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Noninvasive assessment of tumor microenvironment using dynamic contrast enhanced MRI and ^{18}F - fluoromisonidazole PET imaging in neck nodal metastases

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Abstract

Purpose—Pretreatment multimodality imaging can provide useful anatomical and functional data about tumors, including perfusion and possibly hypoxia status. The purpose of our study was to assess non-invasively the tumor microenvironment of neck nodal metastases in patients with head and neck (HN) cancer by investigating the relationship between tumor perfusion measured using Dynamic Contrast Enhanced MRI (DCE-MRI) and hypoxia measured by ^{18}F -fluoromisonidazole (^{18}F -FMISO) PET.

Methods and Materials—Thirteen newly diagnosed HN cancer patients with metastatic neck nodes underwent DCE-MRI and ^{18}F -FMISO PET imaging prior to chemotherapy and radiation therapy. The matched regions of interests from both modalities were analyzed. To examine the correlations between DCE-MRI parameters and standard uptake value (SUV) measurements from ^{18}F -FMISO PET, the non-parametric Spearman correlation coefficient was calculated. Furthermore, DCE-MRI parameters were compared between nodes with ^{18}F -FMISO uptake and nodes with no ^{18}F -FMISO uptake using Mann-Whitney U tests.

Results—For the 13 patients, a total of 18 nodes were analyzed. The nodal size strongly correlated with the ^{18}F -FMISO SUV ($\rho=0.74$, $p<0.001$). There was a strong negative correlation between the median k_{ep} ($\rho=-0.58$, $p=0.042$) and the ^{18}F -FMISO SUV. Hypoxic nodes (moderate to severe ^{18}F -FMISO uptake) had significantly lower median K^{trans} ($p=0.049$) and median k_{ep} ($p=0.027$) values than did non-hypoxic nodes (no ^{18}F -FMISO uptake).

Conclusion—This initial evaluation of the preliminary results support the hypothesis that in metastatic neck lymph nodes, hypoxic nodes are poorly perfused (i.e., have significantly lower k_{ep} and K^{trans} values) compared to non-hypoxic nodes.

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Keywords

Dynamic Contrast Enhanced-MRI (DCE-MRI); ^{18}F -fluoromisonidazole (FMISO) PET; ^{18}F -fluorodeoxyglucose (FDG); head and neck (HN) cancer

Introduction

The use of multimodality (MM) imaging is rapidly gaining acceptance in oncology for the study of tumor microenvironment characteristics, including tumor vascular/perfusion status and tumor cell hypoxia, which have been shown to be related to treatment outcomes (1). Multimodality imaging allows the acquisition of both functional and anatomical images by exploiting the unique strengths of different imaging techniques (1). The present study focuses on the application of MM imaging techniques using gadopentetate dimeglumine (Gd-DTPA)-based dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and ^{18}F -fluoromisonidazole (FMISO) positron emission tomography (PET) in studying neck nodal metastases.

DCE-MRI is a useful noninvasive method for characterizing the pathophysiological microenvironment of tumors (2). DCE-MRI involves assessing changes in signal intensity over time. With proper compartmental modeling, using models like the Brix-Hoffmann model (3), the modified analysis by Port et al. (4), or the Tofts model (5), the data may yield results on tumor-vessel permeability, tumor perfusion, and extracellular-extravascular volume fraction, i.e., data related to the tumor microenvironment (6). On the other hand, hypoxia imaging has been most extensively studied with ^{18}F -FMISO PET in the clinical setting (7,8). This fluorinated radiotracer was developed from the nitroimidazole compound misonidazole as a hypoxic cell radiosensitizer (9). It is thought to be a surrogate imaging marker for hypoxia (7,8,10).

DCE-MRI and ^{18}F -FMISO PET are typically acquired and assessed separately. In a recent study of an animal tumor model, Cho et al. (11) found a negative correlation between perfusion as assessed by DCE-MRI and hypoxia as measured by late ^{18}F -FMISO PET uptake, hence providing the evidence for the hypothesis that poorly perfused tumors are hypoxic (12). The study also established the utility of combined MRI and PET measurements for imaging the tumor microenvironment and identifying regions of tumor hypoxia and well-perfused tissue (11).

Clinical studies in head and neck (HN) cancers have assessed perfusion or hypoxia separately (7,8,13–18). Hoskin et al. performed DCE-MRI on 13 HN cancer patients before and after radiotherapy and suggested that treated patients in whom tumors have high MR signal enhancement might be considered for dose escalation (14). Rasey et al. found marked intra- and inter-tumor variability of hypoxia and emphasized that complete, non-invasive hypoxia measurements in individual tumors are important for patient-specific treatment planning (8). Recently, Lee et al., using the same radiotracer, illustrated the feasibility of dose escalation of the gross tumor volume in HN cancer patients (7).

Several investigators have reported tumor oxygenation (using invasive Eppendorf pO_2 measurements) in HN cancers to be associated with poor outcome (19,20). Nordsmark et al. performed pre-treatment measurements of tumor oxygen tension in a multicentric trial with 397 HN cancer patients and showed that tumor hypoxia is associated with a poor prognosis (20). Thus, the detection and quantification of hypoxia might provide a prerequisite for the clinical implementation of hypoxia-directed therapies that could potentially improve outcomes in HN cancer patients (21). Although often considered the gold standard, invasive

Eppendorf pO₂ histography has disadvantages as it is limited by sampling, unable to differentiate hypoxic and necrotic tissue, and cannot access all tumors. In contrast, ¹⁸F-FMISO PET is only sensitive to the presence of hypoxia in viable cells, can cover the entire region of interest and is well tolerated by patients (22). The imaging techniques Gd-DTPA-based DCE-MRI and ¹⁸F-FMISO PET have been proposed separately as promising tools for predicting treatment response for HN cancer (7,8,14,17). As yet, however, no clinical studies have compared data from these modalities for the assessment of the tumor microenvironment. The purpose of our study was to assess non-invasively the tumor microenvironment of neck nodal metastases in patients with HN cancer by investigating the relationship between tumor perfusion measured using DCE-MRI and hypoxia measured by ¹⁸F-FMISO PET.

Methods and Materials

Patients

The institutional review board (IRB) granted a waiver of informed consent for this retrospective study that included thirteen patients with metastatic lymph nodes who underwent ¹⁸F-FMISO PET (IRB No. 04-070) and DCE-MRI as part of clinical MRI. Our study was compliant with the Health Insurance Portability and Accountability Act. PET examinations were performed 6±9 (mean ± SD) and 3±9 days after MRI for ¹⁸F-FMISO and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG), respectively in these 13 HN cancer patients with neck nodal metastasis before beginning chemo-radiation therapy. The imaging details for MRI and PET/CT examinations have been described previously (7,23). All patients underwent needle biopsy at the primary tumor location (14±11 days before MRI). To ensure that the tumor microenvironment would be unchanged, biopsies of the nodes were not done. Patient characteristics are listed in Table 1.

For simplicity, we have referred to ¹⁸F-FMISO as FMISO and ¹⁸F-FDG as FDG for the rest of this paper.

MRI studies

MRI data were acquired on a 1.5 Tesla G.E. Excite scanner (General Electric, Milwaukee, WI) with a 4-channel neurovascular phased-array coil for signal reception and a body coil for transmission. The study consisted of MRI covering the entire neck (23). The MR acquisition parameters for the neck survey were as follows: rapid scout images, multiplanar (axial, coronal and sagittal) T2-weighted, fat-suppressed, fast-spin echo images (TR = 5000 ms, TE = 102 ms, averages = 2, slice thickness = 5.0 mm and gap = 2.5 mm), and multiplanar T1-weighted images (TR = 675 ms, TE = 8 ms, averages = 2, slice thickness = 5.0 mm and gap = 2.5 mm). Standard T1- and T2-weighted imaging were followed by proton density MR imaging acquired (for the purpose of determining the longitudinal relaxation rate constant R₁ for each DCE-MRI data point) in the axial plane (TR = 350 ms, TE = 2 ms with a 30° flip angle (α), 2 excitations, 15.63-kHz receive bandwidth, field of view (FOV) = 18–20cm, slice thickness = 5–6 mm, zero gap and a 256×128 matrix). This was followed by axial T1-weighted DCE-MR imaging (described below) and then post-contrast T1-weighted imaging in the axial and coronal planes.

DCE-MRI

Dynamic perfusion studies of the nodes were acquired using a fast multi-phase spoiled gradient echo sequence. Antecubital vein catheters delivered a bolus of 0.1 mmol/kg Gd-DTPA (Magnevist; Berlex Laboratories, USA) at 2 cc/s, followed by saline flush using an MR-compatible programmable power injector (Spectris; Medrad, Indianola, PA, USA). The entire node was covered contiguously with 5–7 mm thick slices, zero gap, yielding 3–6

slices with 3.75–7.5 sec temporal resolution. Acquisition parameters were similar to those described above for proton density imaging except that the TR = 9 ms and 40–80 time course data points were collected. For both proton density images and DCE-MRI the 256×128 matrix was zero filled to 256×256 during image reconstruction.

PET studies

All PET scans were performed on a GE Discovery LS PET/CT scanner (GE Medical Systems, Waukesha, WI) consisting of an Advance NXi PET and a LightSpeed CT unit (7). For the PET studies, patients were scanned in the supine position and immobilized using an immobilization device, an Aquaplast mask (Orfit Industries, Wijnegem, Belgium) that extended to the shoulders (7). Markers were used on the flat insert to ensure proper patient positioning (7).

FDG/FMISO

Before the FDG PET examination, patients fasted for at least 6 hours, but liberal water intake was allowed. An activity of approximately 15 mCi of FDG was then injected intravenously. After a 45- to 60- minute uptake period, a PET/CT study was acquired on the GE Discovery LS PET/CT with the patient in the same treatment position as described by Lee et al. (7) Fluorine-18-labeled fluoride was produced by the Memorial Sloan-Kettering Cancer Center/Cornell Cyclotron Radiochemistry Core Facility by proton irradiation of an enriched ^{18}O water target in a small-volume niobium chamber with an approximate specific activity of 1–2 Ci/ μmol at the end of the bombardment time and tested for quality assurance. The details for PET imaging to assess tumor uptake and biodistribution are described by Lee et al. (7). Blood samples were obtained immediately before and after the PET/CT session. No fasting state was required for the patients. FMISO was injected into the patients approximately 120–150 minutes before scanning. Each of the FMISO studies covered two PET axial FOVs at the tumor position, at 8 min/FOV. The average duration for all patients between FMISO injection and PET/CT acquisition was 162 min. The FMISO emission data were corrected for attenuation, scatter, and random counts and subsequently reconstructed (7).

Image analysis

DCE-MRI—MRI data was analyzed with IDL 5.4 (Research Systems Inc., Boulder Co). For the tumor tissue time course data, region of interests (ROIs) were manually drawn by an experienced neuroradiologist (> 10 yrs of experience) outlining the contrast-enhanced neck nodes for signal intensity measurements. All the slices containing the tumor were outlined and analyzed. The total number of pixels within the entire ROI was converted into the tumor volume (mm^3) in MatLab (The MathWorks). Out of 13 patients, 4 patients had more than one node (ROI). The exact location of each ROI per patient was noted and tabulated by the neuro radiologist to facilitate the matching of the ROIs later between the MRI and PET studies.

Quantitative DCE-MRI analyses of the tumor tissue time course data was performed using the two-compartment Tofts model in all ROIs (5). A population-based arterial input function was used (23) that was derived from the carotid arteries in head and neck patients. This approach included a phantom study to generate a calibration curve of signal intensity ratio of T_1 -weighted image over proton density image versus T_1 (23). With this calibration curve, it was possible to convert signal intensities into Gd-DTPA concentrations. The model fitted the tissue contrast agent concentration, $C_t(t)$, time course for the extraction of the K^{trans} and v_e parameters from the whole tumor (multiple slices), as shown in the following Kety-Schmidt method-related equation:

$$C_t(t) = K^{\text{trans}} \int_0^t C_p(t') \exp(-K^{\text{trans}} v_e^{-1} (t - t')) dt' \quad [1]$$

The analyses yielded the pixel K^{trans} (the volume transfer constant between the plasma and the extravascular extracellular space (EES) in min^{-1}), v_e (the volume fraction of the EES which is dimensionless and also referred to as interstitial space), and k_{ep} (the rate constant describing the contrast transfer between the EES and plasma in min^{-1} , which equals the ratio K^{trans}/v_e). Quantitative DCE-MRI analyses of the tumor tissue time course data was done in all the patients per ROI on a pixel-by-pixel basis. A histogram analysis was performed on all pixels within the ROI, which yielded median, standard deviation, and skewness of the distribution of all pixels. Histograms were normalized to the total number of tumor voxels to allow direct comparison between patients. The median is a number separating the higher half of the population from the lower half. The standard deviation describes the width of the distribution, and the skewness characterizes the asymmetry of the distribution.

FDG/FMISO PET—All data were reviewed on a standard clinical workstation (GE PACS with AW extension). PET images were first reviewed in 3 orthogonal planes (transaxial, coronal, sagittal) and a maximum-intensity projection image. Afterward, the CT, PET, and PET/CT fusion images were displayed simultaneously. One board-certified nuclear medicine physician with > 10 years of experience in PET reviewed all PET/CT studies. The nuclear medicine physician was provided with the excel sheet that had the MRI location for each node (ROI) studied and he matched the ROI's from the MR images to the PET/CT images. Matched ROIs were analyzed based on visual and semiquantitative analysis, using the attenuation-corrected PET emission images. For semi-quantitative analysis, regions of interest were placed over the areas of focal FDG uptake in the neck nodal metastases. The intensity of FDG uptake in these regions was measured using the standardized uptake value (SUV), normalized to body weight. The maximum-pixel SUV was recorded. The imaging data initially available in units of microcuries per milliliter per voxel were decay corrected to the time of injection and converted into SUV units. For FMISO, semi-quantitative analysis included calculation of tumor-to-blood ratios for hypoxic tracer uptake and conversion to SUV measurements. Additionally, FMISO uptake by the tumor was graded using a dichotomous score: no uptake (score 0) or moderate-severe uptake (score 1).

Statistical Analysis

To examine the correlations between DCE-MRI parameters and SUV measurements from FMISO PET, the non-parametric Spearman correlation coefficient (ρ) was calculated. The same Spearman test was used to examine the correlation between SUVs of FMISO and FDG PET. The correlations were interpreted using the guidelines from Cohen et al (24), with absolute correlations of <0.3 considered weak, 0.3–0.5 considered moderate, and 0.5–1.0 considered strong. This study is aimed at relating DCE-MRI parameters with PET (as mentioned above) but not at assessing associations of parameters obtained from individual examinations with each other (such as all individual DCE-MRI parameters). DCE-MRI parameters were compared between nodes with FMISO uptake and nodes with no FMISO uptake using 2-sided non-parametric Mann-Whitney U tests. For all statistical tests ($p < 0.05$) denotes significance.

Results

All 13 patients were untreated at the time of imaging, and all had biopsy proven squamous cell carcinoma. For the 13 patients, a total of 18 lymph nodes were analyzed, as 4 patients had more than one metastatic node (Table 1). The ^{18}F FDG SUV for the 18 lymph nodes was 8.8 ± 5.7 (mean $\pm$ SD). The nodal size measured on MRI strongly correlated with the FMISO SUV ($\rho = 0.74$, $p < 0.001$) but not with DCE-MRI parameters, i.e. median K^{trans} , v_e and k_{ep} ($p > 0.5$ for all three parameters). Table 2 shows the correlations between FMISO SUV and DCE-MRI parameters. There was a strong negative correlation ($\rho = -0.58$, $p = 0.042$) between the median k_{ep} and the FMISO SUV. Additionally, the association between the FDG SUV and FMISO SUV was statistically significant ($p < 0.01$), with a strong Spearman correlation of $\rho = 0.70$.

Figures 1 and 2 show MRI and PET images of a patient with a large hypoxic node and a patient with a small non-hypoxic node, respectively. The hypoxic node in 1G shows substantial FMISO uptake, whereas the non-hypoxic node in 2G displays FMISO distribution comparable to the background noise (i.e., no substantial uptake). Furthermore, the slope of the Gd-DTPA uptake is steeper in the non-hypoxic node (2F) than in the hypoxic node (1F). Table 3 allows comparison of the lymph nodes' hypoxic characteristics (derived from FMISO PET exams) with their quantitative DCE-MRI parameters. A Mann-Whitney U test showed that hypoxic lymph nodes were significantly larger in size (mean $\pm$ SD: $148 \pm 119 \text{ mm}^3$) than non-hypoxic nodes ($35 \pm 52 \text{ mm}^3$). It also showed that hypoxic nodes had significantly lower median K^{trans} ($p = 0.049$) and median k_{ep} ($p = 0.027$) values than did non-hypoxic nodes. Figure 3 displays the average distribution plots of the calculated K^{trans} (3A) and k_{ep} (3B) parameters for the hypoxic (black bars) and non-hypoxic nodes (white bars). The histograms depicting hypoxic nodes show significant shifts to lower K^{trans} (3A) and k_{ep} (3B) values, indicative of lower perfusion in hypoxic nodes. Furthermore, although the k_{ep} data points are spread out more to the right of the mean than to the left for both the hypoxic and the non-hypoxic nodes, this asymmetry, as determined by the k_{ep} skewness, is significantly larger in the hypoxic nodes ($p = 0.021$). Finally, Figure 4 depicts box plots of the average K^{trans} (4A) and k_{ep} (4B) values for hypoxic and non-hypoxic nodes. For both K^{trans} and k_{ep} , hypoxic nodes have significantly smaller values ($p < 0.05$), as indicated by a Mann-Whitney U test.

Discussion

Our study investigated whether pre-therapy DCE-MRI parameters correlate with hypoxia as measured by FMISO PET in neck nodal metastases in 13 newly diagnosed HN cancer patients. The results of our study support the hypothesis that hypoxic nodes are poorly perfused compared to nodes without hypoxia (12). A negative correlation between FMISO uptake (measure of hypoxia) and the median k_{ep} perfusion value was observed, and hypoxic nodes had lower median k_{ep} and median K^{trans} values than did non-hypoxic nodes. Furthermore, hypoxic nodes had a more asymmetric distribution of k_{ep} values than did non-hypoxic nodes. Finally, tumor size strongly correlated with FMISO uptake, which is in agreement with the results of a previous study by Dunst et al. (25), which showed a strong correlation between total tumor volume and hypoxic volume in 125 patients with HN squamous cell cancer.

Tumor progression requires a vascular network adequate to meet the metabolic needs of growing tumor tissue. As local tissue perfusion decreases, hypoxia develops because of an insufficient vascular supply of oxygen to the growing tumor mass. It has been shown that the presence of tumor hypoxia is an established vital factor in tumor progression and in resistance of tumors to therapy (26). Well-oxygenated cells are more sensitive to the

cytotoxic effects of ionizing radiation compared with poorly oxygenated cells (12). Hypoxia can also cause genome changes that select cells that are resistant to apoptotic signals, thus favoring the proliferation of resistant cell populations and promoting the development of cells with more aggressive phenotypes (27). Therefore, hypoxia in tumor tissue is an important prognostic indicator of chemotherapy and/or radiation therapy response (28).

To the best of our knowledge, ours is the first clinical study in patients with metastatic neck lymph nodes which indicates that noninvasive DCE-MRI and FMISO PET measurements of tumor perfusion and hypoxia, respectively, are inversely correlated. Several studies in the literature are in agreement with our results, although the techniques and subjects used in these studies differ, in some cases substantially. Our group recently published a study comparing perfusion and hypoxia parameters derived from DCE-MRI studies and from early FMISO uptake PET studies, respectively, in a rat prostate tumor model (11). The results suggested that tumor vasculature was a major determinant of early FMISO uptake. Furthermore, a negative correlation between the DCE-derived perfusion and late FMISO uptake was observed. These preclinical results are in agreement with the results of the present clinical study.

Scholbach et al. (29) recently performed a clinical study, in which the metastatic lymph nodes of 24 HN cancer patients were assessed for tissue oxygenation and perfusion using direct polarography and ultrasound, respectively. Although the assessment techniques used were inherently different, the end result was remarkably similar: an inverse relationship between hypoxia and tissue perfusion was found (29).

Our study also found that FMISO uptake correlated with FDG uptake, suggesting that in pretreatment HN metastatic nodes, hypoxic conditions leads to increased glucose uptake. These results are in accordance with other previous clinical HN studies (16,30,31). However, Rajendran et al. (16) examined HN cancers, soft tissue sarcomas, breast cancer and glioblastoma multiforme and found that highly metabolic tumors are not necessarily hypoxic. Therefore, FDG uptake should not be considered a surrogate marker for hypoxia (16). This will be the subject of future studies.

Firstly, the major limitation of our study was that a pixel by pixel analysis of DCE-MRI and FMISO PET images was not performed. However, it is important to note that DCE-MRI was performed as part of a diagnostic MRI examination yielding high resolution MR images and not as part of a radiation treatment planning study which uses exact matching with the PET study but provides lower resolution images. PET studies utilized an Aquaplast immobilization mask and a specific head rest. This led to different patient orientations during the two imaging (MRI and PET) examinations. For a pixel-by-pixel comparison, the factors that affect patient positioning would need to match each other exactly for the MRI and the FMISO PET examinations. These issues of image co-registration would be resolved best by the use of combined MRI/PET systems, which are currently entering the clinical arena (32). Secondly, it has previously been shown that there are potential limitations with single time-point FMISO imaging, which have led to the proposal of a dynamic scanning approach (11,33). In such an approach, the kinetic information of the tracer uptake and retention behavior in each PET image voxel can be analyzed using a mathematical compartment model, similar to the ones used for DCE-MRI, to generate parametric maps of putative hypoxia tracer trapping (33). Thirdly, FMISO PET images typically have low signal-to-noise characteristics as uptake of FMISO in tumors is relatively low. Therefore, the contrast between healthy tissue and tumors is typically low (34).

For future studies, multimodality imaging using DCE-MRI and ^{18}F -FMISO PET should ensure that patient positioning is the same as in PET, to enable a pixel-by-pixel co-registration that will help in radiation treatment planning.

Conclusion

Our preliminary results support the hypothesis that in metastatic neck lymph nodes, hypoxic nodes are poorly perfused (i.e., have significantly lower k_{ep} and K^{trans} values) compared to non-hypoxic nodes.

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Figure 1.

MRI and ^{18}F -FMISO PET images illustrating the hypoxic right neck lymph node of patient 2 (male, 62 years old, primary tonsil cancer). Coronal (A) and sagittal (B) T1-weighted and axial (C) short tau inversion recovery (STIR) images highlight the anatomy. The node is indicated with a white arrow. (D) Shows the post-contrast multi-phase spoiled gradient echo of the corresponding slice in (C). The node is outlined in yellow. The insert (E) in (D) displays the calculated parametric K^{trans} map of the node. In (F), the DCE-MRI signal (converted into Gd-DTPA concentrations) over the acquisition time is illustrated. The stars indicate the individual data points (averaged over the ROI), the thin black line is the fit, and the thick black line indicates the slope. Finally, in (G) the corresponding ^{18}F -FMISO image is shown, indicating ^{18}F -FMISO uptake in the node outlined in yellow.

Figure 2.

MRI and ^{18}F -FMISO PET images illustrating the non-hypoxic left neck lymph node of patient 1 (male, 51 years old, primary tonsil cancer). Captions for MR images A to F are similar to Figure 1 and G is the corresponding ^{18}F -FMISO image.

Figure 3. Average distribution histogram plots for the DCE-MRI parameters K^{trans} (A) and k_{ep} (B). The mean values for the hypoxic nodes are shown with black bars, whereas the mean values for non-hypoxic nodes are shown in white. Error bars indicate the standard error of the mean. K^{trans} and k_{ep} are given in min^{-1} .

Figure 4.

Box plots of the individual K^{trans} (A) and k_{ep} (B) values for nodes with and without ^{18}F -FMISO uptake. K^{trans} and k_{ep} are given in min $^{-1}$. Box plots display minimum, first quartile, median, third quartile, and maximum of the distribution of the values for the nodes.

* denotes $p < 0.05$ (Mann-Whitney U test).

Table 1

Patient characteristics.

Subject	Age (y) / sex	Primary cancer	Stage	# Nodes
1	51 / M	Tonsil	III	2
2	62 / M	Tonsil	IVa	1
3	48 / M	Tonsil	IVa	2
4	80 / M	BOT	IVb	1
5	47 / M	BOT	IVa	2
6	56 / M	Tonsil	IVa	1
7	66 / M	BOT	IVb	1
8	58 / M	BOT	IVa	3
9	48 / M	Tonsil	IVa	1
10	63 / M	BOT	IVb	1
11	65 / M	BOT	IVa	1
12	53 / M	BOT	IVa	1
13	60 / M	Larynx	III	1

M, male; BOT, base of tongue; # Nodes, number of metastatic neck lymph nodes.

Table 2

Spearman rank correlation coefficients for ^{18}F -FMISO uptake and DCE-MRI parameters, calculated over all 18 nodes.

DCE-MRI parameters	Correlation with ^{18}F -FMISO SUV
K^{trans} median	$\rho = -0.36$
K^{trans} SD	$\rho = -0.09$
K^{trans} skewness	$\rho = 0.43$
V_e median	$\rho = 0.26$
V_e SD	$\rho = 0.29$
V_e skewness	$\rho = -0.33$
k_{ep} median	$\rho = -0.58^*$
k_{ep} SD	$\rho = 0.29$
k_{ep} skewness	$\rho = 0.34$

K^{trans} : volume transfer constant (min^{-1}); v_e : extravascular extracellular space volume fraction; k_{ep} : redistribution rate constant (min^{-1}); SD: standard deviation; SUV: standardized uptake value.

* $p < 0.05$

Table 3

Differences in DCE-MRI parameters for hypoxic versus non-hypoxic lymph nodes.

DCE-MRI parameters	¹⁸ F-FMISO uptake (Hypoxic Lymph nodes) n = 10	No ¹⁸ F-FMISO uptake (Non Hypoxic Lymph nodes) n = 8
K ^{trans} median	0.27 ± 0.06 *	0.40 ± 0.17
K ^{trans} SD	0.13 ± 0.05	0.13 ± 0.03
K ^{trans} skewness	0.55 ± 0.71	0.13 ± 0.58
V _e median	0.64 ± 0.17	0.51 ± 0.21
V _e SD	0.24 ± 0.05	0.19 ± 0.08
V _e skewness	-0.13 ± 0.59	0.36 ± 0.80
k _{ep} median	0.49 ± 0.16 *	0.78 ± 0.27
k _{ep} SD	0.33 ± 0.11	0.40 ± 0.25
k _{ep} skewness	4.04 ± 3.17 *	1.15 ± 1.14

Median values are reported in units of the respective parameters; K^{trans}: volume transfer constant (min⁻¹); v_e: extravascular extracellular space volume fraction; k_{ep}: redistribution rate constant (min⁻¹); SUV: standardized uptake value; SD: standard deviation. All values are reported as mean ± SD

*
p < 0.05 (Mann-Whitney U test)