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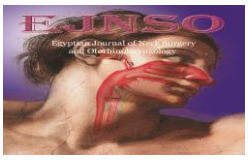

Role of diffusion magnetic resonance imaging (DWI) in laryngeal cancer

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Abstract:

Background and Purpose: To detect sensitivity and specificity of diffusion-weighted imaging (DWI) as a non-invasive technique in detection of de-novo cases of cancer larynx.
Patients and Methods: Patients included in this research were patients suspected of de-novo cancer larynx; this study is a prospective randomized comparative clinical trial.
Results: The mean apparent diffusion coefficient (ADC) of laryngeal lesions (0.73± SD 0.23 x10-.3 mm2) was lower ($p<0.001$) than the mean of the normal part of the larynx in the same patients (1.09± SD 0.099 x 10-.3 mm2). The cut-off value of the ADC using receiver operating characteristics was >0.87 X 10-.3 mm2/s with the area under the curve (AUC) 0.979, with highly significant p-value >0.0001, with sensitivity 88.89% and specificity 100% and accuracy 94.45%, while conventional MRI show sensitivity of 83.33% and specificity 50% and accuracy of 66.66% with an insignificant p-value.
Conclusion: DWI is an easily reproducible and non-invasive technique that can accurately explore the larynx and became a very important diagnostic tool of laryngeal diseases. This study demonstrated the cut-off point of ADC value for discrimination of malignant lesion is >0.87x 10-.3 mm2/s with restricted diffusion in DWI images.
Keywords: Diffusion-weighted imaging, laryngeal cancer, new technology in de novo cancer larynx

Introduction

Laryngeal cancer is one of the commonest head and neck tumors worldwide; it represents 4.5% of all malignant tumors. [1] Direct laryngoscopy is a methodology for deep examination of the entire larynx under general anesthesia and allows taking a biopsy for histopathological study. Although it is a routine method but has many disadvantages as being invasive, needs general anesthesia, and needs surgeon's experience. [2]

Direct endoscopy view is limited to the lumen with restriction of transmural analysis, as well as, due to the complexity of anatomy of the larynx and

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multiple areas as anterior commissures, ventricle, a subglottic region cannot be fully evaluated by direct laryngoscopy. Computed tomography (CT), magnetic resonance imaging (MRI), and direct endoscopy under general anesthesia are different modalities of diagnosis of cancer larynx commonly used nowadays for evaluation of the entire larynx. [2]

Diffusion-weighted imaging (DWI) has become a new purposeful imaging technique that relies on protons motion corresponding to living tissue (Brownian motion), and Apparent diffusion coefficient (ADC) that measures molecular diffusion.[3] Nowadays, DWI is extensively used in otorhinolaryngology to distinguish benign lesions from malignant tumors, track metastasis of lymph node, follow up residual or recurrent lesions after head and neck irradiation or chemoradiotherapy or after chemotherapy or post-surgery, and to expect the impact of different ways of treatment modalities by using DWI and ADC value. [4]

Patients and Methods:

This prospective randomized comparative clinical trial was conducted in the otorhinolaryngology department and radio-diagnosis department in Assiut University Hospital from September 2016 to April 2019, after obtaining approval from the Medical Ethics Committee, Faculty of Medicine, Assiut University.

Inclusion criteria: Twenty-two consecutive patients were included in this study. The inclusion criteria included patients who clinically suspected of having cancer larynx (long history of one or more of the following: dysphonia, stridor, dysphagia, chocking, hemoptysis, neck swelling) telescopic examination was done in all patients showing leukoplakia, erythroplakia, or friable necrotic lesion (glottic, supraglottic, subglottic or transglottic)

Exclusion criteria MRI cannot be performed in patients with absolute or relative contraindication to MRI (e.g., pacemaker, cochlear implant, metallic implant, or claustrophobia). Patients having minimally associated pathological lesions like a laryngeal nodule, polyp, or cysts were also excluded. Treated patients either surgically or by radiotherapy or chemotherapy were also excluded.

Patients were subjected to the following:

1-Clinical assessment

A. **Full Clinical history includes** patients' age, sex, chief complaint, special habits, and general medical history.

B. Clinical examination.

1- Loco-regional examination of the larynx mainly site, extension, the character of the primary lesion, and regional lymph node examination. Direct examination of the larynx using 90-degree Storz ® endoscope (Germany) 8mm x 179mm autoclavable stainless steel easy for maintenance.

2- Examination of patients' general medical condition.

C. **Laryngoscopic examination** under general anesthesia using an orotracheal tube or through a tracheostomy tube.

D. Histopathology of the lesion: Biopsy was taken during laryngoscopy.

2-Radiological assessment

1- Conventional non-contrast MRI preliminary to DWI examination :

Patient preparations:-

To get an optimal DWI examination patient preparation is of importance in the optimization of the technique:

i. Psychological support of patients (including the scanner environment

and during imaging, patients informed to breathe slowly and instructed to swallow seldomly or by hyperextending the neck),

ii. Confirmation for the absence of any paramagnetic material with the patient.

iii. A monitoring technique (e.g., respiratory and cardiac gating, presaturation pulse techniques) for elimination of motion artifacts from breathing and cardiac pulsation, 4- Regarding tracheostomized patients DWI was done after (48-72h) without tracheostomy tube to avoid artifact.

MRI scans protocol:

In our study, MRI examination was performed using a (1.5 Tesla) superconducting MR imager (Achieva, Philips Medical Systems, The Netherlands B.V). A circularly polarized surface coil was placed over the neck, the receiver coil should be separated from the chest wall to prevent movement; however, it must be near the neck. Recommended protocols include:

a. **Sagittal T2WI images** are obtained initially to plan the location of axial images.

b. **Axial T1 –weighted turbo spin-echo (TSE)** images extended from hyoid bone to the lung apex with {a repetition time (TR) of 430 ms and echo time (TE) of 12 ms }, 2- **axial T2-weighted turbo spin-echo (TSE)** {a repetition time (TR) of 4252ms and echo time (TE) of 100 ms } sequences with or without spectral presaturation with inversion recovery (SPIR) with a 0.5mm intersection gap a slice thickness of 4 mm with, matrix size 228x512, a field of view (FOV) 23x25 cm.

c. **Coronal T2 & Short-Tau Inversion Recovery (STIR) images** were obtained for the evaluation of masses that extended below the cervicothoracic Junction.

2- **Diffusion MRI:**

DWI was acquired single-shot echo-planar image (EPI) with 20 slices in the axial plane 0.5 mm intersection gap; 5 mm slice thickness, a field of view 23x28 cm, and matrix size 94x160, {a repetition time (TR) of 4000-4280 ms and echo time (TE) of 94-110 ms. The images were acquired using *b*-values (*b* 0 and 1000 mm^2/s.).

Hypothesis:

This study hypothesized that adding DWI and ADC map to the routine MRI protocol used in patients with clinically suspected, laryngeal mass by telescopic examination will increase its diagnostic performance. To prove this hypothesis we compared the results of conventional MRI and DWI.

1. ADC maps were measured from many images taken by different b values. ADC is the sum of motion in three-dimensional planes (three orthogonal directions); ADC was measured by applying multiple regions of interest (ROIs) over normal laryngeal tissue to exclude any suspected lesions, and over lesions to measure their ADC values. ROI applied by radiologist and median size of 30 mm^2 to calculate ADC value on ADC maps.
2. Correlation between DWI readings and histopathological results were performed in all cases, where punch biopsy was taken by direct laryngoscope under general anesthesia (2–5 days) after MRI examination (pathologists do not know suspected clinical diagnosis)

Statistical analysis:

Data were analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA).

Means, standard deviations, medians, ranges, and percentages were calculated. Test of significances: Chi-square test was used to compare the difference in the distribution of frequencies among different groups. Using paired t-test to evaluate the mean ADC at laryngeal tumor and ADC of remaining normal part of the larynx of same patients .

Validity statistics sensitivity, specificity, positive and negative predictive value accuracy were calculated. We used the receiver operating characteristic (ROC) is curved to evaluate the diagnostic capability of the ADC value for detection of de novo laryngeal mass, we used multiple thresholds of ADC values to select the best cut off value, the ROC curve is created by plotting sensitivity against the specificity at various threshold settings. Significant p-value was considered when it is <0.05, highly significant when p <0.0001.

Results:

Twenty-two patients were included in this study. Twenty were smokers (90.9%). Their ages ranged from 50 to 88 years with a mean age of 62.4 years SD ±10.71, and a male predominance of 95.5% (21 patients). Hoarseness of voice was the main presenting symptom by (77.72 %), then stridor by (13.6%), and finally dysphagia by (13.6%)).

As regard the site of involvement of malignant lesions by laryngoscopy under general anesthesia, it was found that glottic carcinoma is most common by (54.55 %) followed by trans-glottic carcinoma by (22.72 %), while regarding the site of involvement of the four histopathologically proved benign lesions, three of them are glottic and the last lesion is supraglottic **(Table 1).**

Conventional MRI (T2 weighted image) stated hyperintense lesions in 17 patients (77.3%), while DWI (qualitative method) stated restricted diffusion in (72.7%), ADC value mean was (0.73) and the range was (0.22-1.2) as seen in (**Table 2, Figure 1 and 2**). The mean ADC of laryngeal lesions was (0.73± SD 0.23 x10-.3), which is highly significant as the p-value was (<0.001), compared to the mean of the normal part of the larynx in the same patients (1.09± SD 0.099 x 10-.3). (**Table3**).

Histopathological examination of the biopsies obtained from all laryngeal mucosal lesions was squamous cell carcinoma of different grading, with the most common type was well-differentiated type by (31.81%), except four cases, which showed chronic non-specific inflammation in two cases and moderate dysplasia in the other two cases with no carcinoma. ADC mean value was ($1.035\pm0.19 \times 10^{-3}$ mm^2/s) in the four cases of benign nature with a highly significant p-value between the two groups of benign and malignant lesions as (P-value was 0.0004*).

Comparison of conventional MRI (signal intensity on T2) and both qualitative and quantitative methods (DWI and ADC value respectively) with direct endoscopy and pathology results, as regards AUC, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy on ROC curve was stated in (**Table 4 and Figure 3).**

Table (1): Personal data of the studied cases and Endoscopic sites of the studied group:

	No. (n=22)	**%**
Age		
Range	50 - 88	
Mean ± SD	62.41±10.71	
Sex		
Male	21	95.5
Female	1	4.5
Smoking		
Smoker	20	90.9
Non smoker	2	9.1
Total	N=22	100
Endoscopic sites of the studied lesions (18 carcinoma and 4 benign lesions)		
Site	No. (n=22)	%
Glottic	12	54.55
Transglottic	5	22.73
Supraglttic	3	13.63
Subgottic	2	9.09
Total	N=22	100

Data number of patients and percentage (%).

Table (2): Data of the patients by conventional MRI and DW-MRI

Diffusion	**No. (n=22)**	**%**
Facilitated	6	27.3
Restricted	16	72.7
Signal intensity on T2	**No. (n=22)**	**%**
Hyperintense	17	77.3
Iso intense	5	22.7
ADC value	**No. (n=22)**	**%**
Range	0.22	1.2
Mean ± SD	0.73±0.23	

Data represented as follows: ADC (mean ±SD), Signal intensity on T2, Diffusion represented by the number of patients, and percentage (%).

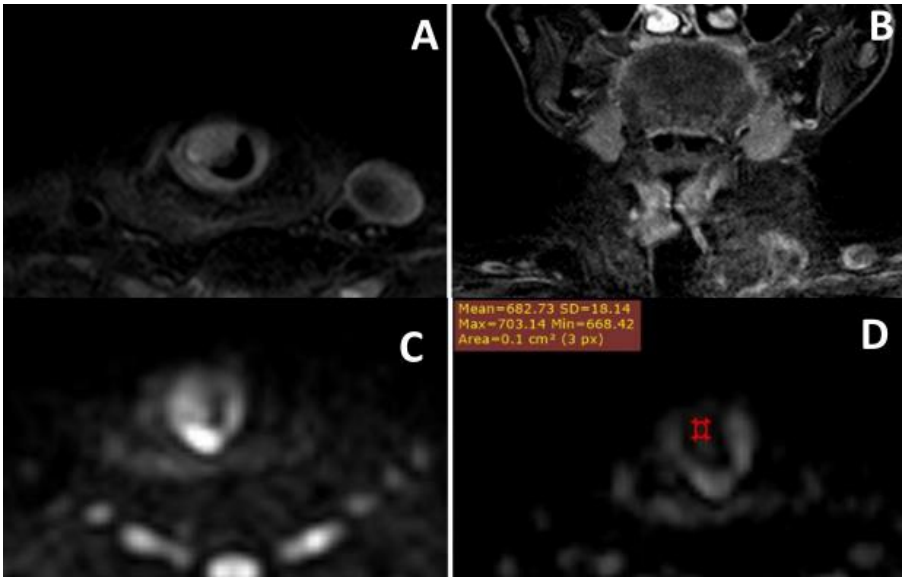


Figure (1):-Male patient, 64ys old, smoker, and was complaining of hoarseness voice. **Laryngoscopic examination showed:** Laryngeal mass involving the right vocal cord. **In conventional MRI examination: Both axial (A) and coronal (B) T2WI show** Right-sided hyperintense laryngeal soft tissue mass seen involving the right glottic and subglottic regions with infiltration of cricoid cartilage at the right side. **Analysis of DWI (C) & ADC value (D) show:** Restricted diffusion with ADC value $0.68x10^{-3}$. This is suggesting the malignant nature of the lesion, and this was confirmed by histological examination which revealed squamous cell carcinoma (grade II).

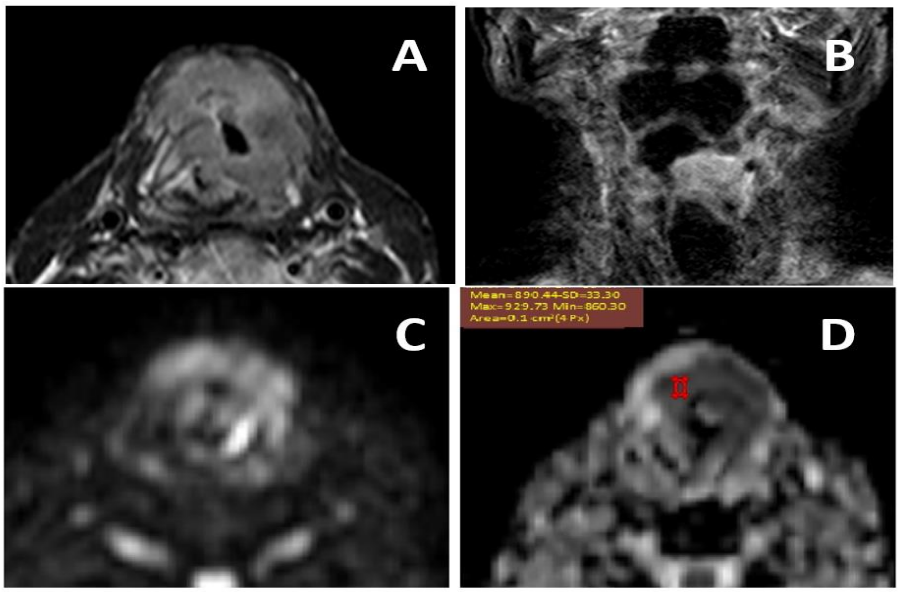


Figure (2): Male patient, 55ys old, and smoker and was complaining of hoarseness of voice. Laryngoscopic examination showed: Large left friable necrotic trans-glottic soft tissue mass involving the laryngeal surface of epiglottis and left vocal cord and anterior commissure associated with fixed left vocal cord and limited mobility of right vocal cord. In Conventional MRI examination: Both axial (A) and coronal (B) T2WI show large left trans-glottic mass infiltrating supraglottic region, left false and true cords, anterior commissure and posterior commissures, lamina of the thyroid cartilage and extends to subcutaneous tissue anteriorly with sub-glottic extension. Analysis of DWI (C) & ADC value (D) show: Restricted diffusion with ADC value about 0.9x10-3 mm2/s. This is suggesting the malignant nature of the lesion and this was confirmed by histological examination which revealed moderately differentiated

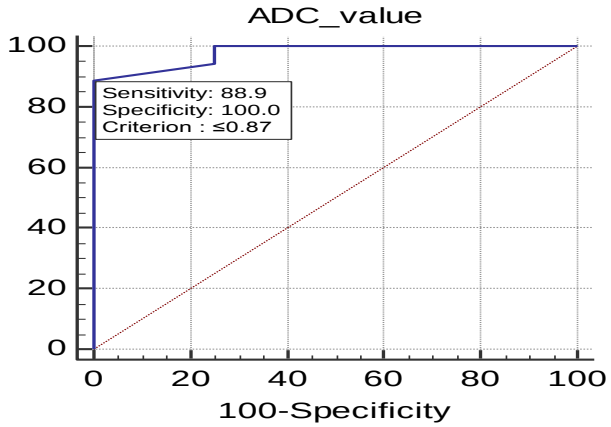
Table (3):-compare between mean ADC of laryngeal carcinoma and mean ADC of normal larynx and compare mean ADC of benign lesions and mean ADC of laryngeal carcinoma.

Mean ADC of laryngeal carcinoma ±SD	Mean ADC of normal larynx ±SD	Paired t-test	P-value
0.73±0.23	1.09± 0.099	6.7	p< 0.0001*
Mean ADC of pathologically benign (4 lesions(1.035±0.19 X 10-3 mm^2/s)	Mean ADC of laryngeal carcinoma (18 patients) ±SD 0.73±0.23	2.4	p<.0.0201*

Table (4): Comparison between pathology result and DWI

	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P. value
ADC value	0.979	88.89	100	100	66.7	94.45	<0.001**
Diffusion	0.792	83.33	75	93.8	50	79.17	0.028*
Signal intensity on T2	0.667	83.33	50	88.2	40	66.67	0.271

Figure (3): ROC curve for ADC value (quantitative method) compared to pathology results (best 0.87).<cut-off value



Discussion:

Due to laryngeal structure complexity which contains various structures as cartilage (ossified or non-ossified), mucosa, fat, and air, muscle, and, numerous normal movements, including speaking, breathing, and also impulses arising from major blood vessels. This issue results in distortion and fat suppression failure and artifacts that can produce non-diagnostic images. Due to previous problems, DWI had little use in the head and neck [5]. Direct endoscopy and biopsy are standard techniques for diagnosis and starting treatment of laryngeal cancer in de-novo cases. [6,7]

Conventional MRI has been used for the detection of laryngeal carcinoma but emerging novel DWI has become a standard technique in the diagnosis of many tumors and in follow up of tumor recurrence by using ADC value and by using restricted/ facilitated method. [8]

This conducted study revealed that the mean age of the patients was (62.4 years SD ±10.71.). Most of them were male gender, and smokers, the majority were diagnosed with laryngeal cancer (81.79%). Glottic carcinoma was the most common site in this study followed by the trans-glottic type .

Conventional MRI (T2 weighted image) found hyperintense lesion in (77.3%). As regard DWI (qualitative method), restricted diffusion was found in (72.7%) and facilitated diffusion in (27.3%) This is in agreement with the study that stated hyperintense lesions in (88.9%) and isointense lesions in (11.1%) also the same the study revealed restricted diffusion in (83.3%) and facilitated diffusion in (16.7%). [9, 10]

Histopathological examination of biopsies obtained from the laryngeal mucosal lesion showed them to be squamous cell carcinoma of different grading (most common type is well-differentiated type seven patients (31.81%), also we found two cases of chronic non-specific inflammation and two cases of moderate dysplasia with no carcinoma in this current study, the mean ADC (0.73± SD 0.23), ADC mean value (1.035±0.19 X 10-3 mm2/s) of the four cases of pathologically benign with a highly significant p-value between two groups (between the benign lesion and malignant lesions (P=0.0004*).

In the current study, we assessed the role of MRI with diffusion as a diagnostic modality for primary, laryngeal cancers compared to endoscopy and histopathological examination being the gold standard diagnostic modality for any malignancy of the aerodigestive tract. The study included twenty-two patients with the primary presentation. We found that DWI (ADC value) had 88.89% sensitivity, 100 % specificity, and 94.45% accuracy compared to histopathological findings of biopsies from the studied group. A highly significant p-value (<0.001**) also found the mean ADC (0.73± SD 0.23), the mean ADC of laryngeal lesions (0.73± SD 0.23 x10-.3 mm2) was lower (p<0.001) than the mean of the normal part of the larynx in the same patients (1.09± SD 0.099 x 10-.3 mm2) p-value is highly significant .

This study also found that the cut-off value of the ADC using receiver operating characteristics >.87 x 10-.3 mm2/s with an area under the curve 0.979 with highly significant p-value >0.0001, with sensitivity 88.89% and specificity 100%, and accuracy 94.45%. While conventional MRI shows a sensitivity of 83.33% and specificity of 50% and accuracy of 66.66% with an insignificant p-value. also, diffusion (restricted versus facilitated technique) with sensitivity 83.33% and specificity 75% and accuracy 79.17% with significant P-value 0.028 (Table 3,) while conventional MRI show sensitivity 83.33% and specificity 50%

and accuracy 66.66% with an insignificant p-value .

This is in agreement with Kwon et al [11] who reported sensitivity in 92%, specificity in 66.6, positive predictive value 87.8%, negative predictive values 76.1, and accuracy 85%, the cut-off ADC value as 1.1 × 10-3 mm2/s to discriminate benign and malignant lesions in the larynx.

Sasaki et al. [12] reported apparent diffusion coefficient of malignant laryngeal tumors (0.87 ± 0.32 × 10-3 mm2/s) were significantly lower than those of benign (1.35 ± 0.29 × 10-3 mm2/s, $p < 0.0001$) and inflammatory (1.50 ± 0.50 × 10-3 mm2/s, $p < 0.0002$) lesions. Friedrich et al [13] reported that the mean apparent diffusion coefficient value for laryngeal squamous cell carcinoma is about 0.64 ± 0.28 × 10-3 mm2/s .

The limitations of the study included a small sample size due to the high cost of imaging and that diffusion-weighted imaging requires certain skill acquisition to be performed and interpreted correctly. Generally, MRI cannot be performed in patients with pacemakers or prosthetic valves. Another drawback of MRI is the long examination time (30-40min) and the necessity for patient compliance.

Conclusion:

DWI is currently considered a diagnostic tool in the head and neck tumors, and a non-invasive technique with the ability to detect new cases of cancer larynx as a new modality that guides the surgeon to the site from which biopsy is taken. In our study, DWI had 88.8% sensitivity, 100% specificity with an accuracy of 94.45.7% in comparison to histopathological findings of biopsies of the studied group, so we concluded that DWI had a diagnostic role in the detection of new laryngeal cancers.

Abbreviations:

CT: Computed Tomography
MRI: Magnetic Resonance Imaging
DWI: Diffusion-weighted imaging
ADC: Apparent diffusion coefficient
SPIR: spectral presaturation with inversion recovery
AUC: Area under the curve
ROC: Receiver operating characteristics
EPI: Echo Planar Imaging
TE: Echo time
TR: Repetition time
STIR: Short-Tau Inversion Recovery
SD: Standard deviation
SPSS: Statistical program for social science
NPV: Negative predictive value
PPV: Positive predictive value

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