The added value of DW-MRI in characterization of tissue in treated head and neck tumors

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Abstract

Introduction: Treatment-induced tissue changes are menacing the early detection of recurrent tumor in the head and neck area. The accuracy of conventional MRI techniques has been similar to CT scan in the post-radiotherapeutic neck. Objective: The aim of this prospective pilot study was to determine the additional value of diffusion-weighted imaging (DW-MRI) to conventional and dynamic contrast-enhanced MR imaging (DCE-MRI) to distinguish recurrent from nontumoral post-treatment changes in different head and neck tumors. Materials and Methods: 20 patients with suspected recurrence of head and neck tumors either at the primary site or in neck nodes underwent imaging with MRI using the following protocols: T1W and fast T2W-SE images; pre and post-contrast DCE with delayed fat-suppressed post-contrast T1W images; DW- MRI, using a b-value = 1000 s/mm². A comparison between the results of the different modalities with the pathology results was done. Results: Time intensity curves (TIC) for DCE-MRI, showed rapid and high amplitude of enhancement with short distribution time in 8 cases, gradual enhancement with slow washout in 5 cases and rapid enhancement with plateau in TIC in 7 patients. The mean ADC value of recurrent lesions was 0.58± 0.24x10⁻³ mm²/s, while the mean value of post-therapeutic changes was 1.47 ± 0.31x10⁻³ mm²/s (p< 0.001). If ADC ≤ 0.94x10⁻³ mm²/s, the lesion is malignant (specificity 100%), while if ADC ≥ 1.4x10⁻³ mm²/s the lesion is benign (sensitivity 100%). Still a value between 0.94 and 1.4x10⁻³ mm²/s is equivocal. Using ROC, an ADC value of 0.94 x10⁻³ mm²/s was chosen as a threshold value to differentiate between recurrent lesions and post-treatment changes, and the best results were achieved with an overall accuracy of 93.3%, sensitivity of 93.3%, specificity of 93.3%, PPV of 100%, and NPV of 100%. Conclusion: Addition of DW-MRI to DCE-MRI has remarkably improved the efficacy of differentiating recurrent head and neck tumors from post-therapy alterations.

Key words: Head and neck neoplasms, recurrence, Magnetic resonance, diffusion Study, apparent diffusion coefficient, time intensity curve.

Introduction:

MRI can be recommended for further appreciation of suspicious cases during follow-up of head & neck tumors. As in other areas of the body, the results obtained with these anatomy-based imaging methods are not always optimal, due to difficulties in identifying early or small volume lesions, as well as differentiating tumor from radiation induced changes1,3.

Recently, the introduction of diffusion-weighted (DW) MRI seems promising as a functional imaging technique3. A number of recent reports suggest that this technique may have interesting applications in the evaluation of head and neck cancer, by distinguishing tumor from non tumoral tissue4.

Diffusion-weighted imaging is a noninvasive MRI technique that shows potential in the characterization of lesions5. It can detect the extent of random movement of water protons in biological tissues, allowing some degree of tissue characterization by showing and quantifying molecular diffusion5,4.
It can measure differences in tissue microstructure, based on the random displacement of water molecules. The amount of signal loss over the range of b-values correlates with the mobility of protons and is quantified by means of apparent diffusion coefficient (ADC), which has an inverse relationship with tissue cellularity.\(^1\)\(^\text{,}\)\(^6\)

DW-MRI may allow the differentiation between neoplastic tissue and post-radiotherapy inflammatory or necrotic tissue as the differences in tissue microstructure are expected to create differences in proton mobility.\(^1\) The differences in restriction of diffusion and thus ADC value may be attributed to differences in cellularity, necrosis and perfusion. Hypercellularity and less extracellular space may lead to restriction of diffusion. As the amount of necrosis increases, the ADC value increases, and hypervascular areas contribute to the higher ADC value.\(^5\)

The purpose of our study was to prospectively determine the diagnostic accuracy of DW-MRI in the discrimination of recurrence from therapy-induced changes in the follow-up of patients treated for head and neck tumors.

**Materials and Methods:**

A pilot study was done on all consecutive patients who presented to the Oncology or Otolaryngology departments, Ain Shams University Hospitals, in the period from January 2008 to November 2008, for regular follow-up after treatment of head and neck tumors. The study was approved by the Ethical Committee of Ain Shams University and a written consent was obtained from all patients, after explaining to them the procedure.

All patients were proven free radiologically after 6 months of completion of their primary treatment. Inclusion criteria were suspicion of recurrence by the presence of newly developed symptoms, or clinically palpable swelling, or by radiological suspicious mass on regular CT scan follow-up, either in the primary treated site or the neck nodes. Exclusion criteria were patients with suspected residual tumor after primary treatment or who were treated within less than 6 months or had no radiological confirmation of disease free interval and patients who did not undergo pathologic confirmation of the suspicious recurrence and patients with major artifacts at DW imaging.

Included in the study were 20 patients (10 men and 10 women; age=21–67 years old; mean = 42.4 years old). The site of the primary was in the larynx (n=5), nasopharynx (n=2), cervical lymph nodes (n=4), oral cavity (n = 4), oropharynx (n=1), salivary glands (n=2) and thyroid gland (n=2). The histologic types of the different tumors were squamous cell carcinoma (n=11), lymphoma (n=4), papillary carcinoma (n=2), adenocarcinoma (n=2), undifferentiated (n=1). Pathological diagnosis was made on specimens obtained by endoscopy for H&E examination or for cytological diagnosis made by fine needle aspiration with ultrasound guidance from the suspected site.

MR technique: All MR examinations were performed using a 1.5-T MR unit (Gyrosan Intera; Philips Medical Systems, Best, the Netherlands) with a standard head and neck coil from the base of the skull to the suprasternal notch for all studies. Acceptable images without distortion for ADC measurement were obtained in all 20 patients.

**Imaging Protocol:** The following sequences were performed in all patients during the same session: Axial, coronal and sagittal spin-echo T1W (500/10 [TR/TE], and fast T2W (4000/100 [TR/TE], 5-6 mm section thickness, 256x256 matrix, 5 mm with 0.6mm gap, field of view [FOV] 20-25 cm).

Conventional precontrast T1W and T2W fast spin echo FSE, dynamic post contrast, and delayed post-contrast fat suppressed images were taken.

Diffusion-weighted echo planar images DW-EPI were acquired before the contrast-enhanced sequences, using a b-value =1000 s/mm. Sensitizing diffusion gradients were acquired in three orthogonal directions and combined into a trace image. Images were generated and ADC values were calculated in the suspected areas either at the primary site and in the draining lymph nodes. One radiologist (C.E.) measured the signal intensity of the lesion with an electronic cursor, within the center of the lesions to avoid any volume averaging, to define the region of interest (ROI) in each patient.

Dynamic contrast enhanced (DCE) MRI was lastly performed with contrast material administered as a rapid bolus injection at a rate of 2 mL/sec. Gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Osaka, Japan) in the standard dose of 0.1mmol/kg body weight followed by 20 ml saline bolus to augment the delivery of the contrast by using a power injector (MEDARD, Spectris MR injector) was used.

Standard axial two-dimensional T1W gradient echo (SPIR) images were obtained once before and four times after rapid bolus injection of the contrast. Image acquisition began immediately after administration of the contrast material and saline bolus at 2, 4, 6, and 8 minutes post-injection. After these 8 minutes, a fat-suppressed post-contrast T1W sequence was obtained. The total examination time was approximately 20 minutes.

Post-processing of MR Imaging Data: DW-MRI were analyzed in a first step by visual inspection of DW images with b-value 1000 s mm\(^2\) in correlation to the co-registered anatomical images for proper ADC-calculation. To obtain the time intensity curve (TIC), the ROIs were then copied from the suspected lesions on DW maps to get identical correct positions on dynamic images automatically by the software allowing for correct determination of signal intensity and thus allowing for accurate TIC construction.

**MR Image Analysis:** All MR images were independently interpreted by three radiologists (C.E.; L.A.; R.B.) who were blinded to the clinical information and histopathologic results. Conventional MR images were reviewed for evaluation of lesion morphology (form, margins, homogeneous or heterogeneous) and the pattern of contrast enhancement.
Post-processing subtraction images were obtained using the computer software by subtracting the pre-contrast images from the various post-contrast images for each individual slice. On these subtracted images, enhancement rates were quantified with ROI–based analysis. By plotting the signal intensity over time, TIC curves were generated for each enhancing lesion. We adopted the TIC classification of Jong et al, 2003 and accordingly, we categorized the tumors into three types: persistent, plateau, and washout. Persistent enhancing curves demonstrate a continued enhancement beyond the first 2 minutes of acquisition and were reported to be consistent with benign lesion. Washout curves were those who reached a peak after 2 minutes of contrast injection, with a rapid washout of the lesion and were more commonly seen in malignant lesions. Plateau curves were those who increased in enhancement and then plateau and level off after 2 minutes of contrast injection a plateau, and were more in favor of indeterminate cases (Figure 1).

A definitive diagnosis was made by each of the radiologists, on the basis of the combined findings of the different examinations. The histopathologic and radiologic findings were correlated after all image analyses had been completed.

Statistical Methods: SPSS statistical software package (v.17, Echosoft Corp, USA, 2008) was used for data analysis. The Diagnostic validity test was done. It includes: The diagnostic sensitivity, specificity, positive predictive value, negative predictive value and efficacy. analysis was constructed to obtain the most sensitive and specific ADC cutoff that yielded the highest accuracy.

Results:

The main line of treatment was a combination of chemotherapy and radiotherapy (CRT) in 7 patients, definitive radiotherapy in 4 patients, combination of surgical resection with post-operative radiotherapy in 7 patients and surgery followed by radioactive iodine in 2 cases with differentiated thyroid carcinoma. All patients had a regular follow-up CT scan. The period of follow up ranged between 7-34 months. Recurrent swelling was the main presentation in 5 cases, while pain was the presenting symptom in 3 cases and bleeding in 2 cases.

The remaining 10 cases had no complaint at the time of follow-up, but CT scan showed suspicious changes in the form of soft tissue mass (n=4), breakdown (n=3) and enlarged cervical LN (n=3).

In 10 cases with suspicious finding by CT scan, conventional MR images showed decrease SI on T1W and increase SI on T2W images respectively. In the rest of the cases, SI was homogenously seen in 5 cases and heterogeneously decreased in 2 cases. No signal intensity was found in 3 cases (Figure 2).

![Figure 1: Graph demonstrating types of time/intensity curves](image1)

![Figure 2: A-B: Axial T1W and postcontrast images & C-D: Axial & Coronal T2W: Showed a 4x3x2 cm mass at the retropharyngeal space, mainly necrotic as low T1 and high T2 signal, with faint post contrast enhancement along its anterior aspect. E: DCE-MR: the anterior part showed relatively moderate uptake of contrast medium followed by plateau with no washout (against pattern of malignancy). F: DW-MRI: The central necrotic part showed low signal. ADC values were 1.7–2x10^{-3} mm^2/s.](image2)
Analysis of ADC values was made on the 20 patients with acceptable images for measurement. The mean ADC value of recurrent lesions was 0.58± 0.24 x10^{-3} \text{ mm}^2/\text{s}, while the mean value of post-therapeutic changes was 1.47 ± 0.31 x10^{-3} \text{ mm}^2/\text{s} (Figure 4). The difference was found to be statistically significant (p< 0.001).

Equivocal TIC patterns (n = 7), were used for testing the validity and to find a cutoff value with the results of histopathology as a gold standard. We found that ADC ≤ 0.94 x10^{-3} \text{ mm}^2/\text{s}, the lesion is malignant (specificity 100%), while if ADC ≥ 1.4 x10^{-3} \text{ mm}^2/\text{s} the lesion is benign (sensitivity 100%). Still a value between 0.94 and 1.4 x10^{-3} \text{ mm}^2/\text{s} is equivocal. Using ROC, an ADC value of 0.94 x10^{-3} \text{ mm}^2/\text{s} was chosen as a threshold value to differentiate between recurrent lesions and post-treatment changes, and the best results were achieved with an overall accuracy of 93.3%, sensitivity of 93.3%, specificity of 93.3%, PPV of 100%, and NPV of 100%.

Application of this cutoff ADC value in the equivocal cases, a precise diagnosis was reached in 7 patients, 3 were proven to be malignant and 3 were proven to be benign.

Discussion:

The head and neck area is a complicated anatomical area, encompassing different organs and viscera present in deep and hidden spaces. Clinical examination of head and neck tumors gives usually incomplete data specially if complicated by effects of different treatment modalities. Recent multi-fractioned high-dose radiotherapy with radiosensitizing chemotherapy or surgery, allows us to obtain tumor control even in advanced malignancy. These treatment modalities can produce edema, fibrous inflammatory reaction, and scarring of the adjacent normal soft tissues. Some recurrent lesions do not enhance after contrast administration, making them indistinguishable from other post-treatment changes. This gives imaging an essential role in the follow-up and early detection of recurrence of patients treated for head and neck tumors.

CT and conventional MR imaging, using SE MRI sequences, are extensively used at present for evaluation and follow-up of patients treated for head and neck tumors. However, these anatomical modalities might not accurately differentiate between recurrence and post-treatment changes. There are ongoing efforts to increase the accuracy of these modalities. Conventional MRI sequences are size related and morphologic criteria lack sufficient reliability in distinguishing post-therapy changes from early recurrence. DCE-MRI can be used to demonstrate early enhancement and early washout of contrast media of viable tumor tissue in contrast to surrounding reactive tissues. This makes it more sensitive and specific than conventional MRI. Recurrent tumors have higher amplitude and shorter distribution time than do postoperative changes. In our study, the TIC pattern in 9 cases was inconclusive with relatively rapid uptake followed by a plateau. The diagnostic performance of TIC alone for discriminating malignant recurrent lesions from benign post-therapeutic changes had an overall accuracy of 63.3%.
The potential for DW-MRI to help distinguish between benign and malignant tissues has been reported successfully, as the differences in tissue microstructure are expected to create differences in proton mobility and may function as a surrogate marker for tissue cellularity. The amount of signal loss correlates with the mobility of protons and is quantified by means of the ADC. There are differences in the ADC between different lesions, with a significantly smaller ADC for malignant lesions than for benign lesions. The ADC value of the pathologically proven recurrence lesions in our study was significantly lower than in other studies. The cutoff value in our study was much lower than the rest of the literature. This may be attributed to the fact that our cases included 5 cases of nodal lymphoma.

The proper choice of areas of sampling for calculation of ADC values is a crucial factor to reduce false results. All areas of gross necrosis should be excluded from the sample (ROI), and multiple ROIs with a mean value should be tried if the lesion shows significant signal intensity heterogeneity. We followed these rules strictly, however, volume averaging and areas of micronecrosis cannot be avoided during ADC measurements.

Inflammatory or post-treatment tissue does not demonstrate restricted diffusion, likely due to relative low cellularity. Recurrent disease, however, contains regions of increased cellularity and thus should demonstrate restricted diffusion.

Marked diagnostic improvement of results was obtained with increase in the overall accuracy when adding DW-MRI to be 93.3% in comparison to the TIC results. Our findings obviously show that adding DW-MRI to DCE-MRI improved the diagnostic certainty in the characterization of head and neck tumors. Referring to ADC values was particularly useful when differentiating between head and neck tumors in cases with indeterminate TIC. With the help of ADC values, we correctly modified the diagnosis in 7 cases, taking results of histopathology as the standard reference. In 4 cases with equivocal rapid uptake and plateau TIC, ADC confirmed malignancy. In another 3 patients, we modified the diagnosis to benign as the ADC value was greater than cutoff.

Nevertheless, technical difficulties are the main drawback of DW-MRI. One of the major problems of performing this technique in the head and neck area is image distortion. Unfortunately, increasing the b value, in an attempt to improve the sensitivity to diffusion, can lead to an increase in the susceptibility artifact and loss of signal. This led to the exclusion of some patients from our study.

The ADC threshold values may not be reproducible between centers because of the differences in technique, differences in the selection of the b values and region of interest. The results may be influenced by the selection of ROI, especially with respect to whether necrotic areas are included or excluded in the calculation of the mean ADC values. The solid component of the lesion should always be the area to be measured.

The second drawback of DW-MRI is the difficulty of interpretation of the ADC maps. A quantitative assessment involving ROI analysis is usually necessary. Further implementation of DWI into routine clinical practice probably will depend on the improved standardization of imaging technique and image interpretation.

Our findings obviously show that adding DW-MRI to dynamic contrast-enhanced MR imaging improved the diagnostic certainty in the characterization of head and neck tumors. Referring to ADC values was particularly useful when differentiating between head and neck tumors in cases with indeterminate TIC was attempted.

DW-MRI not only may allow differentiation between neoplastic tissue and post-radiotherapy inflammatory, but also can delineate the solid viable part of the lymph node for biopsy. We precisely defined the location of restricted diffusion before referral of patients to the Otolaryngologist for biopsy.

In conclusion, the ability of DW-MRI to probe tissue microstructure is an interesting complement to the currently used imaging procedures in the evaluation of the post-radiotherapeutic neck. Addition of DW-MRI to DCE-MRI increased the accuracy of early detection of recurrence in the follow-up of patients with head and neck tumors. Combining functional imaging with anatomic details had obviously aided in the diagnostic effectiveness in these problematic cases.
References:


