Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2012 January 1; 82(1): 299–307. doi:10.1016/j.ijrobp.2010.11.022.

Tumor Metabolism and Perfusion in Head and Neck Squamous Cell Carcinoma: Pretreatment Multimodality Imaging with ¹H-Magnetic Resonance Spectroscopy, Dynamic Contrast-Enhanced MRI and ¹⁸F-FDG PET

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Abstract

Purpose—To correlate proton magnetic resonance spectroscopy (¹H-MRS), dynamic contrast-enhanced MRI (DCE-MRI) and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) in nodal metastases of patients with head and neck squamous cell carcinoma (HNSCC) for assessment of tumor biology. Additionally, pretreatment multimodality imaging (MMI) was evaluated for its efficacy in predicting short-term response to treatment.

Methods and Materials—Metastatic neck nodes were imaged with ¹H-MRS, DCE-MRI and ¹⁸F-FDG PET in 16 patients with newly diagnosed HNSCC before treatment. Short-term radiological response was evaluated at 3–4 months. The correlations between ¹H-MRS (choline concentration, Cho/W), DCE-MRI (volume transfer constant, K^{trans} ; volume fraction of the extravascular extracellular space, v_e ; and redistribution rate constant, k_{ep}) and ¹⁸F-FDG PET (standard uptake value, SUV; and total lesion glycolysis, TLG) were calculated using non-parametric Spearman rank correlation. To predict the short-term response, logistic regression analysis was performed.

Results—A significant positive correlation was found between Cho/W and TLG ($\rho = 0.599$, $p = 0.031$). Cho/W correlated negatively with heterogeneity measures $std(v_e)$ ($\rho = -0.691$, $p = 0.004$) and $std(k_{ep})$ ($\rho = -0.704$, $p = 0.003$). SUVmax values correlated strongly with MRI tumor volume ($\rho = 0.643$, $p = 0.007$). Logistic regression indicated that $std(K^{trans})$ and SUVmean were significant predictors of short-term response ($p < 0.07$).

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All authors in this manuscript have no conflict of interest.

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Conclusion—Pretreatment multi-modality imaging using ^1H -MRS, DCE-MRI and ^{18}F -FDG PET is feasible in HNSCC patients with nodal metastases. Additionally, combined DCE-MRI and ^{18}F -FDG PET parameters were predictive of short-term response to treatment.

Keywords

Head and neck squamous cell carcinoma; ^1H -MRS; DCE-MRI; ^{18}F -FDG PET; short-term treatment response

Introduction

^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) is commonly used in head and neck squamous cell carcinoma (HNSCC) for tumor staging, monitoring of treatment response, detection of recurrence and radiotherapy planning (1–5). Most primary and metastatic cancers show enhanced glucose metabolism (6). The standardized uptake value (SUV) of ^{18}F -FDG is a semiquantitative measure of glucose metabolism which has been shown to predict biological aggressiveness and treatment response (7).

Similarly, non-invasive MRI techniques, including proton magnetic resonance spectroscopy (^1H -MRS) and gadopentetate dimeglumine (Gd-DTPA)-based dynamic contrast-enhanced MRI (DCE-MRI), have shown potential in HNSCC for assessment of treatment response and outcome (8). ^1H -MRS reveals the metabolite composition of tumors. Choline (Cho, a product of phospholipid metabolism) and lactate (product of glycolysis) are the metabolites most commonly studied in-vivo. Elevated levels of choline-containing compounds in tumors are thought to reflect membrane synthesis, and thus indirectly also elevated cell proliferation rate (9). In DCE-MRI, sequential images are obtained during the passage of a contrast agent through a tissue of interest. Using compartmental modeling, DCE-MR images can be converted into parameters reflecting characteristics of tumor vascularity (10).

In patients with HNSCC who undergo chemoradiation therapy, radiologic response assessment at 3–4 months after completion of treatment has been proven to be beneficial (11). Based on the results of this short-term evaluation, the treating physician is able to determine whether additional aggressive treatment should be pursued. Information from pretreatment MMI could potentially be used to further optimize clinical management of patients with HNSCC and to develop individualized treatment plans for patients (12).

To date, no reported clinical studies in HNSCC have correlated ^1H -MRS, DCE-MRI and ^{18}F -FDG PET data. The goal of the present feasibility study was to correlate data from pretreatment ^1H -MRS, DCE-MRI and ^{18}F -FDG PET of metastatic neck nodes in HNSCC patients for assessment of tumor metabolism and perfusion in vivo. Additionally, the study examined whether MMI data could be used to predict short-term response to treatment.

Materials and Methods

Patients

Our study was approved by the institutional review board and was compliant with the Health Insurance Portability and Accountability Act. Inclusion criteria for the study were as follows: biopsy-proven squamous cell carcinoma; presence of nodal metastasis in the neck; ability to give informed consent; the lack of contraindications to MRI. After giving informed consent, 76 patients were enrolled in our prospective MRI study from July 2006 to September 2009. Of these, 29 patients had both ^1H -MRS and DCE-MRI, and also pretreatment ^{18}F -FDG PET as part of their regular clinical care (chemoradiation or surgery). Out of these 29, 16 patients underwent chemoradiation as primary treatment, and had MMI

results available for retrospective analysis. Thus, the final population included 16 patients (3 females and 13 males, with an average age of 58 ± 7 years (mean $\pm$ SD)). The patients' primary tumor locations were as follows: base of tongue, 9, tonsil, 6, and nasopharynx 1. Patient characteristics are given in Table 1, and more detailed information is available in Table 2. For the 16 patients, the period between needle biopsy at the primary tumor site and MRI examination was 7 ± 3 days (mean $\pm$ SD); PET examinations were performed 11 ± 4 days (mean $\pm$ SD) before MRI, which took place prior to chemoradiation therapy. To ensure that the tumor microenvironment would be unchanged, biopsies of the nodes were not done.

A complete medical history was obtained and tumor assessment was performed at baseline. Short-term radiological response was assessed at 3–4 months after the completion of treatment by clinical evaluation and imaging studies; short-term response was defined as follows: no palpable discrete nodal disease in the neck, neck lymph nodes ≤ 1.5 cm on imaging, and no residual abnormal ^{18}F -FDG uptake on PET (1,11,13). All patients had a follow-up clinical evaluation at ≥ 3 months and were categorized as having either complete response (no evidence of disease on clinical and imaging examination) or incomplete clinical response (measurable disease).

^1H -MRS and DCE-MRI

MRI data from all 16 patients were acquired on a 1.5 Tesla G.E. Excite scanner (General Electric, Milwaukee, WI) with a 4-channel neurovascular phased-array coil. MR imaging covering the entire neck was performed, as described previously (14–15). The neck survey consisted of rapid scout images, multiplanar (axial, coronal and sagittal) T2-weighted, fat-suppressed, fast-spin echo images, and multi-planar T1-weighted images (14). During ^1H -MRS, spectra were acquired for the tumor identified on T2-weighted images by a neuro-radiologist, and a volume of interest ($>8\text{mL}$) was placed over the node, using TE 136 ms, TR 1.6 s, and 256 averages. Localization and water suppression were achieved with point-resolved spatially localized spectroscopy (PRESS) and chemical shift selective suppression, respectively. A spectrum (16 averages) of unsuppressed water was also recorded. Proton density (PD) images were acquired, on the same node studied by ^1H -MRS, for the purpose of determining the longitudinal relaxation rate constant R_1 for each DCE-MRI data point in the axial plane. The acquisition parameters for the PD images were as follows TR of 350 ms, TE of 2 ms with a 30° flip angle (α), 2 excitations, 15.63-kHz receive bandwidth, 18–20-cm field of view, 5–6-mm slice thickness, zero gap and a 256×128 matrix. DCE-MRI was 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, Wayne, NJ) at 2 cc/s, followed by a saline flush. The entire node was covered contiguously with 5–7-mm thick slices with zero gap, yielding 3–8 slices with 4.0–5.9-sec temporal resolution. The temporal resolution was sufficient to obtain nonbiased and accurate K^{trans} according to criteria published by Lopata et al. (16). Acquisition parameters for DCE-MRI were similar to those for PD imaging except that the TR was 9 ms and 40–80 time course data points were collected. For both PD images and DCE-MRI the 256×128 matrix was zero filled to 256×256 during image reconstruction.

^{18}F -FDG PET

All patients had their PET examinations performed on PET or combined PET/computed tomography (CT) scanners: GE Advance NXi (n=1), Discovery ST (n=9) Discovery LS (n=2) (GE Medical Systems, Waukesha, WI), and Siemens Biograph (n=4) (Siemens/CTI, Nashville/TN) (Table 2). The details for these examinations have been described previously (17). With this equipment, a low-dose CT scan (120–140 kV, approximately 80 mA), which is used for attenuation correction of PET emission images as well as for anatomic localization of PET abnormalities, was acquired first. This was followed by acquisition of

PET emission images of the head and neck for 5 min. Images were reconstructed using iterative algorithms. Attenuation correction was routinely applied. Patients were scanned in the supine position. Before the examination, patients fasted for at least 6 hours, but liberal water intake was allowed. Patients were injected with 444–555 MBq of ^{18}F -FDG intravenously. After a 60-minute uptake period, a PET/CT study was acquired with the patient in the same treatment position. Plasma glucose was < 150 mg at the time of imaging.

Image Analysis

For each patient, imaging findings from ^1H -MRS, DCE-MRI and ^{18}F -FDG PET were analyzed for the largest of the metastatic nodes identified by the neuroradiologist on T2-weighted MR imaging.

^1H -MRS and DCE-MRI Analyses—The ^1H -MRS spectra were analyzed using the LCModel software package (Version 6.2-1L) (18). LCModel automatically calculates a weighted coherent average over the multiple channels and analyzes the resultant spectrum (18). The metabolite basis set (PRESS, TE 136 ms, 1.5 T) included simulated macromolecule peaks. For each spectrum, the parts per million (ppm) range included for analysis was 2.7 to 3.8 ppm. The ‘only-cho-2’ setting was used, which provides concentration estimates for Cho in arbitrary units, relative to water (Cho/W). No corrections for relaxation were performed. The Cramer-Rao lower bound (CRLB), which simultaneously accounts for both resolution and noise level (18), was calculated as an estimate of the error in metabolite quantification (19). Metabolite estimates were excluded from analysis, if the CRLB exceeded the 50% range (19).

DCE-MRI data were analyzed with IDL 5.4 (Research Systems Inc., Boulder Co). For the tumor tissue time course data, regions of interest (ROIs) were manually drawn by an experienced neuro-radiologist (> 10 yrs of experience). Each ROI encompassed a whole metastatic node. The same nodes assessed with ^1H -MRS were assessed by DCE-MRI. All the slices containing each node were outlined and analyzed. The total number of pixels within the entire ROI was converted into the tumor volume (mm^3). Quantitative DCE-MRI analyses of the tumor tissue time course data was performed using the two-compartment Tofts model in all ROIs (20). A population-based arterial input function derived from the carotid arteries in head and neck cancer patients was used (21). The model fitted the tissue contrast agent concentration and yielded quantitative parameters K^{trans} (volume transfer constant in min^{-1}), v_e (volume fraction of the extravascular extracellular space (EES) which is dimensionless), and k_{ep} (rate constant in min^{-1} , which equals the ratio K^{trans}/v_e). DCE-MRI analyses of the tumor tissue were performed on a pixel-by-pixel basis. A histogram analysis was performed on all pixels within the ROI, which yielded the mean and standard deviation (std) of the distribution of all pixels. Histograms were normalized to the total number of tumor voxels to allow direct comparisons between patients. The standard deviation describes the width of the distribution and is indicative of the heterogeneity of the tumor (22).

Additionally, necrosis was assessed by the radiologist for the neck nodal metastasis in each patient on both the pre T2-weighted images and the post Gd-DTPA contrast T1-weighted images by means of visual inspection. Necrosis has hyperintense signal on T2-weighted and hypointense signal on post-contrast T1 weighted images. The MRI reading was scored on a scale of [0–2] with 0= no necrosis; 1= mild necrosis; and 2= severe necrosis.

^{18}F -FDG PET Analysis—All patients had full PET/CT data available for retrospective review on a standard clinical workstation (GE PACS with AW extension). One board-certified nuclear medicine physician with > 10 years of experience in head and neck imaging

reviewed these PET/CT studies. PET images in 3 orthogonal planes (transaxial, coronal, sagittal) and a maximum-intensity projection image were first reviewed (17). Afterward, the CT, PET, and PET/CT fusion images were displayed simultaneously. The nuclear medicine physician was provided with the location of each node studied as well as T2-weighted MR images of the node, on which the ^1H -MRS spectroscopy PRESS excitation box was overlaid. The nuclear medicine physician matched the ROIs from these MR images to the PET/CT images, and analyzed them visually and semiquantitatively, using the attenuation-corrected PET emission images. For semiquantitative analysis, ROIs were placed over the areas of focal ^{18}F -FDG uptake in the neck nodal metastases. The intensity of ^{18}F -FDG uptake in the ROIs was measured using the standardized uptake value (SUV), normalized to body weight. The maximum SUV (SUVmax) and the mean SUV (SUVmean) of each node were recorded, using a threshold of 50%. In addition, the total lesion glycolysis (TLG) was calculated as SUVmax $\cdot$ the tumor volume (in mm^3) (23). 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.

Statistical Analysis

All statistical calculations were performed using the software SPSS 15.0 for Windows. Correlations for the metastatic neck nodes between ^1H -MRS (Cho/W), DCE-MRI ($\text{mean}(\text{K}^{\text{trans}})$, $\text{std}(\text{K}^{\text{trans}})$, $\text{mean}(\text{v}_e)$, $\text{std}(\text{v}_e)$, $\text{mean}(\text{k}_{\text{ep}})$, and $\text{std}(\text{k}_{\text{ep}})$), ^{18}F -FDG PET (SUVmax, SUVmean, TLG) values, and tumor volume were calculated using nonparametric Spearman rank correlation. 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. Additionally, to investigate whether the ^1H -MRS, DCE-MRI and ^{18}F -FDG PET findings were affected by necrosis, tumor lesions were divided into three categories: 0=no necrosis; 1=mild to moderate necrosis; and 2=severe necrosis. Subsequently, a one-way ANOVA (using the degree of necrosis as an explanatory factor) was applied on these measures to assess the potential effect of necrosis. A P value < 0.05 was considered to indicate statistical significance.

To assess the predictive value of MRI and PET data for short-term response, logistic regression analysis was performed using the parameters Cho/W, $\text{mean}(\text{K}^{\text{trans}})$, $\text{std}(\text{K}^{\text{trans}})$, $\text{mean}(\text{v}_e)$, $\text{std}(\text{v}_e)$, $\text{mean}(\text{k}_{\text{ep}})$, $\text{std}(\text{k}_{\text{ep}})$, SUVmax, SUVmean, and TLG. The forward stepwise (LR) method of analysis was used (variable entered if $P < 0.10$, variable removed if $P > 0.15$). After creation of the multivariate model the predicted probabilities were saved. An ROC curve was constructed with these probabilities to assess the accuracy of the multivariate model for the prediction of short-term response. To assess the possible synergy between significant predictors of short-term response, regression analyses were performed for each significant predictor separately, and for all significant predictors combined.

Results

Out of 16 HNSCC patients, 1 was excluded from the final ^1H -MRS analysis due to high CRLB values (Table 2). In the remaining 15 patients, the median CRLB for Cho/W was 18 (range, 8 to 43); and the average voxel size was 8.4 ± 4.1 mL (mean $\pm$ SD).

DCE-MRI data were analyzed for all 16 patients. Additionally, complete sets of ^{18}F -FDG PET/CT results were obtained for 14 patients, as TLG could not be estimated for two patients due to data processing issue. All Spearman rank correlation coefficients are given in Table 3. Figures 1–3 show representative T2-weighted MRI, PET/CT, ^1H -MR spectroscopy and DCE-MRI data obtained from the neck region in one patient.

A strong positive correlation was found between the choline concentration (Cho/W) and ^{18}F -FDG TLG ($\rho = 0.599$, $p = 0.031$) (Figure 4A). Additionally, a strong negative correlation was found between Cho/W and $\text{std}(k_{\text{ep}})$ ($\rho = -0.704$, $p = 0.003$) (Figure 4B) as well as between Cho/W and $\text{std}(v_e)$ ($\rho = -0.691$, $p = 0.004$).

There was a strong positive correlation between ^{18}F -FDG measures SUVmax, SUVmean, and TLG with MRI tumor volume ($\rho = 0.643$, $p = 0.007$; $\rho = 0.565$, $p = 0.023$; and $\rho = 0.587$, $p = 0.027$, respectively) (Figure 4C).

A one-way ANOVA revealed that necrosis had a significant effect on, $\text{std}(v_e)$ ($p = 0.005$), and $\text{std}(k_{\text{ep}})$ ($p < 0.001$). Necrotic nodes had higher $\text{std}(v_e)$, and $\text{std}(k_{\text{ep}})$ values than nodes without necrosis.

At short-term response evaluation, 11 patients had complete response and 5 patients had incomplete clinical response (Table 2). The logistic regression analysis of the PET/CT, ^1H -MR spectroscopy and DCE-MRI data indicated that $\text{std}(K^{\text{trans}})$ ($p = 0.07$), and SUVmean ($p < 0.001$) were the only significant predictors of short-term response for the 13 patients with a full dataset (including Cho/W and TLG). The short-term responses could be predicted correctly in all these 13 patients using $\text{std}(K^{\text{trans}})$ and SUVmean, and the area under the ROC curve was 0.93 [95% CI 0.80 1.00] (Figure 5). Separate logistic regression analyses were performed for both significant predictors (using 16 patients). The regression analysis for SUVmean yielded a correct prediction of outcome of 81.3% and an ROC AUC of 0.87; $\text{std}(K^{\text{trans}})$ yielded a correct prediction of 69.2% and an AUC of 0.5; and using both SUVmean and $\text{std}(K^{\text{trans}})$ yielded a correct prediction of 100%, and an AUC of 0.96.

Discussion

Untreated HNSCC patients with nodal metastases underwent pretreatment MMI with ^1H -MRS, DCE-MRI and ^{18}F -FDG PET. Although there is no direct biological one-to-one link between these non-invasive imaging techniques, we found strong correlations between selected imaging parameters (Cho/W, ^{18}F -FDG SUV parameters). Two recent studies showed that the combination of DCE-MRI, ^{18}F -FDG PET, and ^{18}F -fluoromisonidazole (FMISO) PET has potential for assisting treatment planning for HNSCC patients. However, both studies were focused on hypoxia, and they did not correlate the data obtained from DCE-MRI and ^{18}F -FDG PET (12,15). The results of our study indicate that data from ^1H -MRS, DCE-MRI and ^{18}F -FDG PET in patients with HNSCC are complementary, and not competitive.

A strong positive correlation between Cho/W and ^{18}F -FDG TLG was observed. High Cho/W concentrations are indicative of an increased membrane choline phospholipid metabolism suggesting high proliferation (25). Khan et al. recently studied patients with HNSCC with both ^{18}F -FDG PET (glucose metabolism) and ^{11}C -labeled choline PET (phospholipid metabolism) and observed a significant correlation between ^{18}F -FDG and ^{11}C -choline SUVs (26). Our results support their inference that increased glucose metabolism is related to increased cellular proliferation. As neither SUVmax nor SUVmean displayed a significant correlation with Cho/W, tumor volume (required for calculating TLG) might be important.

A strong negative correlation was observed between Cho/W and $\text{std}(k_{\text{ep}})$ as well as between Cho/W and $\text{std}(v_e)$. Standard deviation measures describing the width of the pixel histogram distribution are indicative of the tumor heterogeneity (22). Our results suggest that areas of dense tumor cell population typically have high choline concentrations, due to a high membrane turnover, whereas heterogeneous head and neck tumors contain areas of low proliferation and often highly necrotic regions, as was suggested by our study. It has previously been shown in patients with gliomas that necrotic tissue has significantly lower

Cho concentrations than non-necrotic tissue (27). Other processes such as hypoxia might also play a role in heterogeneity (15), but hypoxia measurements were not obtained in this study. In a recent study, we employed FMISO PET/CT and DCE-MRI in patients with HNSCC, and showed that hypoxic nodes are poorly perfused (i.e., have significantly lower K^{trans} and k_{ep} values) compared with nonhypoxic nodes (15).

In accordance with the literature (28), MRI tumor volume, correlated strongly with SUVmax, SUVmean, and TLG from ^{18}F -FDG PET/CT.

Pretreatment DCE MRI parameter $\text{std}(K^{\text{trans}})$ and ^{18}F -FDG measure SUVmean were significant predictors for short-term response as assessed by radiological evaluation 3–4 months after completion of treatment. This is in accordance with previous studies, in which pretreatment DCE-MRI (29) and ^{18}F -FDG PET (30) were predictive of response to therapy in HNSCC. Pretreatment DCE-MRI and ^{18}F -FDG PET might therefore help physicians with evidence-based treatment planning. As the separate predictive performance of both significant predictors ($\text{std}(K^{\text{trans}})$ and SUVmean) was inferior to the performance of both predictors combined, a synergic action of the two modalities was demonstrated.

Our study has some limitations. Firstly, the number of patients was low ($n=16$). Secondly, the minimum ROI that can be achieved by ^1H -MRS is dependent on the signal-to-noise ratios of the metabolites studied. We studied choline only, as creatine was not visible. Studying lactate would require another specialized sequence for data acquisition (31), which was beyond the scope of this clinical study. The use of surface coils instead of phased-array coils would have been ideal for acquiring data from superficial tumors; However, in the present study, ^1H MRS was part of a clinical exam, and thus switching coils during the examination was not feasible. Though even with optimal techniques, ^1H MRS of necrotic tumors will still be a challenge, as such tumors may show very low choline concentrations, resulting in high CRLB values.

Finally, another limitation was that a pixel by pixel analysis of DCE-MRI and ^{18}F -FDG PET images was not performed. It should be noted that the patient orientations during the two imaging (MRI and PET) examinations were different. DCE-MRI was performed as part of a diagnostic clinical MRI examination whereas PET was in most cases performed as part of a radiation treatment planning study. To enable a pixel-by-pixel comparison, the patient positioning would need to be exactly the same for MRI and ^{18}F -FDG PET.

The present feasibility study shows interesting a priori results with DCE-MRI, ^1H MRS and FDG-PET data. Such pretreatment data may have translational applications in three areas: treatment planning, prediction of short-term treatment response or outcome, and monitoring treatment. MMI data shows in-vivo the heterogeneity of the nodal metastases in HNSCC patients and our initial results have shown that it can predict short-term response. In the future, if pretreatment MMI data can help distinguish tumors with a “good” from those with a “poor” prognosis, its use may allow patient-specific treatment. Specifically, it will help identify patients at risk earlier so that they can be considered for treatment with anti-angiogenic agents, hypoxia-targeting therapy or gene therapy. Additionally, MMI data will further improve our understanding of tumor biology in-vivo and help us unravel new treatment strategies.

Conclusion

Pretreatment multi-modality imaging using ^1H -MRS, DCE-MRI and ^{18}F -FDG PET is feasible in HNSCC patients with nodal metastases. Additionally, DCE-MRI and ^{18}F -FDG PET parameters were predictive of short-term response to treatment. Since PET and MRI

are complementary, rather than competitive, future work with combined MRI/PET systems would provide further insight into the biology.

Acknowledgments

Study funding: National Cancer Institute/National Institutes of Health (grant number 1R01CA115895). We thank Ada Mueller for manuscript editing.

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Figure 1.

Representative multiplanar MRI and ^{18}F -FDG PET/CT images illustrating the right neck lymph node of patient 2 (male, 37 years old, primary nasopharyngeal cancer). (A) Coronal T1-weighted, (B) axial STIR with ^1H -MRS voxel overlaid, and (C) axial T1-weighted postcontrast MR images showing the anatomy of the neck. The node is indicated with a white arrow in (A) and (C). The voxel of interest for ^1H -MRS is indicated in red in (B). In (D) the corresponding ^{18}F -FDG intensity map is shown overlaid on a CT, indicating ^{18}F -FDG uptake in the node.

Figure 2.

(A) Localized ^1H -MR spectrum from the node of patient 2. (B) LCModel analysis of the spectrum, highlighting the choline resonance. The in vivo spectrum (thin grey curve) has been estimated with the LCModel output (thick black curve), and the difference between these spectra (residue) is plotted at the top. tCho, choline; Lip/Lac, lipid and lactate resonances.

Figure 3.

The DCE-MRI Gd-DTPA contrast uptake curve and calculated outcome measures for the node of patient 2. (A) DCE-MRI signal, converted into Gd-DTPA concentrations, as a function of acquisition time. 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. (B) The corresponding distribution histogram plot for the DCE-MRI parameter K^{trans} (in min^{-1}).

Figure 4.

Scatterplots displaying correlations between imaging measurements. (A) Cho/W concentrations (arbitrary units) as a function of ¹⁸F-FDG TLG values (mm³g/mL). (B) Cho/W concentrations (arbitrary units) as a function of std(k_{ep}) (min⁻¹). (C) MRI tumor volume (mm³) as a function of SUVmax (g/mL).

Figure 5. ROC curve constructed using the predicted probabilities of the logistic regression model for the obtained imaging parameters (significant predictors: $\text{std}(K^{\text{trans}})$ and SUVmean). AUC: area under the curve.

Table 1

Patient characteristics

Characteristics	Value
No. of patients	16
Demographic	
Mean age (y)	58
Range (y)	43–70
No. of men	13 (81%)
Location of primary tumor	
Base of tongue	9 (56%)
Tonsil	6 (38%)
Nasopharynx	1 (6%)
Presenting Stage	
Stage III	1 (6%)
Stage IV	15 (94%)

Table 2

Patient characteristics, treatment regimes, imaging information, patient selection, and outcome

Subject	Age / sex	Primary Cancer	Stage	Primary Treatment	Chemotherapy	Radiation target (dose in cGy)	PET system	Included imaging	Short-term Response
1	52 / m	Tonsil	IVa	CRT*	cisplatin	OP 7000, LAN 5040	GE Advance NXi [†]	h,d,p [‡]	ICR
2	37 / m	NPC	IVa	CRT	cisplatin, fluorouracil	NP 7000, LAN 5000	GE Discovery ST	h,d,p	CR
3	43 / m	Tonsil	IVa	CRT*	cisplatin	OP 7000, LAN 5000	GE Discovery LS	h,d,p	ICR
4	62 / m	BOT	IVa	CRT	cisplatin	OP 7000, LAN 5040	GE Discovery LS [‡]	h,d,p [‡]	CR
5	62 / m	Tonsil	IVa	CRT*	cisplatin	OP 700, LAN 5040	GE Discovery ST	h,d,p	ICR
6	59 / m	BOT	IVa	CRT	cisplatin, bevacizumab	OP 7000, LAN 5040	GE Discovery ST	h,d,p	CR
7	61 / f	BOT	IVa	CRT	cisplatin, bevacizumab	OP 7000, LAN 5040	GE Discovery ST	h,d,p	ICR
8	57 / f	BOT	IVa	CRT	cisplatin, bevacizumab	OP 7000, LAN 5040	Siemens Biograph	h,d,p	CR
9	65 / m	BOT	IVa	CRT	cisplatin	OP & N 7000	GE Discovery ST	d,p	CR
10	60 / m	BOT	IVa	CRT	cisplatin, bevacizumab	OP & N 7000	Siemens Biograph	h,d,p	CR
11	70 / m	BOT	IVa	CRT	cisplatin, bevacizumab	OP 7000, LAN 5040	GE Discovery ST	h,d,p	ICR
12	68 / m	Tonsil	IVa	CRT	cisplatin, bevacizumab	OP 7000, LAN 5040	Siemens Biograph [‡]	h,d,p	CR
13	51 / f	Tonsil	IVa	CRT	cisplatin	OP 7000, LAN 5040	GE Discovery ST	h,d,p	CR
14	55 / m	BOT	IVa	CRT	cisplatin	OP 7000, LAN 5000	GE Discovery ST	h,d,p	CR
15	50 / m	Tonsil	IVa	CRT	cisplatin	OP 7000, LAN 5000	GE Discovery ST	h,d,p	CR
16	62 / m	BOT	III	CRT	cisplatin	OP 7000, LAN 5412	Siemens Biograph	h,d,p	CR

m: male, f: female, BOT: base of tongue, NPC: Nasopharyngeal, CRT: chemoradiation therapy, OP: oropharynx, LAN: low anterior neck, N: neck, NP: nasopharynx, h: ¹H-MRS, d: DCE-MRI, p: ¹⁸F-FDG PET, CR: complete response, ICR: incomplete clinical response. The row 'Included imaging' indicates modalities per patient included for analysis.

* Had surgery as salvage treatment.

[†] PET/CT was performed outside our Center.

[‡] TLG could not be calculated

Table 3

Spearman rank correlation coefficients for ^1H -MRS, DCE-MRI and ^{18}F -FDG PET data

	volume	Cho/W	mean(K^{trans})	std(K^{trans})	mean(v_e)	std(v_e)	mean(k_{ep})	std(k_{ep})	SUVmax	SUVmean	TLG
<i>volume</i>	1	-	-	-	-	-	-	-	-	-	-
<i>Cho/W</i>	-.018 ^a	1	-	-	-	-	-	-	-	-	-
<i>mean(K^{trans})</i>	-.324	.510 ^a	1	-	-	-	-	-	-	-	-
<i>std(K^{trans})</i>	.201	-.399 ^a	.150	1	-	-	-	-	-	-	-
<i>mean(v_e)</i>	-.135	.379 ^a	.661 ^{**}	-.007	1	-	-	-	-	-	-
<i>std(v_e)</i>	.353	-.691 ^{a**}	-.607 ^{**}	.482	-.233	1	-	-	-	-	-
<i>mean(k_{ep})</i>	-.194	-.307 ^a	-.163	.331	-.756 ^{**}	.027	1	-	-	-	-
<i>std(k_{ep})</i>	.047	-.704 ^{a**}	-.642 ^{**}	.496	-.665 ^{**}	.734 ^{**}	.625 ^{***}	1	-	-	-
<i>SUVmax</i>	.643 ^{**}	-.207 ^a	.161	.455	.355	.242	-.312	-.140	1	-	-
<i>SUVmean</i>	.565 [*]	.050 ^a	.278	.370	.459	.142	-.368	-.253	.973 ^{**}	1	-
<i>TLG</i>	.587 ^{b*}	.599 ^{c*}	.304 ^b	.149 ^b	.292 ^b	-.140 ^b	-.257 ^b	-.376 ^b	.550 ^{b**}	.587 ^{b*}	1

Cho/W = choline concentration; std = standard deviation; K^{trans} = volume transfer constant; v_e = extravascular extracellular volume fraction; k_{ep} = redistribution rate constant, SUVmax = maximum SUV value; SUVmean = average SUV value; TLG = total lesion glycolysis.

* $p < 0.05$,

** $p < 0.01$.

All correlations were calculated using independent data points from 16 patients, except for ^a 15 patients, ^b 14 patients, and ^c 13 patients. Inter-modality correlation coefficients are printed in 'grey italic'.