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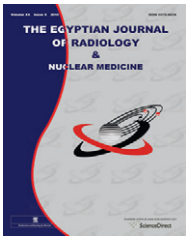

ORIGINAL ARTICLE

Feasibility of diffusion weighted MR imaging in differentiating recurrent laryngeal carcinoma from radionecrosis

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KEYWORDS

DWI;
ADC;
Laryngeal carcinoma;
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Tumor recurrence

Abstract *Purpose:* To assess the feasibility of apparent diffusion coefficient (ADC) generated from diffusion weighted magnetic resonance imaging as a non invasive technique to differentiate tumor recurrence from radionecrosis in patients with laryngeal carcinoma.
Materials and methods: Twenty one patients suspected of tumor recurrence underwent MRI including diffusion weighted imaging (DWI) (*b* 0 and 1000). ADC maps were generated and ADC values were measured at the lesion sites and the normal laryngeal tissues, and were compared with the histopathological results.
Results: The mean ADC of tumor recurrence $\{1.04 \pm 0.34 \times 10^{-3}\ mm^2/s$ (SD)$\}$ was significantly lower ($p < 0.0001$) than the mean ADC of the normal laryngeal tissues in the same patient ($1.48 \pm 0.099 \times 10^{-3}\ mm^2/s$) while the mean ADC of radionecrosis ($1.79 \pm 0.41 \times 10^{-3}\ mm^2/s$) was significantly higher ($p < 0.04$) than the mean ADC of the normal laryngeal tissues ($1.49 \pm 0.095 \times 10^{-3}\ mm^2$). The mean ADC of tumor recurrence is significantly lower ($p < 0.0001$)

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than the mean ADC of radionecrosis with 1.16×10^{-3} mm^2/s is the best cut value for differentiating tumor recurrence from radionecrosis.

Conclusion: ADC can differentiate tumor recurrence from radionecrosis in laryngeal carcinoma.

1. Introduction

Conventional imaging techniques can detect tumors by identification of anatomic distortion or change in tissue appearances. However, the effects of therapy may obscure or mimic recurrent disease (1).

DWI technique gives information about water molecule diffusion motions of tissues (2). In biologic tissues, totally free diffusion of molecules does not exist due to restriction, such as that owing to cell membranes or molecular boundaries (3). The extent of translational diffusion of molecules measured in the human body is referred to as the apparent diffusion coefficient (ADC). ADCs are expected to vary according to the microstructures and pathophysiologic states of tissues (4).

DWI was used successfully in the evaluation of brain lesions but its application in the head and neck region has been limited because the images in this area are likely to have motion related artifacts from respiratory and swallowing movements, and susceptibility artifacts due to the anatomic heterogeneity of the area or the presence of dental work, as well as adjacent air and bone (5). However the development of new applications allows the use of DWI in the head and neck region for the differential diagnosis, recurrence diagnosis and assessment of response to therapy (2,6–13).

Hypercellular tissue, such as occurring within malignant tumors, will show low ADC values. Non-tumoral tissue changes such as edema, inflammation, fibrosis, and necrosis are expected to show low cellularity, in strong contrast with viable tumor. This results in high ADC (14). So DWI can be used to evaluate the larynx for tumor recurrence after prior radiotherapy (1,15–17).

The aim of this study is to assess the feasibility of ADC generated from DWI as an alternative non invasive technique to differentiate tumor recurrence from radionecrosis in patients with suspected tumor recurrence after radiotherapy from laryngeal carcinoma.

2. Materials and methods

2.1. Patients

Our prospective study included 21 patients (16 male and 5 female patients with mean age, 59 years; age range, 47–66 years). Inclusion criteria in this study were patients suspected of tumor recurrence 2–6 months after completion of radiotherapy for laryngeal carcinoma. Exclusion criteria were contraindication to MR imaging (e.g., pacemaker, metallic implant, or claustrophobia). All patients underwent MR imaging including conventional and diffusion weighted imaging then biopsies were taken from the lesions for histopathological examination within 2–5 days of MRI examination. The study followed the principles of the Declaration of Helsinki and Informed consent was taken from all the patients.

2.2. MR imaging protocol

Each patient included in the study underwent MR imaging on a 1.5-T MR (Achieva, Philips Medical Systems, The Netherlands B.V.). After localizer images, conventional images were obtained including transverse T1-weighted images ((500–600/8–9) repetition time ms/echo time ms) and T2-weighted fast spin echo images (3000/100) were obtained in the transverse plane, with a section thickness of 4 mm, an intersection gap of 0.4 or 0.5 mm, a field of view (FOV) of 170–250 mm and a flip angle of 90°. A total of 20 transverse images cover the lesions. When necessary, one or more pulses of T1- or T2-weighted sequences were added in the coronal and sagittal plane, with the same pulse sequence parameters. T1-weighted images were performed before and after administration of 15 ml of gadopentetate dimeglumine. Additional coronal and sagittal T1 sequences after contrast administration were done depending on tumor localization.

DWI were acquired with 20 slices in the transverse plane, 3–4 mm slice thickness, 1 mm intersection gap, FOV 20 cm, TR/TE2000-2600 ms/64-70 ms. The images were acquired using *b*-values (*b* 0 and 1000). Apparent diffusion coefficient (ADC) maps were automatically calculated by MRI machine software and included in the sequence. On ADC map multiple regions of interest (ROIs) were placed over the normal areas of the larynx at the supraglottic, glottic and infraglottic levels and averaged, excluding the site of any suspect lesions, then, the (ROIs) were placed over the lesion and ADC were measured. MR

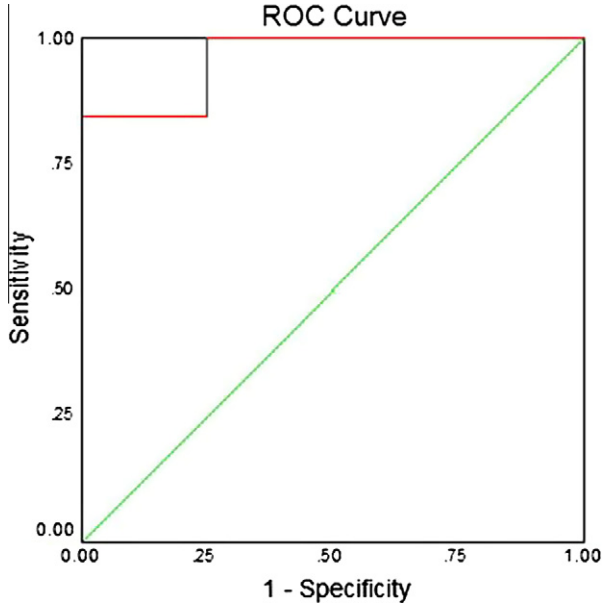

Figure 1 ROC curve for use of ADC values in differentiating tumor recurrence from radionecrosis. The area under the curve is 0.962.

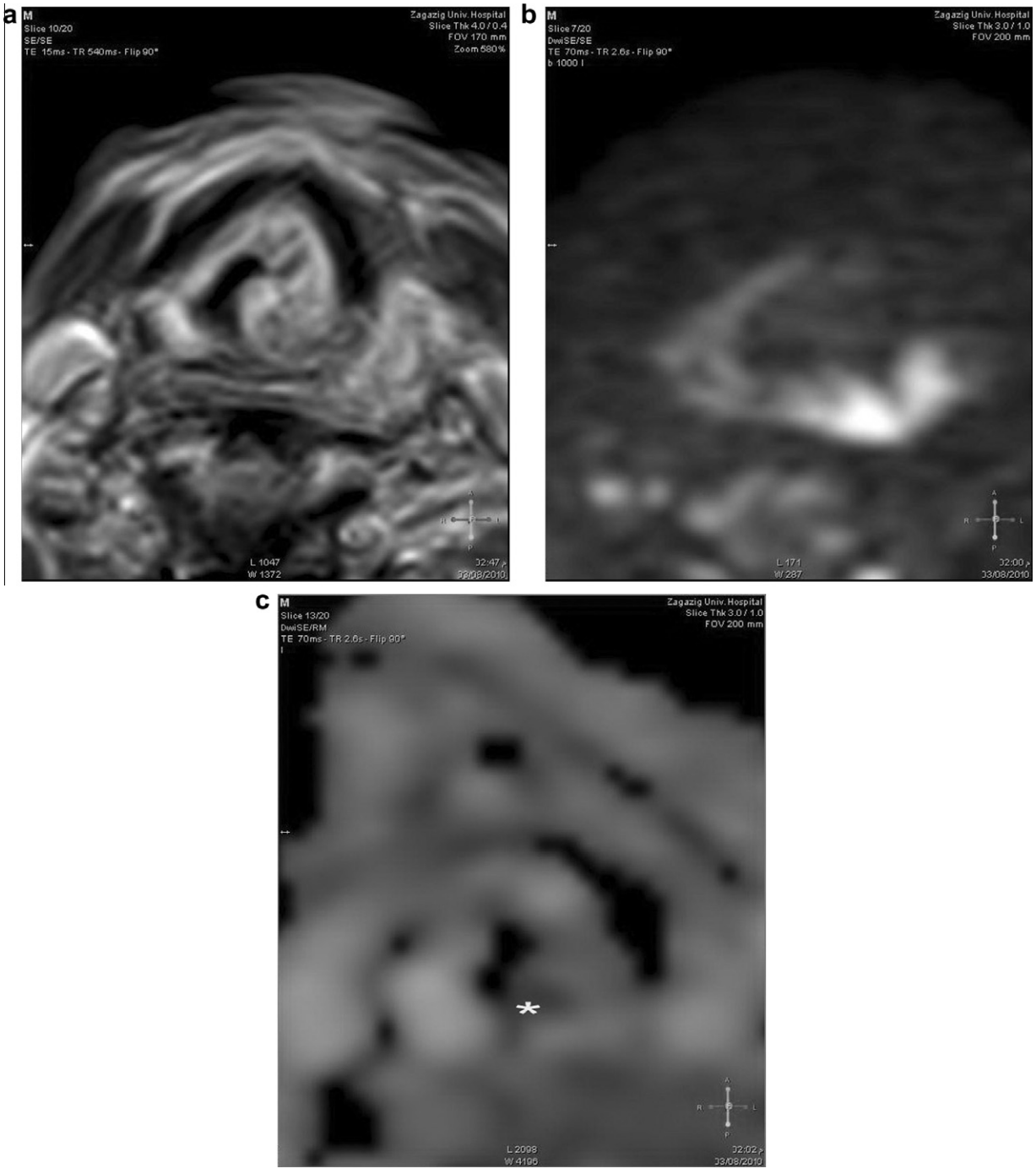

Figure 2 Axial contrast enhanced T1 weighted MR image shows heterogeneously enhanced lesion at the left hemi-larynx causing encroachment upon the lumen (a). The lesion shows high signal intensity at DWI *b* 1000 (b) and low signal intensity (∗) at ADC map (c). Pathologically the lesion was proved to be recurrence.

images including DWI were evaluated independently by the two radiologists sharing the study.

2.3. Statistical analysis

Statistical analysis was done using SPSS version 10. The mean and standard deviation were calculated for the ADC values of recurrent tumors and radionecrosis at the sites of the lesions and the other normal laryngeal sites in the same patients. Using paired *t*-test to evaluate the mean ADC at tumor recurrence, radionecrosis and normal laryngeal tissues in the same patients, and independent *t*-test to evaluate the mean ADC at tumor recurrence and radionecrosis. The probability (*p* value) was considered significant when ($p < 0.5$).

We used the receiver operating characteristic (ROC) curve to evaluate the diagnostic capability of the ADC value for use in the differentiation between tumor recurrence and radionecrosis, and then we used multiple thresholds of ADC values

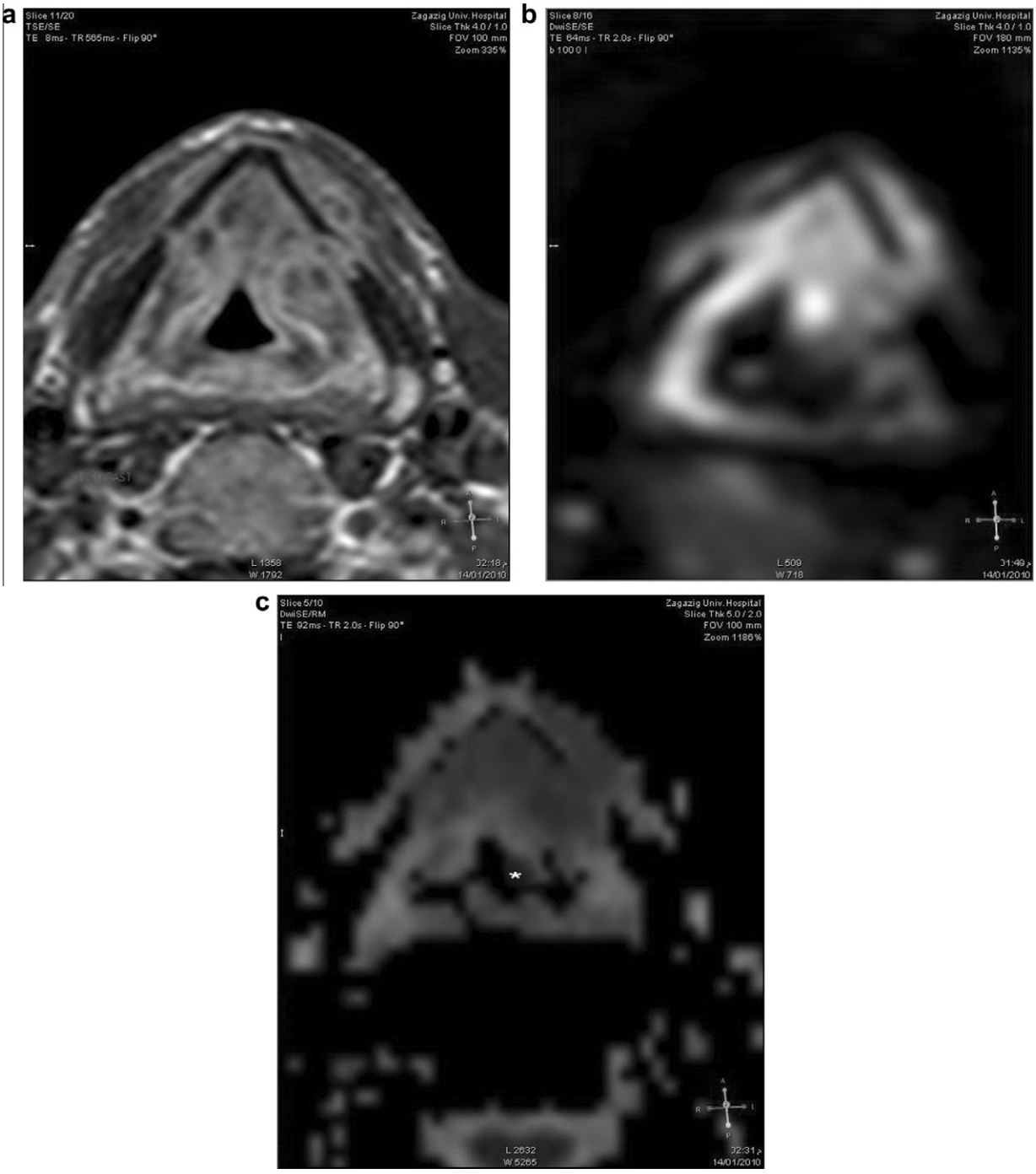

Figure 3 Axial contrast enhanced T1 weighted MR image shows heterogeneously enhanced lesion involving the glottis region more on the left side of the larynx (a). At DWI *b* 1000 (b) the lesion displays high signal intensity however it shows low signal intensity (∗) at ADC map (c). This lesion was proved pathologically to be recurrence.

in order to select the best one determined by kappa test for differentiating tumor recurrence from radionecrosis.

3. Results

A total of 21 patients with suspected tumor recurrence after radiotherapy from laryngeal carcinoma underwent MRI including conventional and diffusion weighted images followed by histopathological examination of the taken biopsies from the lesions within 2–5 days of MRI examination.

According to the histopathological examination the patients were divided into 13 patients with tumor recurrence and eight patients with radionecrosis. In DWI the images were acquired using *b* values (*b 0 and* 1000).

In tumor recurrence (Figs. 2 and 3) the lesions were hyperintense or asymmetric hyperintensity (due to focal lesion of abnor-

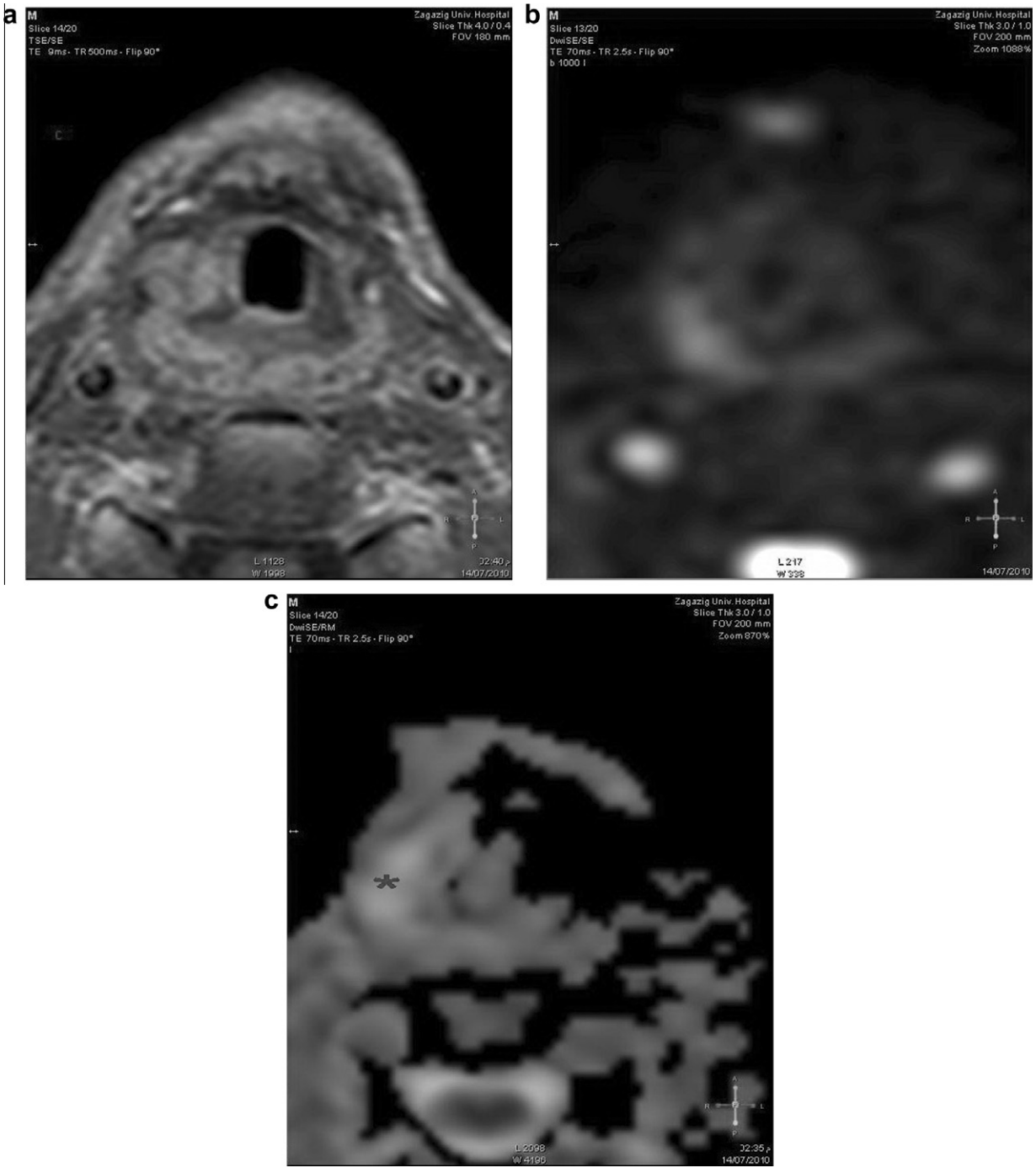

Figure 4 Axial contrast enhanced T1 weighted MR image (a) shows heterogenously enhancement lesion at the infraglottic laryngeal region. No significant asymmetrical hyperintensity can be detected by DWI *b* 1000 (b). ADC map (c) shows hyperintensity (∗) at the same site of the lesion. The lesion was pathologically proved to be inflammatory changes with no tumor recurrence.

mally high signal intensity than the surrounding laryngeal tissue) on DWI (*b* 1000) and hypointense on ADC map. The mean ADC for tumor recurrence was $1.04 \pm 0.34 \times 10^{-3}$ mm^2/s and was significantly lower ($p < 0.0001$) than the mean ADC of the normal laryngeal tissues within the same patients which was $1.48 \pm 0.099 \times 10^{-3}$ mm^2/s.

In radionecrosis (Fig. 4) the lesions were hypointense or of slight symmetric hyperintesity (no clear focal lesion of abnormal high signal intensity) on DWI (*b* 1000) and hyperintensity on the ADC map. The mean ADC for radionecrosis was $1.79 \pm 0.41 \times 10^{-3}$ mm^2/s and was significantly higher ($p < 0.04$) than the ADC of the normal laryngeal tissues within the same patients which was $1.49 \pm 0.095 \times 10^{-3}$ mm^2/s.The mean ADC of the tumor recurrence was significantly lower ($p < 0.0001$) than the mean ADC of radionecrosis (Table 1).

The ROC curve for use of ADC values in differentiating tumor recurrence from radionecrosis is shown in Fig. 1. The area under the ROC curve 0.962, 95% CI: 0.888–1.035.

Table 1 Mean ADC values in recurrent, radionecrosis lesions, and normal tissue.

Lesion ADC (mean ± SD)*		Normal ADC (mean ± SD)	Paired *t*-test	*p* Value
Recurrence (13)	1.04 ± 0.34	1.48 ± 0.099	5.34	< 0.0001
Necrosis (8)	1.79 ± 0.41	1.49 ± 0.095	2.39	< 0.04

* Independent *t*-test of ADC of tumor recurrence to ADC of radionecrosis = 4.55, *p* value < 0.0001.

Table 2 Validity of ADC in prediction of recurrence at different ADC values.

ADC value	Sensitivity %	Specificity %	PPV %	NPV %	Kappa test	*p* Value
0.85	23	100	100	44	0.18	0.14
1.01	69	100	100	67	0.63	0.002
1.16*	85	88	92	78	0.7	0.001
1.49	85	75	85	75	0.59	0.006
2.22	100	13	65	100	0.15	0.19

* Best cut off value for differentiating recurrence from radionecrosis.

When applying ADC value of 1.16×10^{-3} mm^2/s to differentiate tumor recurrence from radionecrosis after radiotherapy from laryngeal carcinoma it showed, sensitivity of 85%, specificity 88%, positive predictive value 92%, negative predictive value 78%, accuracy using kappa test 0.7 and *p* value of 0.001 (Table 2).

4. Discussion

A new emerging functional technique that has now a role in cancer imaging is the DWI which gives information about tissue cellularity and integrity of cell membranes (1). DWI was reported to discriminate treatment induced tissue changes from tumor recurrence after chemo(radiotherapy) as hypercellular tissue such as occurring within malignant tumors will show low ADC values. Non tumoral tissue changes such as edema, inflammation, fibrosis and necrosis are expected to show low cellularity in strong contrast with viable tumors and leads to higher ADC values (13). DWI also appears to offer a better discrimination between neoplastic disease and inflammatory changes than PET. DWI is a method that can be performed at a lower cost than PET, without the need for an external tracer, and without exposure of the patient to ionizing radiation (14).

Our study included 13 patients with tumor recurrence. The lesions were hyperintense on DWI (*b* 1000) and hypointense on the ADC map. The mean ADC of these lesions was significantly lower than the mean ADC of the normal laryngeal tissues in the same patients. These findings are in agreement with the previous four cases study (18) that had two cases with tumor recurrence which were hyperintense on *b* 1000 and hypointense on the ADC map, the ADC of the first case was 0.83×10^{-3} mm^2 s^{-1} at the lesion site and 1.43×10^{-3} mm^2 s^{-1} at the normal sites while the ADC in the second case was 0.96×10^{-3} mm^2 s^{-1} at the lesion site and 1.41×10^{-3} mm^2 s^{-1} at the normal sites. We also had eight patients with radionecrosis; the lesions show no asymmetric or slight symmetric hyperintesity on DWI (*b* 1000) and were hyperintense on the ADC map. The mean ADC was significantly higher than the ADC of the normal laryngeal tissues in the same patients. This is inconsistent with the previous study (18) that had two cases with radionecrosis; in the first patient the *b* 1000 images showed no asymmetric hyperintense signal and the ADC map showed diffuse hyperintensity with an ADC value of 1.84×10^{-3} mm^2 s^{-1} while in the second patient the DWI showed only slight symmetric hyperintensity on the *b* 1000 images in the laryngeal soft tissues and appeared hyperintense on the ADC map, with ADC value of 1.87×10^{-3} mm^2 s^{-1}. Previous studies (19,20) compared the ADC changes with the treatment response in patients with squamous cell carcinoma of the head and neck. These studies (19,20) showed that there is a significant increase in ADC in complete treatment responders than partial responders in the first week after chemotherapy.

The mean ADC of the tumor recurrence was significantly lower than the mean ADC of radionecrosis. This is consistent with the other previous studies (18,3) that studied the characterization of head and neck lesions with DWI and found that the mean ADC of malignant lesions such as lymphoma and carcinoma is significantly lower than the benign solid and benign cystic masses. Our study is also consistent with the previous study (21) where the mean ADC value of residual or recurrent head and neck tumors ($1.17 \pm 0.33 \times 10^{-3}$ mm^2/s) was less than that of post therapeutic changes ($2.07 \pm 0.25 \times 10^{-3}$ mm^2/s). Other studies (2,9) compared the DWI in both well and poorly differentiated carcinoma and reported that the ADC values of well differentiated carcinoma are higher than those of poorly differentiated carcinoma as the increases in the cellularity and cellular turnover which are frequently observed in malignant tumors, reduce the extracellular matrix and the diffusion space of water protons in the extracellular and intracellular dimensions, with a resultant decrease in ADC values.

The ADC value of 1.16×10^{-3} mm^2/s was the best cut off value for differentiating tumor recurrence from radionecrosis. The previous study (3) found that the ADC value of 1.22×10^{-3} mm^2/s or less was the best cut off value for predicting malignancy, with highest accuracy of 86%, with 84% sensitivity, 91% specificity, 93% positive predictive value and 78% negative predictive value. Previous study (21) used an ADC value of 1.30×10^{-3} mm^2/s as the threshold value for differentiating residual or recurrent head and neck lesions from post therapeutic changes, the best results were obtained with an accuracy of 87%, sensitivity of 84%, specificity of 90%,

positive predictive value of 94%, and negative predictive value of 76%.

One of the limitations of this study is the small number of the studied population, second is a technical limitation as we used only two b values ($b = 0$ and 1000) which may affect the accuracy of the measured ADC, third is the susceptibility artifacts from air inside the larynx which make it difficult to measure ADC values in small lesions.

In conclusion, DWI is a non invasive alternative technique that can be used in patients with suspected tumor recurrence after radiotherapy from laryngeal carcinoma to discriminate tumor recurrence from radiation induced changes. Being a short time examination sequence DWI can be safely added to the standard MRI protocol in order to achieve better diagnostic criteria with minimum patient discomfort.

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