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Prediction of treatment response in head and neck carcinomas using IVIM-DWI: Evaluation of lymph node metastasis

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ABSTRACT

Purpose: To obtain diffusion and microperfusion measures in lymph node metastases of head and neck squamous cell carcinomas (HNSCC) using intravoxel incoherent motion (IVIM) imaging. The obtained IVIM parameters were used to characterize lymph nodes in the staging phase and longitudinal follow-up was performed to evaluate the potential predictive value of these parameters considering therapy response.

Methods: Fifteen patients with lymph node metastases of histologically confirmed locally advanced HNSCC were examined using diffusion weighted imaging (DWI) before a nonsurgical organ preserving therapy. DWI imaging was performed at 3 T using eight different *b*-values ranging from 0 to 800 s/mm^2. Using the IVIM-approach, the perfusion fraction *f* and the diffusion coefficient *D* were extracted using a biexponential fit. A follow-up period of 13.5 months was available for all patients. One patient with a macroscopically necrotic lymph node was excluded from analyses. A region of interest (ROI)-analysis was performed in all patients.

Results: Locoregional failure (LRF) was present in 3 of 15 patients within 13.5 months follow-up. The initial *f*-value was significantly higher ($p = 0.01$) in patients with LRF ($14.5 \pm 0.6\%$ vs. $7.7 \pm 2.6\%$) compared to patients with locoregional control (LRC). The initial diffusion coefficient *D* did not differ significantly ($p = 0.30$) between the two groups ($0.97 \pm 0.15 \times 10^{-3}$ mm^2/s vs. $0.88 \pm 0.13 \times 10^{-3}$ mm^2/s).

Conclusions: Our results indicate that a high initial perfusion fraction *f* in lymph nodes may predict poor treatment response in patients with HNSCC due to locoregional failure.

1. Introduction

Diffusion weighted imaging (DWI) with the associated apparent diffusion coefficient (ADC) is a well-established technique in the evaluation of probable lymph node metastases. With this method, the differentiation between benign lymph nodes and lymph node metastasis in head and neck squamous cell carcinomas (HNSCC) could be improved in comparison to morphologic images [1–2]. A lower ADC-value in metastastic lymph nodes is apparent [1–2]. According to previous analyses using contrast enhanced perfusion MRI/CT, also a hyperperfusion and hypervascularisation of cervical lymph node metastasis in HNSCC compared to benign lymph nodes were described [3–5].

An advanced imaging technique, the so-called intra-voxel incoherent motion (IVIM) model [6], allows the simultaneous measurement of the signal stemming from the vascular compartment (perfusion fraction *f*) and the diffusion restriction (diffusion coefficient *D*) without application of contrast medium. This technique is based on diffusion weighted imaging (DWI) with an increased number of *b*-values. By analyzing the DWI data using an increased number of *b*-values, a pronounced signal decay at low *b*-values can be obtained in well perfused tissue [6–7]. Previous studies using

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an inversion recovery DWI sequence with blood suppression confirmed, that this pronounced, non-monoexponential signal decay at low *b*-values is caused by signal from the vascular compartment caused by a combination of blood volume, blood flow and T_2-signal [8]. By applying a biexponential fit on diffusion weighted data, the perfusion fraction *f* and the perfusion free diffusion parameter *D* can be separated [8–9]. In contrast to the well-established ADC-value, which is influenced by cellularity and perfusion effects [6–7], these new surrogate markers are related to tissue microstructure (diffusion coefficient *D*) and to the vascular compartment (perfusion fraction *f*). Using this techniques in head and neck tumors at the primary tumor site, the differentiation of diverse head and neck tumors could be improved [10]. In addition, this technique may hold a great potential in tumor characterization and prediction of treatment response in HNSCC [11]. The purpose of this study was to characterize the perfusion fraction *f* and the diffusion coefficient *D* in lymph node metastasis of HNSCC previous to therapy with regard to its ability to predict treatment response.

2. Materials and methods

2.1. Subjects

The study was approved by the local Institutional Review Board and performed in accordance with the ethical standards of the Declaration of Helsinki. Exclusion criteria from this study were age below 18 years and general contraindication for MRI. Written informed consent was obtained from all participants.

In this single-center study twenty-two consecutive patients with histological confirmed locally advanced HNSCC were recruited from the department of radiation therapy. In fifteen of these patients, potential lymph node metastases were present in the baseline examination covered by DWI images. The potential lymph node metastases were retrospectively analyzed. Morphological suspicious lymph nodes with a short axis of at least 15 mm were considered as being lymph node metastases [12]. In patients with several lymph node metastases, the largest lymph node covered by the DWI sequence was selected for analyses. Of these fifteen patients, nine suffered from oropharyngeal, three patients from hypopharyngeal and three patients from laryngeal carcinoma. The mean age at inclusion was 54.5 ± 7.6 years (range: 43–69 years; 6 women, 9 men).

Baseline MRI was performed before a nonsurgical organ preserving therapy. Each patient obtained radiotherapy in combination with chemotherapy and/or immunotherapy. The chemotherapy regimen was variable. Patients received either carboplatin/cisplatin and 5-fluoruracil alone ($n = 10$) or in combination with doxataxel ($n = 4$). In patients receiving immunotherapy ($n = 12$), cetuximab was added. All patients were followed-up clinically and imaging-based for 13.5 months after the end of treatment or until locoregional failure was present, respectively. Imaging-based assumed locoregional failure was histological confirmed by biopsy.

2.2. Magnetic resonance imaging

The baseline MRI examination and follow-up examinations (1.5, 4.5, 7.5 and 13.5 months after completion of therapy) were performed using the same scanning protocol. Patients were examined using a 3 T scanner (MAGNETOM Trio, Siemens Medical Solutions, Erlangen, Germany) using a 4-channel neck array coil. For DWI a single-shot echo-planar imaging (SE-EPI) pulse sequence in axial orientation was performed with these parameters: TR/TE: 1300/50 ms, 13 slices, slice thickness: 3 mm, inplane resolution: $3 \times 3\ mm^2$, field of view (FOV): $240 \times 240\ mm^2$, 10 averages, bandwidth: 3472 Hz/pixel, *k*-space based parallel imaging technique GRAPPA acc. factor 2, total imaging time: 4:51 min. Eight different *b*-values were acquired ranging from 0 to 800 s/mm^2 ($b = 0, 50, 100, 150, 200, 250, 700, 800\ s/mm^2$). Three diffusion directions were used. Trace weighted images were computed from the acquired images and were used for further analysis. Besides DWI, morphologic images including T_1- and T_2-weighted TSE sequences as well as T_2 Tirm (turbo-inversion recovery-magnitude) sequences were acquired. After application of contrast medium (0.1 mmol/kg bodyweight Gadobutrol), T_1 TSE images with fat saturation were acquired.

2.3. Postprocessing and data analysis

To calculate the perfusion fraction *f* and the diffusion coefficient *D*, the diffusion weighted data were post-processed using the MITK (Medical Imaging Interaction Toolkit) software [13] according to the IVIM model [6]:

$$\frac{S}{S_0} = (1 - f) \times \exp(-b \times D) + f \times \exp(-b \times (D + D^*))$$

Here, S_0 corresponds to the signal without- and *S* to the signal with diffusion weighting. The parameter estimation was based on the assumption that the diffusion measurement is influenced mainly by two effects, a perfusion related effect introduced by the molecules moving in the capillary network (pseudodiffusion coefficient, D^*) and extravascular effects of passive diffusion (*D*). Since a simultaneous nonlinear fit for all parameters *D*, D^*, and the weighting coefficient *f* can be instable, measurement at *b*-values greater than 170 s/mm^2 were used in a first step to estimate *f* and *D* as proposed previously [14]. D^* was then calculated in a second step by using exhaustive search.

For these quantitative analyses, a region of interest (ROI) analysis was performed. A single experienced radiologist first identified the corresponding area on the diffusion weighted images by comparing these data with morphological images. ROIs were than drawn on diffusion weighted images including the whole volume of the lymph node metastasis (in few cases the enlarged lymph node was subtotally covered by the DWI sequence) while excluding large necrotic areas and adjacent cervical vessels. One patient was excluded from analyses because of a macroscopically completely necrotic lymph node metastasis. The signal intensities within each ROI were averaged first and subsequently the IVIM-parameter *f* and *D* were calculated. These baseline values of *f* and *D* were compared to the clinical outcome within a follow-up of 13.5 months after the end of treatment. According to these follow-up results, the patients were divided into two groups, one representing the patients with locoregional control (LRC) and the other including patients with locoregional failure (LRF).

2.4. Statistics

Statistical analyses were performed using SPSS (version 19; IBM SPSS; Chicago, IL). All quantitative measurements are presented as mean ±standard deviation (SD). An independent *t*-test was performed to detect significant changes in the baseline values between patients with LRC and patients with LRF. *p*-values of less than 0.05 were considered to represent a significant difference.

3. Results

In total, lymph node metastases in fourteen patients were analyzed before a nonsurgical organ preserving therapy using the IVIM approach. After a follow-up period of 13.5 months after conclusion of treatment, a locoregional failure (LRF) occured in three of these fourteen patients. Eleven patients presented a locoregional