Original Article

Value of ADC Thresholds to Diagnose Head and Neck Lesions: Can ADC Values Replace Biopsy?

Baş-Boyun Lezyonlarının Teşhisinde ADC Eşik Değerlerinin Kullanımı: ADC Değeri Biyopsinin Yerini Alabilir mi?

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ABSTRACT

Introduction: We aimed in this study to evaluate the usefulness of DWI in tissue characterization of head and neck lesions, to investigate the difference in ADC values for distinguishing malignant and benign head and neck lesions (group A), lymphoma and carcinoma (group B), malignant and benign lymph nodes (group C) and to determine threshold values for these distinctions.
Methods: We included 95 lesions in 88 patients. 84 lesions were histopathologically confirmed. DWI using single-shot echo-planar imaging with b factors of 0, 400 and 800 sec/mm^2 were performed on 1.5TMR unit. Groups were compared using Kruskal-Wallis test.
Results: Statistically significant difference was found in group A, group B and group C. When an ADC value of 1.13×10^{-3} mm^2/s was used for predicting malignancy in group A, the sensitivity, specificity and accuracy were 85.7%, 71.7%, 78.9%, respectively. If 0.85×10^{-3} mm^2/s was used as a threshold value for differentiating in group B the best results were obtained with an accuracy of 83.7%, sensitivity of 92.9% and specificity of 78.3%. When 0.95×10^{-3} mm^2/s was used as a threshold value for differentiating in group C the highest accuracy of 82.8%, with 90.5% sensitivity and 71.4% specificity was obtained.
Discussion and Conclusion: DWI can be used to characterize head and neck lesions based on ADC values, but cannot replace biopsy.

Keywords: Diffusion-weighted imaging, head and neck masses, ADC threshold, ADC measurement.

ÖZET

Giriş ve Amaç: Bu çalışmada, baş boyun lezyonlarının doku karakterizasyonunda difüzyon ağırlıklı görüntülemenin kullanımını değerlendirmek adına, malign ve benign baş boyun lezyonları (grup A), lenfoma ve karsinom (grup B), malign ve benign lenf nodları (grup C) ayrımını yapabilmek için ADC değerleri arasındaki farklılıkları araştırdık ve bu ayrımlar için eşik değerler belirlemeyi amaçladık.
Yöntem ve Gereçler: Çalışmaya 88 hastadaki 95 lezyonu dahil ettik. 84 lezyon histopatolojik olarak doğrulandı. 1.5T MR ünitesinde 0, 400 ve 800 sn/mm^2 b değerleri ile difüzyon ağırlıklı görüntüleme yapıldı. Gruplar Kruskal-Wallis testi kullanılarak karşılaştırıldı.
Bulgular: Grup A, grup B ve grup C'de istatistiksel olarak anlamlı fark bulundu. Grup A'da maligniteyi öngörmek için 1.13×10^{-3} mm^2/s'lik bir ADC değeri kullanıldığında, duyarlılık, özgüllük ve doğruluk sırasıyla %85.7, %71.7 ve %78.9 idi. Grup B'de ayrım yapmak için eşik değer olarak 0.85×10^{-3} mm^2/s kullanıldığında en iyi sonuçlar %83,7 doğruluk, %92.9 duyarlılık ve %78,3 özgüllük ile elde edildi. Grup C'de ayrım yapmak için eşik değer olarak 0.95×10^{-3} mm^2/s kullanıldığında en yüksek doğruluk %82.8, duyarlılık%90.5 ve özgüllük %71.4 ile elde edildi.
Tartışma ve Sonuç: Difüzyon ağırlıklı görüntüleme ADC değerleri kullanılarak baş ve boyun lezyonlarını karakterize etmek için kullanılabilir, ancak biyopsinin yerini alamaz.

Anahtar Kelimeler: Difüzyon ağırlıklı görüntüleme, baş ve boyun kitleleri, ADC eşik değeri, ADC ölçümü.

First Received: 06.10.2021, Accepted: 23.11.2021 doi: 10.5505/aot.2022.68442

Introduction

Head and neck masses represent a wide array of pathologies. Different routine sequences of magnetic resonance imaging (MRI) may not accurately exclude malignancy. Diffusion-weighted imaging (DWI) has been used as an aid for imaging these masses [1, 2].

In diffusion-weighted MRI, image contrast depends on the motion of water molecules [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 of tissues or pathophysiologic states that are intrinsic to different tissues.

DWI with calculation of ADC values has been investigated in the past to distinguish benign and malignant head and neck lesions [4]. In literature, it is indicated that malignant head and neck masses show restricted diffusion, whereas in benign lesions this restriction decreases as the lesion progresses to a cystic inner structure, yet more, elevated diffusion is observed. Therefore, low ADC values are obtained in malignant lesions [5].

The purpose of our study is to evaluate the usefulness of DWI in tissue characterization of head and neck lesions.

Material and Methods

Subjects

Our study involved 95 head and neck lesions in 88 patients (49 men, 39 women, age range: 3 months to 86 years, mean age 52 years) over a 2-year period, retrospectively. Patients who underwent head and neck MRI including DWI, for lumps prediagnosed by clinican, were enrolled to the study. This study was approved by Başkent University Medicine and Health Sciences Research Ethics Committee (project number: KA12/67).

Of the histopathologically confirmed 84 lesions, 41 were diagnosed by biopsy and 43 were surgically removed. The rest 11 lesions, such as hemangioma, lymphangioma, thyro-glossal duct cyst and glomus caroticum tumor, were diagnosed by typical radiological findings based on MRI or angiography. In patients with multipl similar masses, the biggest lesion was chosen to work on. Patients who had taken chemotherapy or radiotherapy, or biopsied before MRI were excluded. All cases were divided into five groups (Table 1).

MRI Acquisition

MRI examinations were performed on 1,5-T (Siemens Avanto) using head coil. In axial and coronal planes T1W, in axial plane T2 turbo spin echo and fat suppressed T2, after contrast administration (gadoversetamide, 0.2mmol/kg) in axial, coronal and sagittal planes fat suppressed T1 images were obtained with a slice thickness of 4 mm.

DWI was performed before contrast administration, obtaining images in axial plane using echo-planar spin-echo T2 (factor b of 0, 400 and 800 s/mm²). The scanning parameters were as follows: Field of view, 250 x250 mm; NEX, 3; matrix size, 104x160; slice thickness, 4 mm; bandwidth, 1250 Hz/pixel. The acquisition time for DWI was 2min 36s. ADC maps were automatically generated. DWI images were collected on a single workstation (Leonardo, Software version syngo MR B17; Siemens, Germany) to calculate ADC values.

Image Analysis

The radiological evaluation was made by a neuroradiologist with 12 years of experience, blinded to the pathologies. In order to achieve best results, three different ROIs were placed on ADC maps in concordance with T1 or T2 images. If it enhances, the most contrast-enhancing area of the lesion was chosen on T1 images. If cystic or necrotic content is present, ROI was placed to comprise only the solid component, avoiding the cystic-necrotic part by taking advantage of T2-weighted images

Table 1. The ADC[1] values of the subtypes and subgroups of head and neck masses

Subtypes	Pathology	Number	ADC value (10^{-3} mm^2/s)		
			Mean±SD	Minimum	Maximum
1.Lymphoma		14	0.64±0.16	0.30	0.93
2.Carcinoma		23	1.09±0.36	0.63	1.40
	2.1. Squamous cell carcinoma	14	1.11±0.29	0.78	1.75
	2.2. Carcinoma metastasis	7	0.93±0.36	0.63	1.70
	2.3. Other carcinomas (Adenoid cystic carcinoma, adenocarcinoma)	2	1	0.80	1.20
			2.03	1.90	2.20
3.Malignant lesions other than lymphoma and carcinoma	(Fibrosarcoma, non-skeletal Ewing sarcoma, PNET[2], plasmocytoma)	5	1.03±0.49	0.43	1.80
4.Benign solid lesions		46	1.50±0.48	0.70	1.66
	4.1. Pleomorphic adenoma	4	1.59±0.22	1.30	1.83
	4.2. Warthin tumor	10	1.32±0.43	0.80	2.10
	4.3. Vascular lesions (Hemangioma, glomus caroticum tumor, arteriovenous malformation)	7	1.98±0.24	1.76	2.36
	4.4. Inflammatory lesions (Benign lymph nodes, necrotizing lymphadenitis, chronic inflammatory lymph nodes, abscess)	14	1.19±0.45	0.70	2.16
	4.5. Other benign solid lesions (Papillomatous squamous lesion, enchondroma, vagal nerve schwannoma, ameloblastoma, Castleman disease, granuloma, inverted papilloma, nasal polyp, vocal cord polyp)	11	1.72±0.42	1.10	2.30
5.Benign cystic lesions	(Lymphangioma, thyroglossal duct cyst, Thornwaldt cyst, parathyroid cyst)	7	2.64±0.59	1.90	3.76
Total		95			

[1] ADC: Apparent Diffusion Coefficient, [2] PNET: Primitive Neuroectodermal Tumors

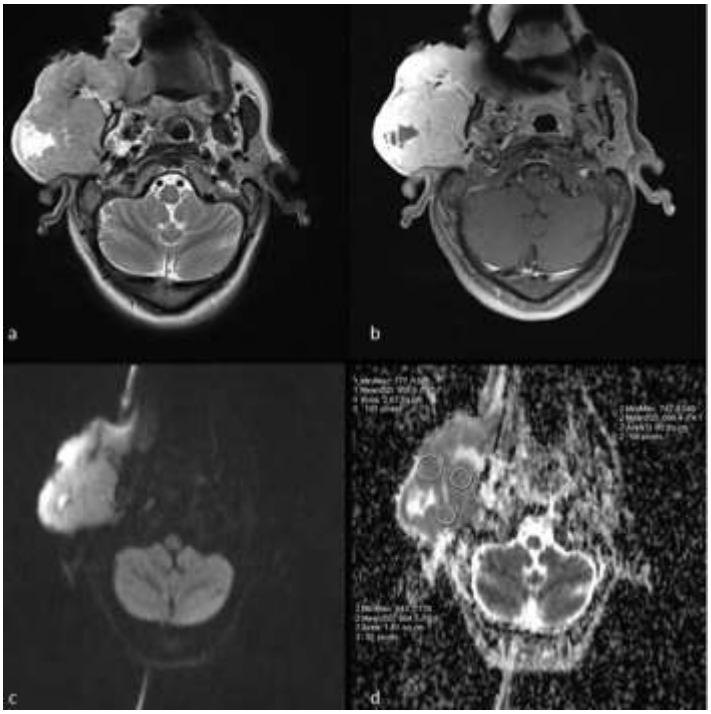

Figure 1 Excluding the cystic/necrotic portions from ROI in a case of epidermoid carcinoma. a. Axial T2-weighted image b. Axial contast fat suppressed T1-weighted image c. DWI d. ADC map (0.95×10^{-3} mm2/s, 0.89×10^{-3} mm^2/s and 0.96×10^{-3} mm^2/s)

(Figure 1). The mean ADC value was calculated afterwards.

Statistical Analysis

The statistical analysis was made using SPSS 15.0 (Statistical Package for Social Sciences, 15.0) and MedCalc programs. Shapiro-Wilk test was used to interpret normality and the data was not normally distributed according to the test. Continuous variables were presented as mean ± standard deviation and median (minimum-maximum). "Kruskal-Wallis Test" was used to evaluate ADC values of the groups. and $p<0.05$ was regarded statistically significant. In order to compare groups in pairs, Mann-Whitney U test was used for post-hoc analysis with Bonferroni correction, where "p" value less than 0.01 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to evaluate diagnostic efficiency of the ADC values to differentiate in between certain groups, and threshold ADC values with highest accuracy were determined.

Results

Out of 95 lesions, 42 were malignant and 53 were benign. We established five groups including lymphoma (group 1), carcinoma (group 2), malignant lesions other than lymphoma and carcinoma (group 3), benign solid lesions (group 4) and benign cystic lesions (group 5). Additionally, carcinoma and benign solid lesions were divided into two and five subgroups, respectively (Table 1). Statistically significant difference was found between all pairs of five groups ($p<0.05$) except between group 2 and group 3. Additionally, the ADC values of pleomorphic adenoma and Warthin tumor subgroups were compared, but there was no statistically significant difference ($p=0.148$).

Group 1 mostly consisted of diffuse large B cell lymphoma. Benign solid lesions, was the

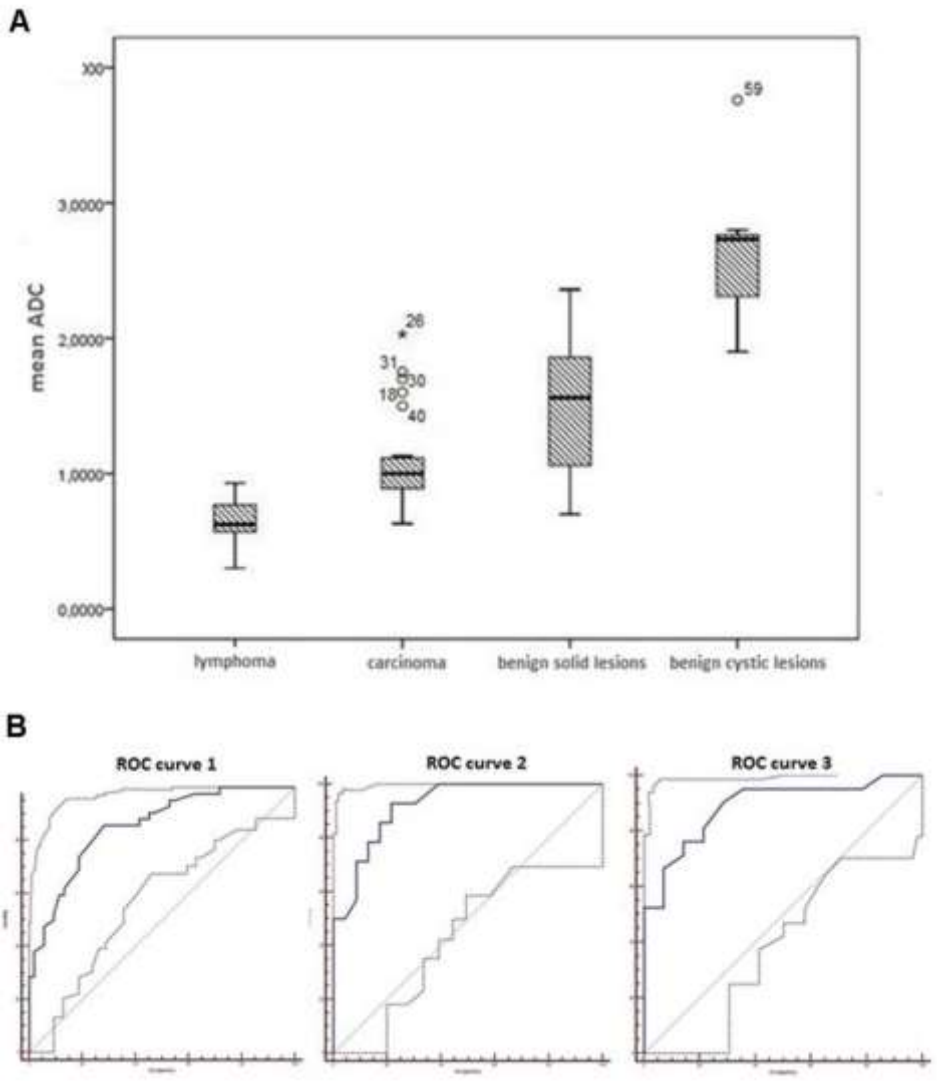

Figure 2 a. Box and whisker plot of the ADC values of 95 head and neck lesions b. ROC curves of the ADC values. In order to distinguish in between group A we used ROC curve 1 (cut off ADC value: 1.13×10^{-3} mm^2/s), in group B we used ROC curve 2 (cut off ADC value:0.85×10^{-3} mm^2/s) and in group C we used ROC curve 3 (cut off ADC value: 0.95×10^{-3} mm^2/s)

largest group in number. Group 1 and carcinoma metastasis subgroup together comprised malignant lymph nodes (n=21), whereas inflammatory lesions subgroup alone comprised benign lymph nodes (n=14). The ADC values of head and neck lesions and the relationship between four main groups are shown on box and whisker plot graphic in Figure 2.

The group with lowest mean ADC value of malignant lesions was lymphoma, while the highest was squamous cell carcinoma (SCC). Among benign lesions, inflammatory lesions and Warthin tumor had the lowest mean ADC values, whereas the highest mean ADC value belonged to cystic lesions.

The ROC curves were used to differentiate malignancy from benign lesions, lymphomas from carcinomas and malignant lymph nodes from benign lymph nodes (Figure. 2). When an ADC value of 1.13×10^{-3} mm^2/s or lower was used for predicting malignancy (group A), the sensitivity, specificity, and accuracy

Table 2. The threshold ADC[1] values used for differentiating in between group A, group B, group C and the statistical data for diagnostic use

Groups compared	ADC threshold value ($\times10^{-3}$ mm^2/s)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy Rate (%)
Group A (Malignant-Benign)	1.13	85.7	71.7	70.6	86.4	78.9
Group B (Lymphoma-Carcinoma)	0.85	92.9	78.3	72.2	94.7	83.7
Group C (Malignant lymph node - Benign lymph node)	0.95	90.5	71.4	82.6	83.3	82.8

[1] ADC: Apparent Diffusion Coefficient

Table 3. Comparative literature threshold ADC[1] values for differentiating in group A, group B and group C

	Authors of the study	Tesla of the MRI system	Number of lesions	Threshold ADC value ($\times10^{-3}$ mm^2/s)
Group A	Wang et al.	1.5	81	1.22
	Abdel Razel et al.	1.5	76	1.25
	Srinivasan et al.	3	33	1.3
	Chang et al.	1.5	114	1.22
	Our study	1.5	95	1.13
Group B	Wang et al.	1.5	81	0.84
	Maeda et al.	1.5	39	0.76
	Our study	1.5	95	0.85
Group C	Abdel Razek et al.	1.5	85	1.38
	Our study	1.5	95	0.95

[1] ADC: Apparent Diffusion Coefficient

were 85.7%, 71.7% and 78.9%, respectively (Table 2). If an ADC value of 0.85×10^{-3} mm^2/s was used as a threshold value for differentiating lymphoma from carcinoma (group B) the best results were obtained with an accuracy of 83.7%, sensitivity of 92.9% and specificity of 78.3%. When an ADC value of 0.95×10^{-3} mm^2/s was used as a threshold value for differentiating malignant lymph nodes from benign lymph nodes (group C), the highest accuracy of 82.8%, with 90.5% sensitivity and 71.4% specificity was obtained.

Discussion

It is not uncommon to encounter lesions that have indeterminate findings on ultrasound, computed tomography and conventional MRI and necessitate further investigation4. Tissue contrast attained by DWI is different from that of conventional MRI. ADCs are expected to vary according to the microstructures of tissues or pathophysiologic states that are intrinsic to different tissues. Generally, malignant tumors have enlarged nuclei, hyperchromatism, and angulation of nuclear contour, and they show hypercellularity. These histopathologic characteristics reduce the extracellular matrix and the diffusion space of water protons in the extracellular and intracellular dimensions, with a resultant decrease in the ADCs [5].

Several studies have been published to evaluate head and neck lesions by using DWI to predict malignancy (Table 3). In this study, we observed that diffusion restriction incre-

Table 4. Comparative mean ADC[1] values of Warthin tumor, pleomorphic adenoma and benign cystic lesions in different studies

	Authors of the study	Tesla of the MRI system	Number of lesions	Threshold ADC value ($\times 10^{-3}$ mm^2/s)
Warthin tumor	Habermann et al.	…	45	0.85±0.10
	Yerli et al.	1.5	30	0.97±0.16
	Our study	1.5	95	1.32±0.43
Pleomorphic adenoma	Habermann et al.	…	45	2.14±0.11
	Yerli et al.	1.5	30	1.74±0.37
	Our study	1.5	95	1.59±0.22
Benign cystic lesions	Sakamoto et al.	1.5	67	2.41±0.48
	Wang et al.	1.5	81	2.05±0.62
	Abdel Razek et al.	1.5	76	2.01±0.21
	Our study	1.5	95	2.64±0.59

[1] ADC: Apparent Diffusion Coefficient

ased along with the malignancy level, prominently in the lymphoma group, whereas elevated diffusion was seen in the cystic component. When such strong diffusion restriction is detected, we can diagnose malignancy without biopsy, especially in lymph nodes. However, when the values we measure are close to the cut-off, some conflicts start to appear. In such cases, we can still use DWI as a guidance to biopsy, as in sampling the areas with lowest ADCs as possible.

In our study, considering the threshold value for predicting malignancy, five malignant tumors were falsely diagnosed as benign lesions. Four of these were primary or metastatic SCC and the remaining one was thyroid papillary adenocarcinoma. According to the pathology results, the four SCCs contained foci of micronecrosis, which may have caused high ADCs. MRI visible necrosis is possible to exclude while placing the ROI in solid components. However, avoiding micronecrotic areas is not possible and that's an unintentional limitation apparently. The small foci of necrosis confirmed only by pathological findings might be the major reason of high ADCs of malignant tumors in our study, because SCC and SCC metastasizing to the lymph node are likely to develop necrosis [5]. Besides, the intense mucin areas determined in one of the lymph nodes of a metastasizing SCC might be another reason for explaining high ADC values, as well as extracellular fluid found abundantly in follicular parts in thyroid adenocarcinoma.

In literature, ADC values in lymphomas were found lower than that of SCCs [5,6]. In our study, we achieved the similar result. Considering the threshold value to differentiate lymphoma from carcinoma, five carcinoma cases showed low ADCs mimicking lymphoma. Three of these were carcinoma metastasis and the rest two were larynx SCC. Poorly differentiated carcinomas have more cellularity, larger and more angulated nuclei with more abundant macro-molecular proteins, and less extracellular space [5]. In our study, the two larynx SCCs mimicking lymphoma were reported as poorly differentiated SCCs in pathologic evaluation. There were two more lesions showing poor differentiation and they both had ADCs very close to the cut-off value. The rest SCCs were all either well differentiated or moderately differentiated. There are common aspects of carcinoma metastasis and lymphoma

histologically and cytologically as well. Carcinoma metastases are high stage malignancies, that would have histologically poor differentiation. The deterministic factor for SCC is squamous differentiation, which is characterized by keratin formation1. It is known that keratin impairs water movement, therefore, the presence of keratin may intensify the ADC decrease in metastatic lymph nodes [7].

Among benign lesions, cystic lesions and vascular lesions had the highest mean ADC values while the group with the lowest ADCs was inflammatory lesions. Benign vascular lesions, as hemangiomas and venous mal-formations, show higher ADCs than that of the other benign solid tumors such as granuloma and pleomorphic adenoma, due to excess extracellular spaces with free diffusion within the vascular lesions [2]. Thirteen of 53 benign lesions showed lower ADCs than the threshold value. These false positive 13 lesions included four Warthin tumors, four reactive lymph nodes, one necrotizing lymphadenitis, one abscess, one granuloma and two chronic inflammation. The hyper-cellular structure of some benign lesions, such as granuloma and abscess, might be responsible for low ADCs in benign category. A proliferation of the epithelial component and intense lymphoid accumulation in the stroma may have limited the motion of the water protons in the extracellular space of the Warthin tumor [5]. For these reasons, DWI remains insufficient to differentiate certain inflammatory lesions from malignant tumors [8].

Although we found significant difference between the ADC values of benign and malignant lesions, in literature, ADCs show diversity among each group. For instance, the mean ADC value of Warthin tumor is reported as (0.85±0.10) $\times10^{-3}$ mm^2/s by Habermann et al. [9] and (0.97±0.16) $\times10^{-3}$ mm^2/s by Yerli et al. [10], where we found (1.32±0.43) $\times10^{-3}$ mm^2/s in our study (Table 4). In both studies statistically significant difference is found between Warthin tumor and pleomorphic adenoma, unlike our study (p=0.148). Ikeda and colleagues suggested that the lower ADC value of Warthin tumors could be explained by the higher protein content in the cystic portions [11]. Those tumors have the highest microvessel count of all parotid gland tumors, and they also exhibit high cellularity. These variable ADCs in Warthin tumor may overlap carcinomas, particularly salivary duct carcinomas [10]. In our study the Warthin tumor group, which consists of 10 cases, has a range of ADCs between 0.80×10^{-3} mm^2/s and 2.10×10^{-3} mm^2/s. The case with the lowest ADC value revealed intense lymphoid cell accumulation in its pathological examination, whereas one of the Warthin tumor cases with high ADCs contained cystic component together with marked mucinous metaplasia on pathology studies. Intense mucinous content and cystic component might explain high ADCs in this subgroup.

The mean ADC value of pleomorphic adenoma was reported as (2.14±0.11) $\times10^{-3}$ mm^2/s and (1.74±0.37) $\times10^{-3}$ mm^2/s in the studies by Habermann et al. [9] and Yerli et al. [10], respectively. In our study we obtained a mean value of (1.59±0.22) $\times10^{-3}$ mm^2/s. Histopathologically, pleomorphic adenomas have a biphasic appearance that reflects the admixture of epithelium and stroma. Most of the epithelial component is of a glandular nature. It could be that water protons move relatively freely in the areas of pleomorphic adenomas that are glandular or contain fluid, and that a high ADC value may indicate a pleomorphic adenoma [10]. The reason of low ADCs in our study might be the stromal component predominating and that there are only a few number of cases of pleomorphic adenoma present. We think that for all these reasons we could not find statistically significant difference between Warthin tumor and pleomorphic adenoma.

The mean ADC for cystic lesions reported in some previous studies were $(2.41\pm0.48)\times10^{-3}$ mm^2/s, $(2.05\pm0.62)\times10^{-3}$ mm^2/s and $(2.01\pm0.21)\times10^{-3}$ mm^2/s [2, 5, 12], whereas we obtained a value of $(2.64\pm0.59)\times10^{-3}$ in our series. The ADC value of a cystic lesion varies depending on its content such as fat, protein, and septa. In case of a prior infection, an increasing protein concentration would be considered to have decreased the water protons movement [5, 12].

The mean ADCs of both lymphoma and metastasizing lymph nodes were significantly lower than that of benign lymph nodes in our study ($p<0.05$), however an overlap was observed occasionally. There were two malignant lymph nodes above and four benign lymph nodes below the threshold value. Both the malignant lymph nodes were metastasizing of which one had a primary of colon adenocarcinoma and the other revealed intense mucinous areas in its pathology report. Another factor that elevates the ADCs in malignant lymph nodes is the foci of necrosis which is seen frequently in carcinoma metastasis. Therefore, the mucinous content, the glandular structure of the colon adeno-carcinoma and the foci of necrosis may explain the elevation in ADC values. In our study, the ADCs of all the lymphomas were below the threshold value. The contributions of different components, such as fibrous scar tissue and granulation tissue, may alter the ADC value by restricting diffusion [13]. This might explain the diversity of ADCs measured in benign lymph nodes and the relatively low ADC values in our study.

The potential contribution of echo-planar DWI in the head and neck is still limited by technical problems regarding susceptibility artifacts, spatial resolution and motion artifact due to swallowing, respiration or blood flow [13].

The categories of patients we evaluated in this study are heterogenous by age which consists of mostly young adults and adults. Pediatric patients remain limited. Further researches are needed to be studied with larger series of pediatric patients on different magnetic strengths. Another restriction of our study is the lack of comparing DWI with positron emission tomography-computed tomography (PET-CT), which is being used for lymphoma patients preferentially. Comparison between these two imaging methods needs to be accomplished, since both of the techniques are based on histopathology and are sensitive to lymph node evaluation [14]. We also realized that ADC measurements of head and neck lesions differ among various studies, yielding to a conflict on cut-off values. That is why we strictly place the ROI in the solid component of the mass with lowest ADC area on the map and make more than one measurements. But still, we think larger populated studies or meta analysis would enlighten this conflict in the future, while our study is a contribute to literature with this broad variety of head and neck masses.

Conclusions

In conclusion, DWI is a fast and sensitive MRI sequence that can be used to characterize head and neck lesions by ADC mapping according to the histopathological variety that reflects their inner structure. Additionally, DWI still cannot replace biopsy, especially in cases with ADCs very close to the cut-off values, but it is a non-invasive diagnostic technique which can prevent certain biopsies or can provide useful additional information about the masses that are scheduled for biopsy or surgery.

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Doi: 10.5505/aot.2022.68442

