CLINICAL INVESTIGATION

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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Purpose: To correlate proton magnetic resonance spectroscopy (1H-MRS), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and 18F-labeled fluorodeoxyglucose positron emission tomography ([18F]FDG PET) of nodal metastases in patients with head and neck squamous cell carcinoma (HNSCC) for assessment of tumor biology. Additionally, pretreatment multimodality imaging 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 patient radiological response was evaluated at 3 to 4 months. Correlations among 1H-MRS (choline concentration relative to water [Cho/W]), DCE-MRI (volume transfer constant [Ktrans]; volume fraction of the extravascular extracellular space [ve]; and redistribution rate constant [krep]), and [18F]FDG PET (standard uptake value [SUV] and total lesion glycolysis [TLG]) were calculated using nonparametric Spearman rank correlation. To predict short-term responses, logistic regression analysis was performed.

Results: A significant positive correlation was found between Cho/W and TLG (r = 0.599; p = 0.031). Cho/W correlated negatively with heterogeneity measures of standard deviation std(ve) (r = 0.691; p = 0.004) and std(krep) (r = -0.704; p = 0.003). Maximum SUV (SUVmax) values correlated strongly with MRI tumor volume (r = 0.643; p = 0.007). Logistic regression indicated that std(Ktrans) and SUVmean were significant predictors of short-term response (p < 0.07).

Conclusion: Pretreatment multimodality imaging using 1H-MRS, DCE-MRI, and [18F]FDG PET is feasible in HNSCC patients with nodal metastases. Additionally, combined DCE-MRI and [18F]FDG PET parameters were predictive of short-term response to treatment. © 2012 Elsevier Inc.

Head and neck squamous cell carcinoma, Proton magnetic resonance spectroscopy, Dynamic contrast-enhanced MRI, [18F]FDG-PET, Short-term treatment response.

INTRODUCTION

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

Similarly, noninvasive magnetic resonance imaging (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 patients for assessment of treatment response and outcome (8). 1H-MRS...
METHODS AND MATERIALS

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 the presence of biopsy-proven squamous cell carcinoma and nodal metastasis in the neck, the ability to give informed consent, and no 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 underwent both 1H-MRS and DCE-MRI and also pretreatment [18F]FDG PET as part of their regular clinical care (chemoradiation or surgery). Of these 29 patients, 16 patients underwent chemoradiation as the primary treatment and had MMI results available for retrospective analysis. Thus, the final study population included 16 patients (3 females and 13 males, with a mean average age 7 years old. Patients’ primary tumors were located at the base of the tongue (9 patients), tonsil (6 patients), and nasopharynx (1 patient). Patient characteristics are given in Table 1, and more detailed information is available in Table 2. For these 16 patients, the period between needle biopsy at the primary tumor site and MRI examination was a mean average 7 days; PET examinations were performed at 11 ± 4 days 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 to establish baseline values. Short-term radiological response was assessed at 3 to 4 months after the completion of treatment by clinical evaluation and imaging studies; short-term response was defined as having no palpable discrete nodal disease in the neck, neck lymph nodes ≤1.5 cm on imaging, and no residual abnormal [18F]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 with a 1.5-Tesla Excite scanner (General Electric, Milwaukee, WI) with a four-channel neurovascular phased array coil. MRI covering the entire neck was performed as described previously (14, 15). Neck survey consisted of acquiring rapid scout images, multiplanar (axial, coronal, and sagittal) T2-weighted, fat-suppressed, fast-spin echo images, and multiplanar T1-weighted images (14). During 1H-MRS, spectra were acquired for the tumor, identified on T2-weighted images by a neuroradiologist, and a volume of interest (>8 ml) was placed over the node, using a echo time (TE) of 136 ms, a repetition time (TR) of 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 by using the same node studied by 1H-MRS to determine the longitudinal relaxation rate constant, R1, for each DCE-MRI data point in the axial plane. Acquisition parameters for PD images were a TR of 350 ms, a TE of 2 ms with a 30° flip angle (α), 2 excitations, 15.6-15.7-Hz receive bandwidth, an 18- to 20-cm field of view, a 5- to 6-mm-slice thickness, zero gap, and a 256 × 128 matrix. DCE-MRI was acquired using a fast multiphase 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 contiguous with 5- to 7-mm-thick slices with zero gap, yielding 3 to 8 slices with 40- to 5.9-s temporal resolution. The temporal resolution was sufficient to obtain nonbiased and accurate Ktrans values 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 to 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.

[18F]FDG PET

All patients underwent PET examinations or combined PET/computed tomography (CT) using the following scanner units, Advance NXi (no. of patients n = 1 patient), Discovery ST (n = 9

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>16</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>58</td>
</tr>
<tr>
<td>Range (y)</td>
<td>43–70</td>
</tr>
<tr>
<td>No. of men</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Location of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Base of tongue</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Presenting stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1 (6)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (94)</td>
</tr>
</tbody>
</table>
patients), Discovery LS (n = 2 patients [GE Medical Systems]), and Siemens Biograph (n = 4 patients [Siemens/CTI, Nashville, TN]) (Table 2). Details for these examinations have been described previously (17). Using 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 intake of water was allowed. Patients were injected intravenously with 444–555 MBq of [18F]FDG. After a 60-min uptake period, a PET/CT study was done with the patient in the same treatment position. Plasma glucose level was <150 mg at the time of imaging.

**Image analysis**

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

### Table 2. Patient characteristics, treatment regimes, imaging information, patient selection, and outcome

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age/sex</th>
<th>Primary cancer</th>
<th>Stage</th>
<th>Primary treatment</th>
<th>Chemotherapy (s)</th>
<th>Radiation target (cGy), site (cGy)</th>
<th>PET system</th>
<th>Imaging modality(s)</th>
<th>Short-term response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/m</td>
<td>Tonsil</td>
<td>IVa</td>
<td>CRT*</td>
<td>Cisplatin</td>
<td>OP 7000, LAN 5040</td>
<td>GE Advance NXi†</td>
<td>h, d, p†</td>
<td>ICR</td>
</tr>
<tr>
<td>2</td>
<td>37/m</td>
<td>NPC</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, fluorouracil</td>
<td>NP 7000, LAN 5000</td>
<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
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<td>Tonsil</td>
<td>IVa</td>
<td>CRT*</td>
<td>Cisplatin</td>
<td>OP 7000, LAN 5000</td>
<td>GE Discovery LS†</td>
<td>h, d, p†</td>
<td>ICR</td>
</tr>
<tr>
<td>4</td>
<td>62/m</td>
<td>BOT</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin</td>
<td>OP 7000, LAN 5040</td>
<td>GE Discovery LS†</td>
<td>h, d, p†</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
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<td>IVa</td>
<td>CRT*</td>
<td>Cisplatin</td>
<td>OP 7000, LAN 5040</td>
<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>6</td>
<td>59/m</td>
<td>BOT</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, bevacizumab</td>
<td>OP 7000, LAN 5040</td>
<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>7</td>
<td>61/f</td>
<td>BOT</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, bevacizumab</td>
<td>OP 7000, LAN 5040</td>
<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>8</td>
<td>57/f</td>
<td>BOT</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, bevacizumab</td>
<td>OP 7000, LAN 5040</td>
<td>Siemens Biograph</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>9</td>
<td>65/m</td>
<td>BOT</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin</td>
<td>OP and N 7000</td>
<td>GE Discovery ST</td>
<td>d, p</td>
<td>CR</td>
</tr>
<tr>
<td>10</td>
<td>60/m</td>
<td>BOT</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, bevacizumab</td>
<td>OP and N 7000</td>
<td>Siemens Biograph</td>
<td>h, d, p</td>
<td>CR</td>
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<tr>
<td>11</td>
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<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, bevacizumab</td>
<td>OP 7000, LAN 5040</td>
<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>12</td>
<td>68/m</td>
<td>Tonsil</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin, bevacizumab</td>
<td>OP 7000, LAN 5040</td>
<td>Siemens Biograph†</td>
<td>h, d, p†</td>
<td>CR</td>
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<tr>
<td>13</td>
<td>51/f</td>
<td>Tonsil</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin</td>
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<tr>
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<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>15</td>
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<td>Tonsil</td>
<td>IVa</td>
<td>CRT</td>
<td>Cisplatin</td>
<td>OP 7000, LAN 5040</td>
<td>GE Discovery ST</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
<tr>
<td>16</td>
<td>62/m</td>
<td>BOT</td>
<td>III</td>
<td>CRT</td>
<td>Cisplatin</td>
<td>OP 7000, LAN 5040</td>
<td>Siemens Biograph</td>
<td>h, d, p</td>
<td>CR</td>
</tr>
</tbody>
</table>

**Abbreviations:** 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-labeled MRS; d = DCE-MRI; p = [18F]FDG PET; CR = complete response; ICR = incomplete clinical response.

* Underwent surgery as salvage treatment.
† PET/CT was performed outside our center.
‡ TLG could not be calculated.
§ Modalities per patient included for analysis.

**1H-MRS and DCE-MRI analyses**

1H-MRS spectra were analyzed using LCModel software (version 6.2-1L) (18). LCModel software automatically calculates a weighted coherent average over multiple channels and analyzes the resultant spectra (18). The metabolite basis set (PRESS, TE 136 ms, 1.5 T) included simulated macromolecule peaks. For each spectrum, the range of parts per million (ppm) included for analysis was 2.7 to 3.8 ppm. The ‘‘only-cho-2’’ setting was used, which provides concentration estimates of Cho in arbitrary units relative to water (Cho/W). No corrections were performed for relaxation. The Cramer-Rao lower bound (CRLB) value, 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 value exceeded the 50% range (19).

DCE-MRI data were analyzed with IDL version 5.4 software (Research Systems Inc., Boulder, CO). For tumor tissue time course data, regions of interest (ROIs) were manually drawn by an experienced neuroradiologist (>10 years of experience). Each ROI encompassed a whole metastatic node. The same nodes assessed with 1H-MRS were also assessed with DCE-MRI. All the slices...
containing each node were outlined and analyzed. The total number of pixels within the entire ROI was converted to tumor volume (mm³). Quantitative DCE-MRI analyses of the tumor tissue time course data were performed using the two-compartment Tofts model in all ROIs (20). A population-based arterial input function derived from the carotid arteries in HNCC patients was used (21). The model fitted the tissue contrast agent concentration and yielded the following quantitative parameters: volume transfer constant (\(k_{\text{trans}}\), volume transfer constant min⁻¹); volume fraction of the extravascular extracellular space (\(v_e\)), which is dimensionless; and redistribution rate constant (\(k_{\text{ep}}\), rate constant min⁻¹), which equals the ratio of \(k_{\text{trans}}\) to \(v_e\). DCE-MRI analyses of the tumor tissue were performed on a pixel-by-pixel basis. A histogram analysis of all pixels was performed within the ROI, which yielded the means and standard deviations (std) of the distribution of all pixels. Histograms were normalized to the total number of tumor voxels to allow direct comparisons between patients. The std 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 produces a hyperintense signal on T2-weighted images and a hypointense signal on postcontrast T1-weighted images. The MRI reading was scored on a scale of 0 to 2, in which 0 = no necrosis, 1 = mild necrosis, and 2 = severe necrosis.

\[^{18}\text{F}\]FDG PET analysis

All patients had full PET/CT data available for retrospective review on a standard clinical workstation (PACS with AW extension; General Electric). One board-certified nuclear medicine physician, who has >10 years of experience in head and neck imaging, reviewed these PET/CT studies. PET images in three orthogonal planes (transaxial, coronal, and sagittal) and a maximum-intensity projection image were reviewed first (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 \(^1\text{H}\)-MRS spectroscopy PRESS excitation box was overlaid. The nuclear medicine physician matched the ROIs from these MR images with those of 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 \(^{18}\text{F}\)FDG uptake in the neck nodal metastases. The intensity of \(^{18}\text{F}\)FDG uptake in the ROIs was measured using the SUV normalized to body weight. The maximum SUV (SUVmax) and the mean SUV (SUVmean) values for each node were recorded using a threshold of 50%. In addition, total lesion glycolysis (TLG) was calculated as SUVmax × tumor volume (mm³) (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 SPSS version 15.0 software for Microsoft Windows. Correlations for the metastatic neck nodes among \(^1\text{H}\)-MRS (using Cho/W), DCE-MRI (using the parameters mean[\(K_{\text{trans}}\]), std[\(K_{\text{trans}}\]), mean[\(v_e\), std[\(v_e\), mean[\(k_{\text{ep}}\), and std[\(k_{\text{ep}}\), and \[^{18}\text{F}\]FDG PET (using SUVmax, SUVmean, and TLG) values and tumor volumes were calculated using nonparametric Spearman rank correlation. Correlations were interpreted using the guidelines from Cohen (24), in which absolute correlations of <0.3 were considered weak, 0.3 to 0.5 were considered moderate, and 0.5 to 1.0 were considered strong. Additionally, to investigate whether the \(^1\text{H}\)-MRS, DCE-MRI, and \[^{18}\text{F}\]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 analysis of variance (ANOVA; using the degree of necrosis as an explanatory factor) was applied to these measures to assess the potential effect of necrosis. A \(p\) value of <0.05 was considered statistically significant.

To assess the predictive value of MRI and PET data for short-term responses, logistic regression analysis was performed using the parameters Cho/W, mean[\(K_{\text{trans}}\]), std[\(K_{\text{trans}}\]), mean[\(v_e\), std[\(v_e\), mean[\(k_{\text{ep}}\), std[\(k_{\text{ep}}\), SUVmax, SUVmean, and TLG. The forward stepwise (logistic regression) method of analysis was used (a variable was entered for a \(p\) value of <0.10; a variable was removed for a \(p\) value of >0.15). After the multivariate model was created, the predicted probabilities were saved. A receiver operating

<table>
<thead>
<tr>
<th>Measures</th>
<th>Volume</th>
<th>Cho/W concn</th>
<th>Mean((K_{\text{trans}}))</th>
<th>std((K_{\text{trans}}))</th>
<th>Mean((v_e))</th>
<th>std((v_e))</th>
<th>Mean((k_{\text{ep}}))</th>
<th>std((k_{\text{ep}}))</th>
<th>SUVmax</th>
<th>SUVmean</th>
<th>TLG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>1</td>
<td>-0.018(*)</td>
<td>0.324</td>
<td>0.201</td>
<td>-0.135</td>
<td>0.353</td>
<td>-0.194</td>
<td>0.047</td>
<td>0.643</td>
<td>0.565</td>
<td>0.587*</td>
</tr>
<tr>
<td>Cho/W concn</td>
<td></td>
<td>1</td>
<td>0.510(*)</td>
<td>0.150</td>
<td>0.661</td>
<td>0.482</td>
<td>0.163</td>
<td>0.331</td>
<td>0.734</td>
<td>0.625</td>
<td>0.625*</td>
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<tr>
<td>Mean((K_{\text{trans}}))</td>
<td></td>
<td>0.150</td>
<td>-0.007</td>
<td>-0.233</td>
<td>0.163</td>
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</tr>
<tr>
<td>std((K_{\text{trans}}))</td>
<td></td>
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<td>0.734*</td>
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<td>0.704</td>
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<td>0.756</td>
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<tr>
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<td>0.149</td>
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<td>std((v_e))</td>
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<td>0.665*</td>
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<td>0.304*</td>
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<td>0.973</td>
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<tr>
<td>std((k_{\text{ep}}))</td>
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<td>0.376*</td>
<td>0.587*</td>
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<td>0.292</td>
<td>0.140</td>
<td>0.292</td>
<td>0.140</td>
<td>0.140</td>
<td>1</td>
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</tbody>
</table>

Abbreviations: Cho/W = choline/water concentration; std = standard deviation; \(K_{\text{trans}}\) = volume transfer constant; \(v_e\) = extravascular extracellular volume fraction; \(k_{\text{ep}}\) = redistribution rate constant; SUVmax = maximum standard uptake value; SUVmean = mean SUV; TLG = total lesion glycolysis.

All correlations were calculated using independent data points from 16 patients, except for the group of 15, 14, 8 and 13, 5 patients indicated. Intermodality correlation coefficients are shown in boldface type.

\(*) p < 0.05.
\(\dagger p < 0.01.\)
characteristic (ROC) curve was constructed with these probabilities to assess the accuracy of the multivariate model for the prediction of short-term responses. To assess the possible synergy among significant predictors of short-term response, regression analyses were performed for each significant predictor separately and for all significant predictors combined.

RESULTS

One of 16 HNSCC patients was excluded from the final $^1$H-MRS analysis due to high CRLB values (Table 2). For the remaining 15 patients, the median CRLB value for Cho/W was 18 (range, 8–43), and the average mean voxel size was 8.4 ± 4.1 ml.

DCE-MRI data were analyzed for all 16 patients. Additionally, complete sets of $[^{18}\text{F}]$FDG PET/CT results were obtained for 14 patients, as TLG could not be estimated for 2 patients due to a data processing issue. All Spearman rank correlation coefficients are listed in Table 3. Figures 1 to 3 show representative T2-weighted MRI, PET/CT, $^1$H-MRS, and DCE-MRI data obtained from the neck region of 1 patient.

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

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

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

At short-term response evaluation, 11 patients had complete responses, and 5 patients had incomplete clinical responses (Table 2). Logistic regression analysis of PET/CT,
1H-MRS, and DCE-MRI data indicated that 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). Short-term responses could be predicted correctly for all 13 patients by using std($K_{\text{trans}}$) and SUVmean, and the area under the ROC curve (AUC) was 0.93 (95% confidence interval, 0.80–1.00) (Fig. 5). Separate logistic regression analyses were performed for both of these significant predictors (using 16 patients). Regression analysis of SUVmean yielded a correct prediction of outcome of 81.3% and an ROC AUC of 0.87; analysis of std($K_{\text{trans}}$) yielded a correct prediction of 69.2% and an AUC of 0.5; and an analysis using both SUVmean and 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 [18F] FDG PET. Although there is no direct biological one-to-one link among these noninvasive imaging techniques, we found strong correlations between selected imaging parameters (parameters Cho/W and [18F]FDG SUV). Two recent studies have shown that the combination of DCE-MRI, [18F]FDG PET, and [18F]fluoromisonidazole ([18F]FMISO) PET has

![Image](image1.png)

**Fig. 2.** (A) Localized 1H-MR spectrum from the node of patient 2. (B) LCModel analysis of the spectrum, highlighting Cho resonance. The in vivo spectrum (thin grey curve) has been estimated with 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.

![Image](image2.png)

**Fig. 3.** DCE-MRI Gd-DTPA contrast uptake curve and calculated outcome measures for the node of patient 2 are shown. (A) DCE-MRI signal, converted to Gd-DTPA concentrations, is shown as a function of acquisition time. Stars indicate 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 $K_{\text{trans}}$ (min$^{-1}$).
potential for assisting treatment planning for HNSCC patients. However, both studies focused on hypoxia and did not correlate data obtained from DCE-MRI and [18F]FDG PET (12, 15). The results of our study indicate that 1H-MRS, DCE-MRI, and [18F]FDG PET data from patients with HNSCC are complementary and not competitive.

A strong positive correlation between Cho/W and [18F]FDG TLG was observed. High Cho/W concentrations are indicative of an increased membrane Cho phospholipid metabolism suggesting high proliferation (25). Khan et al. (26) recently studied patients with HNSCC by using both [18F]FDG PET (for glucose metabolism) and [11C]labeled Cho PET (for phospholipid metabolism) and observed a significant correlation between [18F]FDG and [11C]Cho SUVs (26). Our results support that study’s implication 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.

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with HNSCC and showed that hypoxic nodes are poorly perfused (i.e., they have significantly lower $K_{\text{trans}}$ and $k_{\text{ep}}$ values) compared with nonhypoxic nodes (15).

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

The pretreatment DCE-MRI parameter std($K_{\text{trans}}$) and the [$^{18}$F]FDG measure SUVmean were significant predictors for short-term response as assessed by radiological evaluation at 3 to 4 months after completion of treatment. This assessment is in accordance with that of previous studies in which pretreatment DCE-MRI (29) and [$^{18}$F]FDG PET (30) were predictive of responses to therapy in HNSCC patients. Pretreatment DCE-MRI and [$^{18}$F]FDG PET might therefore help physicians with evidence-based treatment planning.

As the predictive performances of each of the significant predictors (std($K_{\text{trans}}$) and SUVmean) separately were inferior to the combined performance of both predictors, a synergic action of the two modalities was demonstrated.

Our study has some limitations. First, the number of patients was low ($n = 16$). Second, the minimum ROI that can be achieved with $^1$H-MRS is dependent on the signal-to-noise ratios of the metabolites studied. We studied only Cho, 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, $^1$H-MRS was part of a clinical examination, and thus, switching coils during the examination was not feasible. Also, even with optimal techniques, $^1$H-MRS studies of necrotic tumors would still have been a challenge as such tumors may show very low Cho 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 patient orientations during the two (MRI and PET) imaging examinations were different. DCE-MRI was performed as part of a diagnostic clinical MRI examination, whereas PET was performed in most cases as part of a radiation treatment planning study. To enable pixel-by-pixel comparison, the patient positioning would have had to be exactly the same for MRI and [$^{18}$F]FDG PET.

The present feasibility study shows interesting a priori results with DCE-MRI, $^1$H-MRS, and [$^{18}$F] 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 show the in vivo heterogeneity of nodal metastases in HNSCC patients, and our initial results have shown that this technique can predict short-term response. In the future, if pretreatment MMI data can help distinguish tumors with a “good” prognosis from those with a “poor” prognosis, use of MMI may allow patient-specific treatment. Specifically, it will help identify patients at risk earlier so that they can be considered for treatment with antiangiogenic 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.

**CONCLUSIONS**

Pretreatment multimodality imaging using $^1$H-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 responses to treatment. Because PET and MRI are complementary rather than competitive, future work with combined MRI/PET systems would provide further insight into the biology of HNSCC.

**REFERENCES**


