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Predictive value of diffusion-weighted imaging without and with including contrast-enhanced magnetic resonance imaging in image analysis of head and neck squamous cell carcinoma

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ABSTRACT

Objectives: To assess disease-free survival (DFS) in head and neck squamous cell carcinoma (HNSCC) treated with (chemo)radiotherapy ([C]RT).
Methods: Pretreatment MR-images of 78 patients were retrospectively studied. Apparent diffusion coefficients (ADC) were calculated with two sets of two *b*-values: 0–750 s/mm^2 (ADC_{750}) and 0–1000 s/mm^2 (ADC_{1000}). One observer assessed tumor volume on T1-WI. Two independent observers assessed ADC-values of primary tumor and largest lymph node in two sessions (i.e. without and with including CE-T1WI in image analysis). Interobserver and intersession agreement were assessed with intraclass correlation coefficients (ICC) separately for ADC_{750} and ADC_{1000}. Lesion volumes and ADC-values were related to DFS using Cox regression analysis.
Results: Median follow-up was 18 months. Interobserver ICC was better without than with CE-T1WI (primary tumor: 0.92 and 0.75–0.83, respectively; lymph node: 0.81–0.83 and 0.61–0.64, respectively). Intersession ICC ranged from 0.84 to 0.89. With CE-T1WI, mean ADC-values of primary tumor and lymph node were higher at both *b*-values than without CE-T1WI ($P < 0.001$). Tumor volume (sensitivity: 73%; specificity: 57%) and lymph node ADC_{1000} (sensitivity: 71–79%; specificity: 77–79%) were independent significant predictors of DFS without and with including CE-T1WI ($P < 0.05$).
Conclusions: Pretreatment primary tumor volume and lymph node ADC_{1000} were significant independent predictors of DFS in HNSCC treated with (C)RT. DFS could be predicted from ADC-values acquired without and with including CE-T1WI in image analysis. The inclusion of CE-T1WI did not result in significant improvements in the predictive value of DWI. DWI without including CE-T1WI was highly reproducible.

1. Introduction

Head and neck cancer accounts for approximately 3% of all malignancies [1]. Treatment selection is based on the best tradeoff between cure rate and quality of life and consists of (a combination) of surgery, chemotherapy and radiotherapy depending on disease stage [2].

With better treatment selection, patients with a high probability of an unfavorable treatment outcome after (chemo)radiotherapy ([C]RT) could undergo primary surgical treatment. The same applies when treatment response to (C)RT can be monitored in an early stage; then (C)RT might be terminated prematurely. After a full (C)RT treatment, salvage surgery with curative intent is still

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possible to perform, however this is not preferred because of a higher risk of complications like impaired wound healing. Moreover, salvage treatment is not always possible because of extension of the residual or recurrent tumor outside its original location. Therefore a minority of patients (21–31%) receives salvage surgery after local failure [3–5].

Diffusion-weighted imaging (DWI) is an emerging magnetic resonance imaging (MRI) technique in response prediction in HNSCC patients treated with (C)RT [6].

DWI is based on differences in water mobility in different tissues which can be quantified into an apparent diffusion coefficient (ADC) [7]. The extent of diffusion weighting depends on the timing and the strength of the gradient and is expressed as a *b*-value. In order to reconstruct an ADC at least two different *b*-values are needed, typically a low (e.g. <150 s/mm^2) and a high *b*-value (e.g. >700 s/mm^2) are used. In hypercellular tissue (e.g. tumor tissue) with a small amount of extracellular space diffusion is restricted, which gives a low ADC-value. In contrary, in hypocellular tissue where diffusion in the extracellular space is facilitated, ADC-values are high. Necrosis and inflammation generally meet these criteria [8,9]. There is still no consensus on the optimal combination of *b*-values, though a combination of $b = 0$ s/mm^2 and $b = 1000$ s/mm^2 is commonly used [9–15].

Diffusion-weighted imaging has shown potential in the prediction of prognosis in patients with head and neck squamous cell carcinoma (HNSCC) treated with (C)RT and to monitor therapy in a very early stage. Higher pretreatment ADC values are associated with adverse prognosis [8,12,13,16]. Furthermore DWI has shown potential to detect central necrosis and (subcentimeter) metastatic lymph nodes [9,15].

Contrast-enhanced imaging is often used to exclude necrosis, which allows that the ADC-value only of the solid part of lesions can be determined [9,15]. To our knowledge there has not been a study that assessed the clinical relevance of using contrast-enhanced imaging for excluding necrosis on DWI. Hatakenaka et al. [10] did suggest that pretreatment ADC would be superior to CE-MRI to predict local failure. Since DWI and contrast-enhanced imaging are based on different properties, both techniques may be synergistic in predicting the outcome of treatment.

The purpose of this study was to assess the prediction of disease-free survival (DFS) and interobserver agreement of DWI without and with including contrast-enhanced T1-weighted imaging (CE-T1WI) in image analysis of HNSCC treated with (C)RT.

2. Methods and materials

2.1. Study population

This retrospective study was approved by the local ethics committee. The requirement for informed consent was waived.

Inclusion criteria were histologically proven HNSCC treated with (C)RT in the oral cavity, oropharynx, hypopharynx or larynx and turbo spin-echo (TSE)-DWI of adequate diagnostic quality for the primary tumor or the lymph node on at least one *b*-value image. Exclusion criteria were previous malignancies in the head and neck area and distant metastases at the start of therapy. All patients were clinically assessed by a head and neck surgeon who performed a physical examination and endoscopic evaluation of the primary tumor. N-stage was assessed using ultrasound-guided fine-needle aspiration cytology. A total of 111 consecutive patients received pre-treatment DWI and (C)RT of the head and neck between August 2009 and December 2011. To allow for optimally comparable data we selected the largest patient group which was scanned on the same MR-system, therefore 18 patients were excluded due to the use of another MR-system. One patient was excluded because no CE-T1WI was acquired. Fourteen patients were excluded because neither the primary tumor nor the largest lymph node was visible on DWI due to small tumor size ($n = 8$) or poor image quality ($n = 4$). Finally, the study consisted of 78 patients. In all 78 patients b1000-imagese were acquired. In 64 of these patients b750-images were also acquired. See Fig. S1 in the Electronic Supplementary Material for a detailed flow-chart of patient inclusion.

Supplementary Fig. S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2014.10.015.

Radiotherapy was delivered to the primary tumor and affected lymph nodes to a total dose of 70 Gy in 35 fractions of 2 Gy in 70 patients. Three patients received a total dose of 69 Gy in 30 fractions of 2.3 Gy. All these 73 patients received an elective dose to the lymph nodes at risk for microscopic tumor. In 4 patients a total dose of 52 Gy was delivered in 16 fractions of 3.25 Gy. One patient received 60 Gy in 25 fractions of 2.4 Gy. In the these last 5 patients, no elective dose to the lymph node regions was given. Thirty-eight patients received additional chemotherapy (i.e. 100 mg/m^2 cisplatin in the first, fourth and seventh week after the start of radiotherapy ($n = 24$) or 400 mg/m^2 cetuximab one week before the start of radiotherapy followed by 250 mg/m^2 every week during radiotherapy ($n = 14$)). Patient, tumor and treatment characteristics are summarized in Table S1 in the Electronic Supplementary Material. Median time between MRI examinations and the start of treatment was 25 days (range, 7–63 days).

Supplementary Table S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2014.10.015.

Follow-up consisted of clinical assessment every 6–8 weeks during the first year, every 2–3 months during the second year and every 3–4 months in the third year. Additional imaging and diagnostic procedures were performed in case of clinical suspicion of recurrent disease, residual disease or distant metastases. Positive biopsy or locoregional disease progression within six months after the end of treatment was considered to be residual disease; after six months it was considered to be a locoregional recurrence.

2.2. MR imaging

Imaging was performed on a 1.5 T system (Signa HDxt; GE Healthcare, Milwaukee, WI, United States), using a standard head and neck coil with 29 elements. For all sequences the FOV was 250 mm. DWI was acquired using two PROPELLER sequences with two sets of two *b*-values: $b = 0$ and 750 s/mm^2 and $b = 0$ and 1000 s/mm^2, respectively. ADC-maps were calculated by using two sets of *b*-values: $b = 0$ and 750 s/mm^2 (ADC_{750}) and $b = 0$ and 1000 s/mm^2 (ADC_{1000}). After the administration of 0.4 ml/kg gadoteric acid (Dotarem; Guerbet, Roissy, France) in 72 patients and 0.2 ml/kg gadobutrol (Gadovist; Bayer Schering AG, Berlin, Germany) in 6 patients, CE-T1WI without fat saturation was acquired. An overview of our imaging protocol is provided in Table S2 in the Electronic Supplementary Material.

Supplementary Table S2 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2014.10.015.

Because of differences in resolution and to correct for patient movement, CE-T1WI and DWI were co-registered using the linear registration software tool FLIRT from the FSL package (FMRIB Center, Oxford, United Kingdom).

2.3. Image analysis

Images were evaluated with Centricity Radiology RA 600 (version 6.1, GE Healthcare, Milwaukee, WI, USA). Volume of the primary tumor and largest lymph node were assessed on T1-weighted images by one reader (JCA) by drawing manual ROIs