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CLINICAL INVESTIGATION **Head and Neck Cancer**

TUMOR METABOLISM AND PERFUSION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA: PRETREATMENT MULTIMODALITY IMAGING WITH ^{1}H MAGNETIC RESONANCE SPECTROSCOPY, DYNAMIC CONTRAST-ENHANCED MRI, AND [^{18}F]FDG-PET

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Purpose: To correlate proton magnetic resonance spectroscopy (^{1}H-MRS), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and ^{18}F-labeled fluorodeoxyglucose positron emission tomography ([^{18}F]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 ^{1}H-MRS, DCE-MRI, and [^{18}F]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 ^{1}H-MRS (choline concentration relative to water [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 [^{18}F]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 ($\rho = 0.599$; $p = 0.031$). Cho/W correlated negatively with heterogeneity measures of standard deviation std(v_e) ($\rho = -0.691$; $p = 0.004$) and std(k_{ep}) ($\rho = -0.704$; $p = 0.003$). Maximum SUV (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 ($p < 0.07$).

Conclusion: Pretreatment multimodality imaging using ^{1}H-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. © 2012 Elsevier Inc.

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

INTRODUCTION

^{18}F-labeled fluorodeoxyglucose positron emission tomography ([^{18}F]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 [^{18}F]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 (^{1}H-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). ^{1}H-MRS

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reveals the metabolite composition of tumors. Choline (Cho; a product of phospholipid metabolism) and lactate (a product of glycolysis) are the metabolites most commonly studied *in vivo*. Elevated levels of Cho-containing compounds in tumors are thought to reflect membrane synthesis and, thus, indirectly, also elevated cell proliferation rate (9). DCE-MRI involves sequential imaging obtained during the passage of a contrast agent through the tissue of interest. Using compartmental modeling, DCE-MR images can be converted into parameters reflecting characteristics of tumor vascularity (10).

In HNSCC patients who undergo chemoradiation therapy, radiologic response assessment at 3 to 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 multimodality imaging (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 patients have correlated ^{1}H-MRS, DCE-MRI, and [^{18}F]FDG PET data. The goal of the present feasibility study was to correlate data from pretreatment ^{1}H-MRS, DCE-MRI, and [^{18}F]FDG PET studies 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.

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 ^{1}H-MRS and DCE-MRI and also pretreatment [^{18}F]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 $\pm$ SD of 58 $\pm$ 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 $\pm$ SD of 7 $\pm$ 3 days; PET examinations were performed at 11 $\pm$ 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 $\leq$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 $\geq$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).

Table 1. Patient characteristics

Characteristic	Value (% of total)
No. of patients	16
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	
III	1 (6)
IV	15 (94)

^{1}H-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) T_2-weighted, fat-suppressed, fast-spin echo images, and multiplanar T_1-weighted images (14). During ^{1}H-MRS, spectra were acquired for the tumor, identified on T_2-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 repitition 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 ^{1}H-MRS to determine the longitudinal relaxation rate constant, R_1, 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, 15.63-kHz receive bandwidth, an 18- to 20-cm field of view, a 5- to 6-mm-slice thickness, zero gap, and a 256 $\times$ 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 contiguously with 5- to 7-mm-thick slices with zero gap, yielding 3 to 8 slices with 4.0- to 5.9-s temporal resolution. The temporal resolution was sufficient to obtain nonbiased and accurate K^{trans} 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 $\times$ 128 matrix was zero-filled to 256 $\times$ 256 during image reconstruction.

[^{18}F]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