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Morbidity of head and neck radiotherapy

Diffusion-weighted magnetic resonance imaging for evaluation of salivary gland function in head and neck cancer patients treated with intensity-modulated radiotherapy

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ABSTRACT

Background and purposes: Permanent xerostomia as a result of radiation-induced salivary gland damage remains a common side effect of radiotherapy (RT) of the head and neck. The purpose of this study was to evaluate the usefulness of diffusion-weighted magnetic resonance imaging (DW-MRI) in assessing the post-RT salivary gland function in patients with head and neck cancer (HNC).

Materials and methods: In this prospective study, 20 HNC patients scheduled for bilateral neck chemoradiotherapy (CRT) with weekly cisplatin went through diffusion-weighted magnetic resonance imaging (DW-MRI) and salivary gland scintigraphy (SGS) prior to and at a mean of six months after completing the treatment. The changes in apparent diffusion coefficient (ADC) before and after treatment were compared with ejection fraction (EF) measured with SGS and the radiation dose absorbed by the salivary glands.

Results: As a result of gustatory stimulation with ascorbic acid, the ADC showed a biphasic response with an initial increase and subsequent decrease. This pattern was seen both before and after RT. Post-RT ADC increased as a function of RT dose absorbed by the salivary glands. A moderate statistical correlation between pre- and post-RT ADCs at rest and EF measured with SGS was found.

Conclusions: DW-MRI seems a promising tool for detection of physiological and functional changes in major salivary glands after RT.

Radiation-induced salivary gland damage and consequential xerostomia is one of the most common and distressing adverse effects of radiotherapy (RT) for head and neck cancer (HNC) [1–2]. Mechanisms of salivary gland damage related to radiation are incompletely understood [3] and interventions for reducing radiation-induced hyposalivation remain limited. Despite the modern highly conformal intensity modulated radiotherapy or proton therapy (IMRT/IMPT) techniques, sparing of the salivary gland function after RT is not always possible [4–5].

Thus far, salivary gland scintigraphy (SGS) and quantitative salivary flow rate measurements have been the mainstay of assessing the salivary gland function in HNC patients. SGS has shown to be feasible of predicting post-RT salivary gland function [6] but the usefulness of this measurement modality is limited by its invasiveness as well as the radiation exposure related to it. Quantitative salivary flow rate measurements are somewhat unspecific and their results are not always comparable between studies [7].

During the past years, diffusion-weighted magnetic resonance imaging (DW-MRI) has gained increasing interest in assessing various conditions affecting salivary glands [8–16]. As an imaging technique able to show the random thermal molecular diffusion of water molecules (i.e. the Brownian motion) in biological tissues, it characterizes tissues and generates image contrasts based on differences in water mobility. The diffusion leads to signal attenuation, which can be quantified as the apparent diffusion coefficient (ADC). In highly cellular tissues, e.g. tumours, the movement of free water is limited, which leads to decrease in ADC. On the contrary, in hypocellular tissues, e.g. necrosis, the diffusion is high, which can be detected as an increase in ADC [17–18].

DW-MRI's feasibility of assessing salivary gland function has been studied in healthy volunteers [19–21] and in patients with various conditions affecting salivary gland function [10–11] as well

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as in HNC patients treated with radiotherapy [12–16]. The previous studies have shown that changes in ADC both before and after gustatory stimulation correlate with changes in salivary gland function. Still, in these studies the alterations in ADC before and after RT and responses to salivary stimulation have varied widely, and their clinical relevance remains incompletely understood. Further interpretation is needed to achieve a better understanding of the usability of DW-MRI in this area.

In this prospective study of 20 patients treated with IMRT for head and neck cancer we aimed at evaluating the feasibility of DW-MRI for assessing the post-RT salivary gland function both at rest and in a stimulated state by matching alterations in ADC to radiation dose absorbed by the salivary glands and comparing the results with SGS.

Patients and methods

This prospective study comprises 21 consecutive patients with histologically confirmed squamous cell carcinoma of the head and neck region who were scheduled for bilateral neck IMRT with a curative intent between May 2012 and July 2013. One patient dropped out of the study due to numerous treatment-related complications, resulting in a total of 20 patients included in the analyses. An institutional Research Ethics Board approval was granted for the study, and informed consent was obtained from all patients prior to participation.

The main patient and tumour characteristics are presented in Table 1.

Prior to treatment, the patients went through standard pretreatment evaluation including clinical head and neck examination, imaging (CT/MRI) and endoscopy. All diagnoses were histopathologically confirmed. The tumours were staged according to the 7th UICC TNM classification. All patients had a good performance status (ECOG 0-1) and none of them had any previous salivary gland diseases or other medical causes of xerostomia.

Treatment

All patients received IMRT-based chemoradiotherapy (CRT) with weekly cisplatin 40 mg/m^2. A thermoplastic head and neck mask (Orfit®) was used for immobilization of the patients. Treatment target delineation was based on treatment planning CT and MRI, both performed in the treatment position.

Irradiation was performed with a 6 MV linear accelerator using a dynamic multileaf collimator with the sliding window principle. In all patients the treatment was given with 2 Gy daily fractions up to the planned dose with a mean treatment duration of 49 days (range, 46–56 days). All patients first received 50 Gy to the elective lymph node areas on both sides of the neck as well as to the macroscopic tumour area(s). Thereafter the RT volume was reduced (once in 11 patients and twice in 9 patients) and the high risk/macroscopic tumour areas were boosted up to 60–70 Gy. In 19 of the patients the CRT was given as a definitive treatment with the total prescribed dose up to 70 Gy; the remaining patient went through neck dissection due to recurrent lymph node metastases of a previously operated carcinoma of the soft palatine whereafter she received postoperative CRT up to 60 Gy.

The mean RT dose to the contralateral parotid gland was aimed at being kept <26 Gy whenever feasible. Also the dosage to submandibular glands was tried to be kept as low as reasonably possible.

Table 1
Patient and tumour characteristics.

Male/female, *n* (%)	16 (80%)/4 (20%)
Age, years (mean)	42–74 (59.5)
Tumour site, *n* (%)	
Larynx	1 (5%)
Oropharynx	19 (95%)
Stage, *n* (%)	
I	0 (0%)
II	3 (15%)
III	3 (15%)
IVa	13 (65%)
IVb	1 (5%)
IVc	0 (0%)

MRI protocol

The imaging was performed with a 1.5 T MR scanner GE Optima® MR450w (GE Medical Systems, Milwaukee, WI, USA). MRI scans were made a mean of 8 days (5–15) prior to the treatment onset and a mean of 6 months (with an exception of one patient who underwent imaging already at 3.7 months) after completion of the treatment.

Prior to treatment the routinely used fast recovery fast spin echo T2-weighted (TE = 89 ms, TR = 9400 ms, matrix size = 416 × 224, slice thickness = 3.5 mm, gap = 1.0 mm, FOV = 260 mm) and contrast-enhanced T1-weighted (TE = 3 ms, TR = 17 ms, matrix size = 256 × 256, slice thickness = 2.0 mm, gap = 0, FOV = 280 mm) RT planning images with six channel Neuro Flex coils were first obtained with the patient wearing an immobilization mask. Then the patients were repositioned to a 32-channel head-neck-spine (HNS) coil and their heads were supported with vendor's cushions. For the purposes of this study, T2-weighted imaging with same parameters as above and DW echo-planar imaging (EPI) were performed. In the post-RT scans, only T2 and DWI sequences with the 32-channel HNS coil were included.

Twenty-nine transverse DWI images (TE = 76 ms, TR = 5700 ms, matrix size = 128 × 128, gap = 0 mm, FOV = 260 mm) were obtained with b factors of 0 and 700 s/mm^2 – the latter value was chosen because it was high enough to exclude the contribution from tissue perfusion but low enough to retain high signal intensity level [22]. The slice thickness varied between 3.5–3.9 mm depending on the patient size and was the same in pre- and post-RT imaging. Entire parotid and submandibular glands were included in each of the scans. The constant acquisition time of each DWI sequence was 90 s including the prescanning time of 39 s and without delay the scanning time of 51 s. The first two DWI series were acquired at rest, whereafter the patients were given two 500 mg tablets of ascorbic acid orally. For salivary stimulation, the patients were advised to bite the tablets. Then, the DWI sequence was repeated a mean of ten times.

ADC maps were saved in the AW® workstation (version 4.6, GE Medical Systems, Milwaukee, WI, USA) using READY View® software, and EPI correction was applied to remove EPI distortions. The ADCs were calculated from the equation: $S(i) = S_0 \times \exp(-b_i \times \mathrm{ADC})$ where $S(i)$ is the signal intensity measured on the ith b value image, b_i is the corresponding b value, and S_0 is the exact signal intensity for $b = 0$ s/mm^2. For DWI analysis, the data were transferred from the AW workstation to the image processing software (MIM 5.6, MIM Software Inc., Cleveland, OH, USA). The ADC was measured on ADC maps using regions of interest (ROIs) placed over each of the salivary glands. For this purpose, all of the salivary glands were manually delineated on DWI sequences, and for anatomical reference also on T2-weighted images. Large vessels, such as the retromandibular vein and the external carotid artery were excluded. DWI scans of each patient were manually registered to each time series to minimize the interpretation bias caused by the geometric distortion in EPI DWI images.