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Research papers

The prediction of the treatment response of cervical nodes using intravoxel incoherent motion diffusion-weighted imaging

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ABSTRACT

Purpose: To investigate the predictive role of Intravoxel Incoherent Motion Diffusion-Weighted Imaging (IVIM-DWI) parameters on cervical nodal response to chemo-radiotherapy (CRT) of head and neck squamous cell carcinoma (HNSCC).

Materials and methods: Patients with pathologically confirmed HNSCC were included in the present prospective study, having at least one positive cervical lymph node (LN). They received concomitant CRT and underwent three serial IVIM-DWI investigations: before, at mid-treatment and after treatment completion. Tissue diffusion coefficient D, perfusion-related diffusion coefficient D* and perfusion fraction *f* were calculated by a bi-exponential fit. The two-sided Mann–Whitney rank test was used to compare the imaging parameters of patients with regional failure (RF) and regional control (RC). A p value lower than 0.05 was considered to be statistically significant.

Results: Thirty-four patients were accrued. Twenty-four out of 34 LN (70.6%) showed persistent RC after a median follow-up time of 27.6 months (range: 12.0–50.2 months), while ten cases of RF (29.4%) were confirmed with a median time of 6.8 months (range: 1.5–19.5 months). Patients with RC showed significantly lower pre-treatment D values compared to the RF patients ($p = 0.038$). At mid-treatment, the patients with RF showed significantly higher D values ($p = 0.025$), and exhibited larger percent reductions in *f* and the product $D^* \times f$ from the baseline ($p = 0.008$ and < 0.001, respectively). No additional information was provided by the examination at the end of treatment.

Conclusion: Pre-treatment and mid-treatment IVIM-DWI showed potential for prediction of treatment response of cervical LN in HNSCC patients.

1. Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the fifth most prevalent type of cancer worldwide. It accounts for approximately 3–4% of all malignancies [1]. Primary chemo-radiotherapy (CRT) is the treatment of choice for locally advanced head and neck squamous cell carcinomas (HNSCC) to attempt organ and function preservation [2]. However, some patients will not benefit from CRT, and must rely on the surgical clearance of the residual/recurrent cancer. The identification of patients who were responsive to treatment, based on pre-treatment or intra-treatment information, may be advantageous to post-treatment evaluation as unnecessary treatment is avoided for potentially non-responsive patients.

It is recognized that morphologic imaging alone is limited, as the treatment response is not only based on the changes in tumor size but also on the initial biological characteristics of the tumor, such as its oxygenation status, proliferative capacity, and perfusion characteristics [3–5]. Thus, the use of functional and metabolic imaging modalities [3] for the identification of novel biomarkers may help to elucidate the pathogenesis of CRT-resistant tumors, and aid clinicians in optimizing and tailoring individual treatment options for patients.

The diffusion-weighted imaging (DWI) is a promising, functional

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imaging modality for patients with HNSCC. It provides an early assessment of the tumor response to CRT [4], and allows for the quick assessment of the lesion without injecting contrast medium. According to several studies, DWI provides quantitative information on the apparent diffusion of water molecules in biological tissue, based on the measurement of the signal attenuation coefficient, or the apparent diffusion coefficient (ADC) [6]. ADC quantification indirectly evaluates tumor cellularity; whereby, a higher resistance towards water diffusivity is typically observed in cancers as a consequence of the increased cell density of the tumoral tissue [6].

The ADC parameter can be analytically derived following post-processing of the diffusion-weighted images. Nonetheless, experimental and clinical studies have suggested that tissue perfusion may influence the value of ADC; this observation further indicates that a simple mono-exponential fit may be inadequate for a correct description of the signal attenuation curve in response to increasing b values [7]. A specialized imaging technique, known as intravoxel incoherent motion (IVIM) imaging, was proposed to account for the effects of microcapillary perfusion on DWI measurements [8]. It acquires multiple diffusion b values, and provides the quantitative parameters that separately reflect tissue diffusivity and tissue microcapillary perfusion. The use of IVIM-DWI allows for the derivation of three additional parameters to ADC: *f*, the perfusion fraction; D*, the perfusion-related diffusion coefficient; and D, the diffusion coefficient related to tissue molecular diffusion.

The potential utility of IVIM imaging in patients with HNSCC is due to the influence of the tumor vasculature and oxygenation status on radioresistance. In several studies using perfusion computed tomography or dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI), the decreased perfusion levels were associated with a higher failure rate, which was attributed to a reduced sensitivity to radiation-induced free radical damage [9–11].

Although there has been growing interest in the use of IVIM-DWI in HNSCC [12,13], only a few studies investigated the potential utility of IVIM-DWI to predict the treatment response to CRT [14,15].

The primary aim of this study is to evaluate the predictive role of IVIM-DWI parameters, evaluated prior to radiation therapy (RT), at mid-RT, and at the end of RT, in the assessment of the cervical lymph nodes' long-term response to CRT.

2. Methods and materials

2.1. Patient population & treatment

A single-institution prospective trial, aimed at evaluating the role of IVIM-DWI in predicting treatment response of HNSSC to CRT, was approved by our institutional ethics committee (RS 266/12). Eligible patients fulfilled all the following inclusion criteria: a) histologically-confirmed diagnosis of HNSCC; b) absence of distant metastases (M0); c) treatment with definitive concomitant chemotherapy and intensity-modulated radiation therapy (IMRT); d) age > 18 years old; e) informed, written consent. Exclusion criteria included general contra-indications for MRI. In the present investigation, we focused our analyses on the incidence of metastatic lymph node (LN). Patients who were included in the present study were required to have at least one cervical lymph node metastasis based on volumetric and/or morphologic criteria (i.e. alterations of the internal architecture, presence of extracapsular spread) as defined by Rao et al. [16].

Patients were staged according to the tumor, node, metastasis (TNM) staging system of the American Academy of Otolaryngology, Head and Neck Surgery [17]. All patients received IMRT and concomitant chemotherapy (cisplatin 100 mg/m^2 for three cycles every 21 days). A seven-field, simultaneous, integrated boost technique was used to deliver 70 Gy, in 33 fractions, to the site of the macroscopic disease (primary tumor and affected LN), 60 Gy to the regions at high risk of developing microscopic disease, and 54 Gy to the regions at low risk of developing microscopic disease.

Considering the clinical relevance of the human papilloma virus (HPV) to the radiation sensitivity of oropharyngeal cancers [18], we determined the HPV status on this subset of patients.

2.2. Follow-up criteria

Follow-up consisted of clinical assessments and imaging examinations. The first follow-up MRI scan was performed 8 weeks after the end of RT; afterwards, MRI was performed every 6 months for the first two years, and then once a year. FDG-PET-CT was performed 12 weeks after the end of RT, and then once a year. At the time of the analysis, patients were categorized into two groups: those with regional control (RC), and those with regional failure (RF). RF was defined as the presence of residual disease following CRT or the recurrence of nodal disease (after initial clearance) during the follow-up. All nodal failures were pathologically confirmed.

2.3. MR imaging protocol

MRI was performed on a 1.5-T system (Optima MR 450w, GE Health-care, Milwaukee, WI, USA) with dedicated 16-channel receive-only radiofrequency coils: a head coil, a surface neck coil, and a spine coil. The patients underwent three serial MRI examinations: before RT, half-way through the course of RT (at the 16th or 17th fraction of RT), and at the end of RT (on the same day as the last dose fraction). The MRI examinations included fast spin-eco (FSE), T2-weighted images, and DWI. FSE T2-weighted images on the coronal plane were first obtained, followed by axial FSE T2-weighted images (acquisition matrix 256 × 256, field of view 26–28 cm, TR/TE = 2260 ms/119; slice thickness 4 mm, spacing between slices 5 mm), acquired from the level of the skull base to the thoracic inlet. DWI were obtained via single-shot spin-echo, and echo-planar imaging (acquisition matrix, 128 × 128; field of view, 26–28 cm; TR/TE 4500 ms/77 ms; slice thickness 4 mm; spacing between slices 5 mm, bandwidth 1953 Hz/pixel). The diffusion-sensitizing gradient duration and diffusion time were 19 and 29 ms, respectively. Nine different b values (b = 0, 25, 50, 75, 100, 150, 300, 500 and 800 s/mm^2) were used, with the diffusion-sensitizing gradients applied in three orthogonal directions to obtain trace-weighted images. The reduced signal-to-noise ratio (SNR) with the largest b values were accounted for by choosing three signal averages for *b* values ranging from 0 to 300 s/mm^2, four for *b* values of 500 s/mm^2, and five for *b* values of 800 s/mm^2. A scan time reduction factor of two was used, with a resulting scan duration of 6 min and 13 s.

The imaging protocol used prior to RT included additional sequences for more complete tumor characterization such as pre-contrast T1-weighted images, and the multi-phase post-contrast T1-weighted series.

2.4. Tumor delineation

Three contiguous sections of LN, each covering the largest cross-sectional area of the lesion, were identified on DWI with *b* = 800 s/mm^2, by two expert HN radiologists (A.V. and F.P.) in consensus, with more than 15 and 6 years of experience, respectively.

Morphological T2-weighted images and/or post-contrast T1-weighted images were used as a guide for tumor delineation. Arterial or venous structures, and bony components were excluded from the volume of interest (VOI).

In patients with several LN metastases, the largest LN was initially selected from the DWI sequence. To improve consistency in the identification of the chosen lymph node across the three serial MRI scans, contouring was performed at the end of treatment when all the scans were available for each patient.

For cases involving regional recurrence in an LN different from that of the largest one, the exact site of the nodal recurrence was identified by the HN radiologists on each MRI scan, and used for the analyses.