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Research article

Utility of MRI with morphologic and diffusion weighted imaging in the detection of post-treatment nodal disease in head and neck squamous cell carcinoma

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A R T I C L E I N F O

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A B S T R A C T

Purpose: To determine the diagnostic performance of morphologic MRI with diffusion weighted imaging (DWIMRI) for the detection of post-treatment lymph node (LN) recurrence of head and neck squamous cell carcinoma (HNSCC).

Methods: This retrospective study is based on 33 HNSCC patients who underwent DWIMRI with apparent diffusion coefficient (ADC) measurements for suspected post-treatment loco-regional failure. Two radiologists, blinded to clinical/histopathological data, analyzed MR images according to established morphologic criteria and measured ADC values by drawing regions of interest on each normal/abnormal looking lymph node (LN). Histopathological findings in 40 neck dissections, 133 LN-levels and 755 LNs served as gold standard.

Results: Malignant LNs had lower ADCmean values than benign LNs ($1.15 \pm 0.35 \times 10^{-3}\,mm^2/s$ versus $1.28 \pm 0.28 \times 10^{-3}\,mm^2/s$, p = .028). The optimal ADCmean threshold to differentiate malignant from benign LNs was $1.1695 \times 10^{-3}\,mm^2/s$. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values (95%CI in parentheses) of DWIMRI with morphologic criteria and ADCmean $< 1.1695 \times 10^{-3}\,mm^2/s$ were: (a) 100%(86.2;100), 44.4%(15.3;77.3), 86.1%(69.7;94.7), and 100%(39.5;100) *per neck dissection*; (b) 83.6%(69.7;92.2), 91.6%(83.0;96.2), 85.4%(71.6;93.4), and 90.5%(81.7;95.5) *per LN-level;* (c) 53.1%(43.5;62.4), 95.5%(93.5;96.9), 67.4%(56.6;76.7), and 92.0%(89.6;93.9) *per LN,* respectively.

Conclusion: The high NPV of DWIMRI irrespective of analysis type (per neck dissection/per neck level/per lymph node) make it a useful follow-up tool after treatment.

1. Introduction

Post-treatment loco-regional failure in head and neck squamous cell carcinoma (HNSCC) includes locally recurrent cancer and lymph node (LN) recurrence [1]. Failure is likely to occur in three different situations: persistent tumor cells after treatment, insufficient neck treatment due to missed metastasis and tumor resistance. More than 90% of post-treatment nodal recurrence develops within the first two years after treatment. Unless treated, most patients die within a year of recurrence. When feasible, loco-regional failures are usually managed with salvage tumor resection and neck dissection to improve survival rates. Post-operative re-irradiation with or without concomitant hyperthermia or chemotherapy may be considered as an alternative. Unresectable loco-regional recurrence is managed with re-irradiation in well-selected patients as primary option, whereas patients that are not good candidates for aggressive curative treatment are assessed for palliative chemotherapy and immunotherapy or best supportive care. Meticulous risk-benefit evaluation is required before opting for salvage neck

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dissection. The factors which influence this decision include the probable risk of neck metastases, the probability of neck dissection associated morbidity and complications, and the possible risk of missing metastases if follow-up is preferred over neck dissection. As elective neck dissections are increasingly regarded as overtreatment, the current trend is to perform therapeutic neck dissection if there is evidence of residual/recurrent nodal disease at clinical examination and cross-sectional imaging [2–4]. However, when to perform therapeutic neck dissection has been a much-vexed question. Post-treatment changes, especially after radio(chemo)therapy make the diagnosis of residual/recurrent nodal disease difficult on clinical examination. Negative or equivocal fine needle aspiration cytology (FNAC) doesn't exclude metastasis and multiple biopsies add to the overall morbidity. A combined approach consisting of clinical evaluation and imaging, with or without adjuvant biopsy/FNAC, is considered as a most prudent approach in clinical practice. An ideal imaging modality should have a high sensitivity for early detection of nodal recurrence and a high negative predictive value to avoid unnecessary neck dissection. The utility and limitations of ultrasound, computed tomography (CT), and FDG positron emission tomography CT (FDG PET-CT) for the detection of post-treatment residual/recurrent nodal disease have been evaluated in various studies [1,4]. Although magnetic resonance imaging (MRI) with morphologic and diffusion weighted imaging (DWI) sequences and more recently PET-MRI are increasingly used to detect local recurrence in the treated neck [5–10] the literature on the role of MRI with morphologic sequences and DWI (DWIMRI) for the detection of post-treatment nodal recurrence is very sparse and is limited to small case series [11].

The purpose of the present study was to evaluate the utility of DWIMRI for the detection of post-treatment nodal recurrence in a larger group of HNSCC patients, in whom neck dissection served as standard of reference. We equally aimed to investigate the factors affecting the diagnostic performance of DWIMRI, such as LN size and type of analysis performed (per neck dissection specimen, per LN level in the neck, and LN per LN).

2. Materials and methods

2.1. Patients

The institutional ethics committee approved this retrospective study, which was performed in accordance with the guidelines of the Helsinki II declaration. Informed consent was waived. We included in this study consecutive adult patients with previous treatment for non-HPV related HNSCC in whom MRI with DWI was performed for suspected loco-regional failure or for follow-up purposes (high risk patients) and who underwent salvage surgery including neck dissection. We deliberately included only patients with histopathologic proof of the lymph node status in the neck in order to allow unequivocal identification of metastatic and benign LNs as suggested by other authors [12–15]. The definition of nodal failure included a histologically proven residual or recurrent metastatic cervical LN. A histologically proven metastatic LN detected after a disease free period of 6 months from the treatment end point was considered a recurrence, whereas a metastatic LN detected before 6 months was rendered as residual/persistent nodal metastasis.

Thirty-seven consecutive HNSCC patients who satisfied all inclusion criteria were included in this study. Four patients (4/37, 11%) were excluded from the study because of poor quality DWI images and the remaining 33 patients were available for further analysis. The indications for salvage neck dissection included biopsy-proven local tumor recurrence with planned tumor resection and additional neck dissection because of the location and size of the recurrent tumor in 26 patients, and suspected nodal recurrence on the basis of clinical and imaging evaluation in 7 patients, respectively. The study population comprised 12 females and 21 males of age ranging from 28 to 81 years (mean and median age of 58.5 and 60 years, respectively). Of the 33 patients, primary tumors were treated only with surgery in 11 cases, and with radiotherapy (RTH) with or without chemotherapy and additional surgery, in 22 cases, respectively.

2.2. MRI technique

The MRI scans available for retrospective analysis were performed on 1.5-Tesla (n = 16) and 3-Telsa (n = 17) MRI scanners. Irrespective of field strength, the MRI protocol included high-resolution imaging with dedicated HN coils, FSE T2W and FSE T1W sequences in the axial plane, a short tau inversion recovery (STIR) sequence in the coronal plane, and axial DWI with SE single-shot echo planar imaging (EPI) with fat suppression (b-values of 0 and 1000 s/mm^2) and with automatically calculated apparent diffusion coefficient (ADC) maps using mono-exponential fitting. After administration of a gadolinium-based contrast agent, T1W sequences with and without fat saturation were obtained in the axial, coronal and/or sagittal plane. All morphological MRI sequences had 3–4 mm thin slices, no gap, a field of view of 230 × 230 mm and a 512 × 512 matrix. DWI sequence parameters were as follows: TR/TE = 3200–7300/75–86 ms, 40 slices, slice thickness = 3 mm, field of view = 230 × 230 mm, matrix = 128 × 128, acquisition time = 3 min 2 s, spectral fat saturation or fat saturation with a STIR technique.

2.3. Image analysis, interpretation criteria and ADC measurements

Two radiologists with > 9 years experience in HN oncology, blinded to all clinical data (patient history and histological data), analyzed the images separately. In cases of discrepant readings, consensus was reached. The evaluation was done LN per LN, level per level and neck side per neck side. The surgical classification of LN levels of the American Academy of Otolaryngology-Head and Neck Surgery was used [16]. The interpretation criteria for metastatic LNs from HNSCC were based on the literature. If *either* MRI morphology *or* DWI *or* both (DWIMRI) suggested a metastatic node, the LN was regarded as metastatic. If *both* morphology *and* DWI suggested a benign node, the LN was regarded as benign. A LN with one or more of the following features on morphologic MRI was regarded as metastatic: (a) minimum short axis diameter > 10 mm, (b) heterogeneous contrast enhancement including the presence of central nodal necrosis, (c) nodal contour irregularity, and (d) rounded shape for all LN levels with the exception of level 1, where rounded benign nodes can be seen [12,13]. As both benign and malignant nodes show restricted diffusivity on qualitative DWI evaluation (visual assessment) due to the presence of densely packed lymphoid tissue [5], we obtained quantitative ADC measurements in all LNs and calculated an ADC threshold for the differentiation between benign and malignant nodes using Receiver Operating Characteristics (ROC) analysis (see below). Quantitative ADC measurements were performed by drawing region of interests (ROIs) on each normal and abnormal looking lymph node using the OsiriX MD version 3 (http://www.osirix- viewer.com). ROIs were drawn on the b-value 1000 images and they were then copied to the corresponding ADC maps. The ROIs included the entire LN in case of solid nodes with < 5–6 mm size. Once the readers felt confident in placing the ROI, they performed several measurements per node. Multiple ROIs were also used in larger solid LNs and in LNs with solid and necrotic components by strictly avoiding measuring necrotic appearing portions, as suggested in the literature; an average ADC of the obtained values per node was calculated. We included all LNs in our evaluation, irrespective of the LN size. In addition, LN size was measured to facilitate radiologic pathologic correlation.

2.4. Standard of references

Due to the retrospective study design, the histopathological findings