear. Although our review is limited to FDG, the most commonly used tracer, it will be of great interest to use PET/MRI with other tracers, such as ^{18}F -fluorothymidine for cell proliferation [92] and ^{18}F -fluoromisonidazole for hypoxia [93]. With many potential possibilities on the horizon for both PET and MRI, PET/MRI is poised to play an important role in future for assessing metastatic lymph nodes in head and neck cancer.

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Fig. 1. 78-year-old man with adenoid cystic carcinoma and nodal metastasis. **A–C**, Axial slices of MRI (**A**), PET (**B**), and fused PET/MRI (**C**) are shown. Nodal metastasis from adenoid cystic carcinoma was suspected on MR image (*arrow*, **A**), but it was regarded as negative on image fusion interpretation because of faint uptake (*arrow*, **C**). Metastasis to lymph node was confirmed by surgery. (Reprinted with permission from [38])

Fig. 2.

70-year-old man with squamous cell carcinoma in tongue base imaged using hybrid PET/MRI scanner.

A–C, FDG PET (**A**), contrast-enhanced T1-weighted MR image (**B**), and PET image overlaid on contrast-enhanced MRI without image coregistration (**C**) show large left level 2 node, indicated by crosshairs. Node is highly FDG avid (standardized uptake value, 9.7). It also shows excellent position match between PET and MRI.

Fig. 3.

68-year-old woman with squamous cell carcinoma of base of tongue who had complete response to treatment.

A–C, Images in each row are from three measurement time points: pretreatment (**A**), 1 week into treatment (**B**), and after completion of treatment (**C**). T2-weighted, T1-weighted, and T1-weighted gadolinium-enhanced images were windowed to have similar image contrast, whereas T2 and apparent diffusion coefficient (ADC) images were scaled on basis of gray-scale bars shown at bottom of corresponding images. Large arrows (T2-weighted image, **A**–

C) indicate same nodal metastatic mass that was followed through treatment course. Small arrow (ADC image, **A**) indicates central region of mass with lower ADC values than peripheral region. (Reprinted with permission from [19])

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