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Role of Diffusion Weighted MRI in the Differentiation between Post Treatment Changes and Residual/Recurrent Head and Neck carcinoma

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Abstract: Background: Squamous cell carcinoma are presents almost 90% of the *Head and neck* tumor and it shows different biological behaviors according to location. Imaging techniques are commonly required in order to define tumor's locoregional extension recurrences of the head and neck area. In Europe, "European Journal of Cancer 2015 had mentioned that MRI is increasingly becoming the preferred examination method as it provides additional information on tumor extension, muscles and lymph nodes involvement, and skull base and intracranial invasion. **Objectives:** The aim of this study is to illustrate the value of diffusion weighted images with ADC measurement in the differentiation between post treatment changes and residual/recurrent carcinoma of the head & neck. **Materials and Methods:** This was a prospective study of 42 treated head and neck cancer patients. The patient cohort consisted of a wide spectrum of head and neck sites, including the oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses, orbits, salivary glands, and infra-temporal fossa. Qualitative analysis of the diffusion images and quantitative analysis of the corresponding ADC maps was performed and the data were correlated with histopathological findings and clinical examinations MR images were performed on a 1.5 T system (Acheiva 1.5 Tesla, Philips Medical Systems) by using a 16 channel sense neurovascular head and neck coil. All patients underwent DWI and CE MRI examinations in addition to conventional MRI. Type of Study: Prospective study, study Setting: Ain shams University hospital, study Population: This study will include 42 patient known with head and Neck carcinoma that received radiotherapy/chemotherapy. **Results:** In this study there are 4 cases of false negative by DWI while by biopsy was found to be positive. All of them in the oral cavity. Two of these cases was found in the base of the tongue, one in the glottic and the other at the sub mandibular region, because all of them at areas which affected by motion of respiration and reflexes may be affect the accuracy. Also some cases have very few malignant cells, which may be technically challenging. The results of this study was similar to other studies with the difference in the ADC cut off point could be attributed to different imaging parameters yet the relatively low sample size could be also contributing factor. **Conclusion:** Combined qualitative and quantitative analysis of DWI is a useful non-invasive technique to differentiate recurrent head and neck malignancies from post-treatment changes using a threshold ADC value.

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Keywords: Diffusion Weighted MRI, Post Treatment Changes, Residual/Recurrent Head and Neck carcinoma

1. Introduction

Squamous cell carcinoma are presents almost 90% of the *Head and neck* tumor and it shows different biological behaviors according to location ***(van Dijk et al., 2012)***. Imaging techniques are commonly required in order to define tumor's locoregional extension recurrences of the head and neck area. In Europe, "European Journal of Cancer 2015had mentioned that MRI is increasingly becoming the preferred examination method as it provides additional information on tumor extension, muscles and lymph nodes involvement, and skull base and intracranial invasion.

After surgery, normal anatomic structures can be extensively distorted. The use of radiation therapy renders physical examination, CT, and MR stander imaging unreliable because of the edema and fibrosis that are often present after treatment. Biopsy is often necessary, but the results of histopathological specimens can be inaccurate because of sampling errors ***(Hermans et al., 2000).*** In MRI the recurrent tumors were found to demonstrate higher signal intensity on T2-weighted images than fibrotic benign changes do. But further studies had shown that non neoplastic inflammation or edema may also be responsible for T2 hyper intensity so this finding is

nonspecific ***(Semiz Oysu et al., 2005).*** The dynamic contrast enhanced magnetic resonance imaging is a useful clinical tool in evaluation of soft tissue neoplasm and lymph nodes in head and neck. It is thought to be a useful predictor of response to radiotherapy for head and neck carcinoma and used to monitor the treatment and distinguish post-therapeutic changes from recurrent mass with greater confidence. It can be used to distinguish between normal and malignant tissue ***(King, 2007).*** The Diffusion weighted magnetic resonance imaging (DWI) is a noninvasive imaging technique that measures the differences in water mobility in different tissue microstructures ***(Vandecaveye et al., 2008)***

In summary: malignant tumors have significantly lower ADC values than benign lesions provided that necrotic areas are excluded from image analysis.

Aim of the Study

The aim of this study is to illustrate the value of diffusion weighted images with ADC measurement in the differentiation between post treatment changes and residual/recurrent carcinoma of the head & neck.

2. Materials and Methods

This was a prospective study of 42 treated head and neck cancer patients. The patient cohort consisted of a wide spectrum of head and neck sites, including the oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses, orbits, salivary glands, and infra-temporal fossa. Qualitative analysis of the diffusion images and quantitative analysis of the corresponding ADC maps was performed and the data were correlated with histopathological findings and clinical examinations MR images were performed on a 1.5 T system (Acheiva 1.5 Tesla, Philips Medical Systems) by using a 16 channel sense neurovascular head and neck coil. All patients underwent DWI and CE MRI examinations in addition to conventional MRI.

Methodology:

Type of Study: Prospective study

Study Setting: Ain shams University hospital

Study Population: This study will include 42 patient known with head and Neck carcinoma that received radiotherapy/chemotherapy.

Inclusion Criteria:

Patients known with head and neck carcinoma on chemo/radiotherapy coming for follow up.

Exclusion Criteria:

Contraindications to magnetic resonance imaging, e.g. claustrophobia, patients with non MR compatible cardiac pacemaker or cochlear implants.

Sample Size: 42 patients.

Study Tools: MRI (Phillips 1.5 Tesla Acheiv).

MRI techniques:

Patient position; supine or sitting depends on patient condition.

MR Imaging using a 1.5 T MR Imaging system (Philips) with a surface head and neck synergy coil.

The study protocol include the following sequences;

i. SE T1w axial section, thickness: 4 mm; FOV: 220 × 220 mm; matrix: 224 × 157);

ii. TSE T2w axial, section thickness: 4 mm; FOV: 220 × 220 mm; matrix: 224 × 157);

iii. STIR axial and coronal, section thickness: 4 mm; FOV: 220 × 220 mm; matrix: 336 × 235);

iv. SE T1w axial and coronal with fat suppression, section thickness: 4 mm; FOV: 220 × 220 mm; matrix: 368 × 256);

v. SE T1w with fat suppression after intravenous injection of 0.1 mmol/kg of gadolinum in transverse, coronal, and sagittal planes.

vi. EPI single-shot DWI sequences were obtained in the transverse plane before contrast agent injection both at standard *b*-values (b = 0 and b = 1000 s/mm^2; TR: 8000 ms; TE: 89 ms;) section thickness: 4 mm; FOV: 240 × 240 mm; matrix: 112 × 89).

vii. DWI data were acquired in 3 orthogonal directions (*X*, *Y*, and *Z*) and combined into a trace image. The average duration of DWI at standard *b*-value (b = 0 and b = 800 s/mm^2) was 58 sec.

Instructions & preparation of the patients:

(1) Reassurance of the patients, simple explanation of the procedures after taking verbal consent from them & instructing the patients to keep motionless & breathe calmly during the examination time.

(2) A venous catheter was placed in a peripheral vein (ante-cubital vein in most cases) being through a long connecting tube to automatic injector to allow easy injection without changing the patient position. The patient cohort consisted of a wide spectrum of head and neck sites, including the oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses, orbits, salivary glands, and infra-temporal fossa. Qualitative analysis of the diffusion images and quantitative analysis of the corresponding ADC maps was performed and the data were correlated with histopathological findings and clinical examinations.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The p-value was considered significant as the following: Probability (P-value): P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant, P-value >0.05 was considered insignificant.

3. Results

Table (1): Demographic data of the studied cases

Demographic Data		**Total no. = 42**
Sex	Female	22 (52.4%)
	Male	20 (47.6%)
Age (years)	Mean ± SD	51.74 ± 8.92
	Range	30 – 68

Table (2): Clinical characteristics of the studied patients with malignant and benign lesions

Clinical characteristics	**Malignant lesions (n=33)**		**Benign lesions (n=9)**		**Significance**
	No.	**%**	**No.**	**%**	
Diagnosis					$^{MC}P=0.079$
Cancer larynx	13	40.56	2	4.7	
Hypopharyngeal cancer	5	11.9	0	0.0	
Nasopharyngeal cancer	4	9.9	2	4.7	
Thyroid cancer	1	2.3	1	2.3	
Oropharyngeal cancer	7	23.8	1	0.0	
Sino-nasal cancer	2	4.7	0	0.0	
Others	1	7.1	3	7.1	
Previous surgery					$X^2=2.677$ P=0.102
Yes	30	90	5	55.5	
No	3	10	4	21	
Surgery and radiotherapy	40	95	8	89	$^{MC}P=0.899$
Radiotherapy	2	5	5	11.9	
Both	42	100	13	30.9	

^{MC}P: Monte Carlo test X^2: Chi-Square test

Table (3): Clinical characteristics of the studied patients

Clinical characteristics		**Total no. = 42**
Previous Surgery	Negative	3 (7.1%)
	Positive	39 (92.9%)
DWI	Negative	17 (40.5%)
	Positive	25 (59.5%)
Diffusion	Benign	15 (35.7%)
	Malignant	27 (64.3%)
ADC value	Mean ± SD	1.13 ± 0.38
	Range	0.3 – 1.78
t enhance	Not enhanced	15 (35.7%)
	Enhanced	27 (64.3%)

Table (4): Results of MRI diffusion among the studied patients with malignant recurrence and post treatment granulation tissue.

Clinical characteristics	**Malignant lesions**		**Benign lesions**		**Significance**
	No.	**%**	**No.**	**%**	
Diffusion [n=42]	**[n=33]**		**[n=9]**		**$\chi^2=7.150$ P=0.006***
Hyper-intense	33	98.3	7	77	
Hypo-intense	5	0.5	2	19	
Mean ADC value [n=74]	**[n=32]**		**[n=10]**		**Z=4.786 P<0.0002***
Min-Max	0.7-1.35		0.69-1.8		
Mean±SD	0.93±0.14		1.36±0.40		

Table (5): Mean ADC value and cutoff point to diagnose post treatment changes from recurrent tumors.

AUC	Cutoff point		Sensitivity	specificity	Accuracy
0.845	1.2	**Mean ADC value**	88.3%	71.2%	77.3%

Case (1)

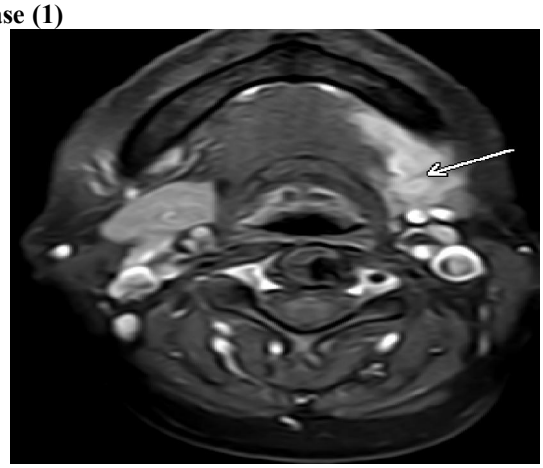
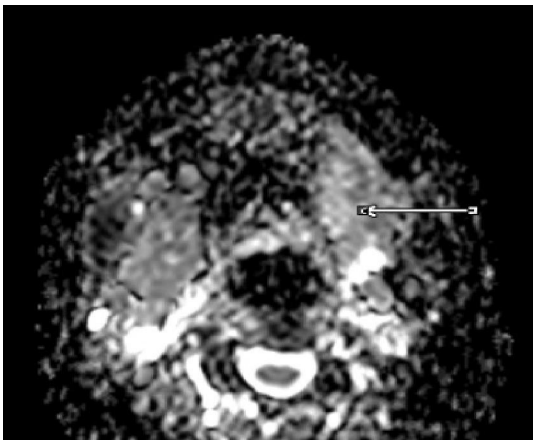


Figure (1): Post contrast T1 WIs showed an enhancing lesion at the operative bed suspected for recurrence



DWI

Figure (2): Diffusion weighted images with ADC maps showed diffusion restriction at the site of the lesion with ADC value 0.77

Case (2)

Figure (3): Post contrast T1 axial WI shows heterogeneous enhancing lesion at the left tongue base.

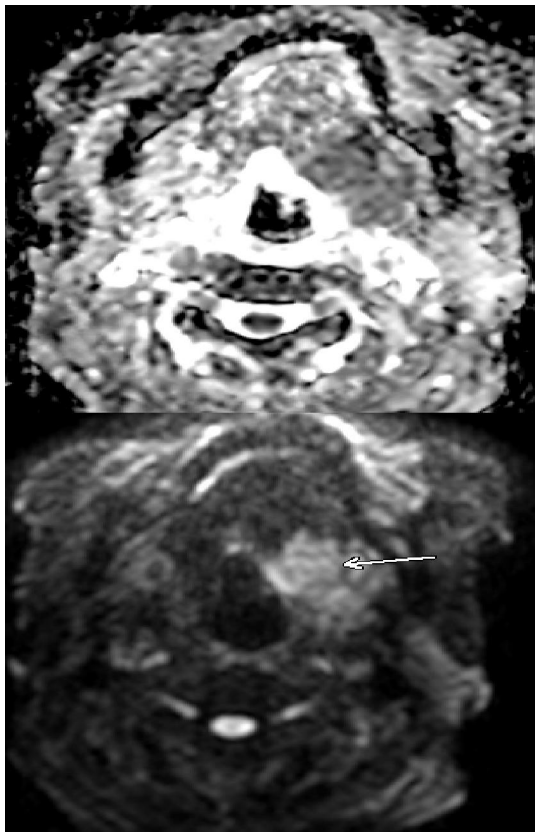


Figure (4): Diffusion weighted images and ADC map shows a soft tissue mass at the tongue base with restricted diffusion and ADC =0.8 confirming that it is a recurrent mass.

Case (3)

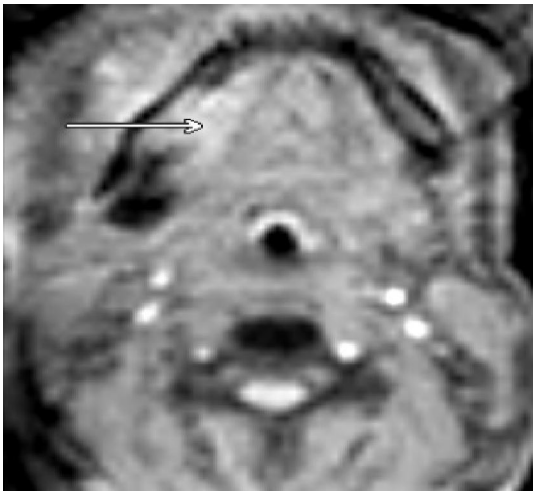


Figure (5): T1 Axial post contrast shows heterogeneous enhancement lesion at the medial aspect of the Mandible

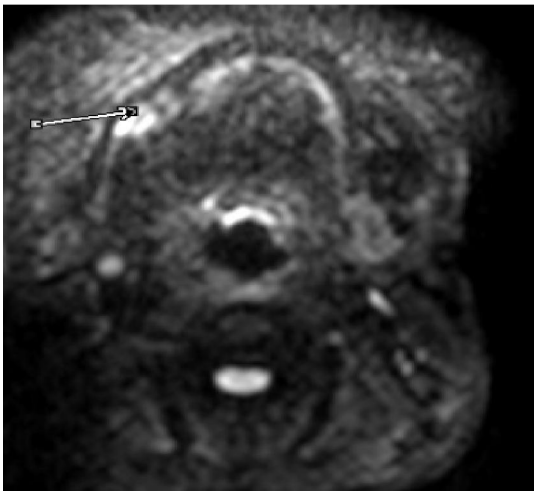


Figure (6): (A) A Shows soft tissue mass at the right side of the mandible with restricted diffusion.

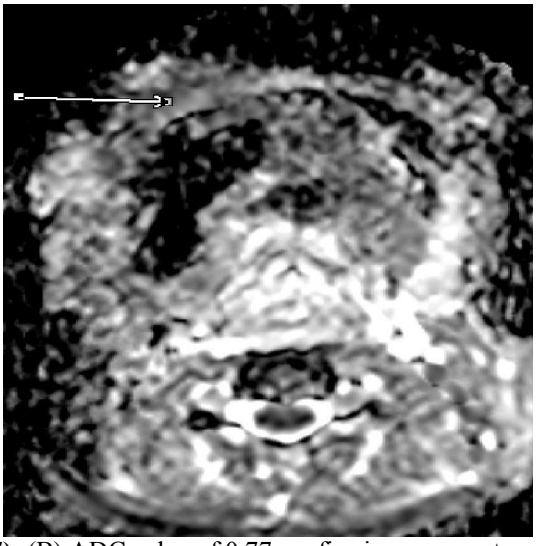


Figure (7): (B) ADC value of 0.77 confirming recurrent malignancy.

4. Discussion

Quantitative analysis of diffusion metrics can help in distinguishing benign from malignant lesions, predicting tumor response to treatment based on pretreatment characteristics, monitoring and assessing the response to treatment as therapy progresses, surveillance areas of prior treatment to detect post treatment changes and recurrent malignant tissue. Imaging surveillance after treatment of head and neck cancers is useful to detect residual or recurrent tumor, even when clinical recurrence is not suspected ***(Hwang et al., 2013)***

In these patients, however, the multidisciplinary treatment with surgery, radiation therapy, and/or chemotherapy that improves patient survival and quality of life complicates interpretation of post treatment follow up imaging studies because surgery can alter anatomy and radiation therapy and chemotherapy can result in edema and fibrosis. These post treatment changes can mimic tumor recurrence, and sometimes it is difficult to distinguish these from residual or recurrent tumor on CT or MR images ***(Zbaren et al., 2006)***

After radiation therapy, residual changes or even masses are commonly observed at the primary or nodal site, and conventional morphologic MR imaging currently encounters difficulty in helping distinguish between benign post treatment alterations

and residual cancer. MR DWI can provide better characterization of tissues and their physiologic processes because it reflects the random motion of water protons, which is disturbed by intracellular organelles and macromolecules located in the tissues. DWI is based on the Brownian motion of water protons in the tissue, which is affected by the microstructure of tissue.

Several previous studies support the value of applying DWI in head and neck cancer for the differentiation and characterization of primary tumor, nodal staging, and the prediction of treatment response ***(Srinivasan et al., 2008).*** In addition, several promising studies have been reported on the usefulness of DWI in the discrimination between recurrent or residual tumor and post treatment changes. These studies have demonstrated that performing DWI and measuring the ADC values may enable differentiation of residual or recurrent tumor from post treatment changes ***(Thoeny and De Keyzer, 2007).***

In this study in which there are 42 patient of which 22 female and 20 male which there age ranging between 30 and 68 years the results showed that qualitative evaluation of the DWI is statistically significant in differentiating post treatment changes and recurrent head and neck cancer (either local or nodal recurrence) using Chi square test, (P=0.007, significant at P≤0.05). Quantitative assessment using the ADC map showed the mean ADC value of post treatment changes (1.36±0.36) to be significantly higher than that of malignant recurrence (0.91±0.17), P<0.0001 using Mann Whitney test. Using receiver operating curve, the best ADC cutoff value to differentiate benign from malignant lesions was $1.2x10^{-3}$ mm^2/s, with 88% sensitivity, 71.2% specificity, 61.% positive predictive value, 92.% negative predictive value and 77% accuracy. Our results showed near total agreement with the results of similar study done by ***(Vandecaveye et al., 2006).***

A study done by Abdel Razek A et al to evaluate the laryngeal malignancy recurrence by diffusion weighted MRI after radiotherapy showed that the ADC value was the most important factor to differentiate recurrence from radiation changes. The optimal cutoff value for the ADC to distinguish between recurrent tumor and postoperative changes was $1.30\times10^3 mm^2/s$ which is higher than the cut off value of our study which it is $1.2\times10^3 mm^2/s$ Ina similar study by Hwang et al, the optimal cutoff value for ADC was 1.460×10^{-3} mm/s. with sensitivity and specifity 84.6%, and 84.8% respectively, which is higher than the results in our study likely secondary to the different parameters in diffusion weighted images acquisition**.**

Nodal metastases are an adverse prognostic factor in patients with head and neck cancer, and accurate detection can help optimize treatment ***(Lee Mc et al., 2013).***

The use of DWI to distinguish malignant from benign cervical nodes has been reported in several studies ***(Payne et al., 2014).*** According to a study done by Perrone et al, the mean ADC value of metastatic and lymphomatous nodes (0.85×10^{-3} mm^2/s) was significantly lower than the mean value of benign nodes (1.448×10^{-3} mm^2/s) ($p<0.01$). Another study Bondt et al also shows the ADC values of malignant lymph nodes were significantly lower compared with benign lymph nodes with mean values of $0.85\pm0.19\times10^{-3}$ and $1.2\pm0.24\times10^{-3} mm^2/s$, respectively.

Also several previous studies support the value of applying DWI in head and neck cancer for the differentiation and characterization of primary tumor, nodal staging, and the prediction of treatment response ***(Srinivasan et al., 2008).*** The ADC is inversely related to tumor cellularity as the increase in cells number and in nucleus dimensions in malignant lesions leads to limitation of diffusion of water molecules and, consequently, to lower ADC values. On the other hand, decreased cellularity and the presence of edema and inflammatory changes in post treatment modification are related to higher ADC values. In a study by Ossama Hassan et al., They found that DW MRI presents higher sensitivity (100%), Positive predictive value (75%), Negative predictive value (100%), accuracy (85%) yet less specificity (71%) than PET/ CT (68% sensitivity, 70% Positive predictive value, 83% Negative predictive value, 78% accuracy and 84% specificity) in the evaluation of Head and Neck malignancy**.**

In this study there are 4 cases of false negative by DWI while by biopsy was found to be positive. All of them in the oral cavity. Two of these cases was found in the base of the tongue, one in the glottic and the other at the sub mandibular region, because all of them at areas which affected by motion of respiration and reflexes may be affect the accuracy. Also some cases have very few malignant cells, which may be technically challenging. The results of this study was similar to other studies with the difference in the ADC cut off point could be attributed to different imaging parameters yet the relatively low sample size could be also contributing factor.

5. Conclusion

Combined qualitative and quantitative analysis of DWI is a useful non-invasive technique to differentiate recurrent head and neck malignancies from post-treatment changes using a threshold ADC value Quantitative analysis of diffusion metrics can

help in distinguishing benign from malignant lesions, predicting tumor response to treatment based on pretreatment characteristics, monitoring and assessing the response to treatment as therapy progresses, and surveilling areas of prior treatment to detect post-treatment and recurrent malignant tissue Overall.

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