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RESEARCH

Contribution of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements in determining response to treatment in lung cancer

Akciğer kanserinde tedaviye cevap belirlenmesinde difüzyon ağırlıklı görüntülemenin (DAG) ve görünür difüzyon katsayısı (ADC) ölçümlerinin katkısı

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Abstract

Purpose: The purpose of this study was to evaluate the role of diffusion-weighted imaging (DWI) in evaluating tumor response to chemotherapy in stage III-IV lung cancer.

Materials and Methods: Chest and DWI were performed with 3T MRI before and after 3 courses of chemotherapy on 32 patients diagnosed with stage III-IV lung cancer. DWI were acquired with a b factor of 50, 400 and 800 s/mm using a single-shot echo-planar sequence. Histopathological types before and after chemotherapy were compared by measuring mean apparent diffusion coefficient (mADC) values on the basis of regression and progression groups.

Results: 32 cases, 7 (18.5%) were in the progression group (PG), and 25 (81.5%) were in the regression group (RG). mADC in the PG was 1.06±0.43 x 10^{-3} before chemotherapy and 0.85±0.24 x 10^{-3} after chemotherapy. mADC in the RG was 0.92±0.27 x 10^{-3} before chemotherapy and 1.20±0.26 x 10^{-3} after chemotherapy. There was a statistically significant difference between the mADC values in the PG and RG before and after chemotherapy. There was no statistically significant difference in mADC values before and after chemotherapy in small cell lung cancer (SCLC) tumor type in the PG . There was a statistically significant difference in mADC values before and after chemotherapy in SCLC and non-

Öz

Amaç: Bu çalışmada evre III-IV akciğer kanserinde kemoterapiye tümör yanıtının değerlendirilmesinde difüzyon ağırlıklı görüntülemenin (DAG) rolünü değerlendirmektir.

Gereç ve Yöntem: Evre III-IV akciğer kanseri tanılı 32 hastaya 3 kür kemoterapi öncesi ve sonrası 3T MRG ile toraks MRG ve DAG uygulandı. DAG, tek atımlık bir eko-düzlemsel dizi kullanılarak 50, 400 ve 800 s/mm'lik bir b faktörü ile elde edildi. Kemoterapi öncesi ve sonrası histopatolojik tipler, regresyon ve progresyon grupları temelinde ortalama görünür difüzyon katsayısı (mADC) değerleri ölçülerek istatistiksel olarak karşılaştırıldı.

Bulgular: 32 olgudan 7'si (%18,5) progresyon grubunda (PG), 25'i (%81,5) regresyon grubunda (RG) yer aldı. PG'deki mADC, kemoterapiden önce 1,06±0,43 x 10^{-3} ve kemoterapiden sonra 0,85±0,24 x 10^{-3} ölçüldü. RG'deki mADC, kemoterapiden önce 0,92±0,27 x 10^{-3} ve kemoterapiden sonra 1,20±0,26 x 10^{-3} ölçüldü. Kemoterapi öncesi ve sonrası PG ve RG'de mADC değerleri arasında istatistiksel olarak anlamlı fark vardı. PG'de küçük hücreli akciğer kanseri (KHAK) tümör tipinde, kemoterapi öncesi ve sonrası mADC değerlerinde istatistiksel olarak anlamlı fark yoktu. RG'de KHAK ve küçük hücreli dışı akciğer kanseri (KHDAK) tümör tiplerinde ve PG'de KHDAK tümör tipinde kemoterapi öncesi ve sonrası mADC değerlerinde istatistiksel olarak anlamlı fark vardı.

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small cell lung cancer (NSCLC) tumor types in the RG and NSCLC tumor type in the PG
Conclusion: DWI and ADC measurements can be used in assessing response to treatment in malignant pulmonary tumors.
Keywords:. Inoperable lung cancer, treatment response, diffusion-weighted magnetic resonance imaging

Sonuç: Malign akciğer tümörlerinde DAG ve ADC ölçümleri tedaviye yanıtı değerlendirmede kullanılabilir.

Anahtar kelimeler: İnoperabl akciğer kanseri, tedavi yanıtı, difüzyon ağırlıklı manyetik rezonans görüntüleme

INTRODUCTION

Chemotherapy is one of the main treatment strategies for patients with locally advanced small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). An early assessment of the therapeutic response of the tumour is important, to replace any ineffective therapy, due to the high toxicity of chemotherapeutic drugs. The Responsive Evaluation Criteria in Solid Tumors (RECIST) are widely used to evaluate tumour response during lung cancer treatment based on conventional imaging procedures, such as computed tomography (CT) and routine magnetic resonance imaging (MRI)[1,2]. Although the estimation of tumour responses based on these modalities is useful, there are also disadvantages. Routine imaging techniques such as CT have limitations in distinguishing tumour necrosis or residual tumour tissue from fibrotic scarring, and functional imaging techniques based on positron emission computed tomography (PET) are increasingly used to monitor early treatment-related changes in tumours' vascularisation and metabolism[3, 4]. There are also disadvantages such as allergies to iodinated contrast material, exposure to high radiation and the high cost–benefit ratio of PET.

Diffusion-weighted imaging (DWI) is a functional imaging technique widely used to examine all areas of the body. Its principal feature is that it shows a tissue's cell density by reflecting the movements of water molecules among cells in the tissue. The apparent diffusion coefficient (ADC) measured with DWI permits a numerical analysis of the tissue's diffusion characteristics. This coefficient decreases as cell numbers and density in tumorous tissues increase. Since it provides functional information concerning the tumour's cellular and cell membrane integrity, DWI has been used in recent years for tumour diagnosis and characterisation, and to monitor responses to treatment[5].

A previous study showed that DWI has great clinical application value and potential in the differential diagnosis of lung cancer[6]. Studies performed with DWI directed towards malignant pulmonary masses have shown that it is highly effective, compared to other imaging modalities, in terms of identifying pulmonary nodules and in differentiating malignant and benign lesions[7, 8]. Despite this, few studies to date have investigated post-treatment ADC changes and their probable role in determining prognoses in patients with lung cancer[9-11]. In the preliminary study of Chang et al. evaluating the efficacy of DWI in assessing response to chemotherapy in lung cancer, they reported that of seven patients with qualified DW images before and during chemoradiotherapy, there was a significant increase in ADC in six who responded to chemoradiotherapy, and a slight decrease in one who did not respond[9]. Tumor cell densities increase due to the increase in DWI signals, and the signal intensity and distribution of DAG may represent the number of cancer cells[12]. Therefore, DWI may have potential value for the evaluation of diagnosis and treatment efficacy in lung cancer. The purposes of this study were to determine changes in ADC values parallel to changes in mass size following chemotherapy and to assess the clinical value of DWI for monitoring early responses in lung cancers.

MATERIALS AND METHODS

Patients

The study was carried out with the permission of the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (Date: 04.12.2015, Decision No: 24237859-641) and written informed consent was obtained from all patients.

A total of 38 patients with a pathological diagnosis of stage III–IV lung cancer who underwent underwent MRI in the radiology department of Karadeniz Technical University Hospital between 1 November 2015 and 30 December 2016 participated in the study. The inclusion criteria were lung masses 1.0 cm and larger in diameter, no history of chemotherapy or radiotherapy and no contraindications for high-field-strength MRI. Six patients were subsequently excluded from the study due to complications arising

after the first course of chemotherapy, or due to a generally impaired condition. Pathological diagnoses were established via a bronchoscopy in 18 patients (56.2%) and using a transthoracic needle biopsy in 14 (43.8%).

MRI technique

A thoracic MRI was performed using a 3.0 Tesla MR device (Siemens Skyra) with a body coil. The patients were placed in supine position and standard thoracic MRI protocol was used; Following the acquisition of localizer and calibration images in the T1 Vibe axial (matrix; 384 x 189, TE/TR (ms); 1.78 / 4.02), T2 true FISP coronal (matrix; 256 x 256, TE/TR (ms); 1.26 / 558), T2 Blade FS axial (matrix; 256 x 256, TE/TR (ms); 163 / 3000), T2 STIR coronal (matrix; 384 x 261, TE/TR (ms); 91 / 3500) and T2 STIR axial (matrix; 175 x 320, TE/TR (ms); 104/4200) thoracic sections were taken. FOV values were adjusted to include the entire thorax, depending on each patient's build. Axial T1WI with FS were obtained both before and after a contrast agent was introduced. Gadopentetate dimeglumine (Gadovist, Bayer Healthcare, Berlin, Germany) was administered at a dose of 0.1 mL/kg, with an injection rate of 3 mL/s, followed by an infusion of 10 mL normal saline.

Diffusion MRI protocol

A multi-section single-shot inversion recovery echo planar sequence in the axial plane without breath-holding was applied at DWI. Values of 50, 400 and 800 s/mm² were used. The matrix value was 108x134, TR (ms) 5900, TE (ms) 53, EPI factor 108, section thickness 6 (mm), section interval 1.2 (mm) 1.2, partial Fourier factor off and band width (Hz per pixel) 2332.

Image analyses

All MR images were uploaded to a picture archiving and communication system (PACS). Images were evaluated independently of histopathology based on the consensus of two two radiologists with 5 (E.B.) and 20 (P.K.) years of experience. Lesion sizes were measured on DWI as the longest dimension, correlating with T2WI. Cavities, necrosis, atelectatic and pneumonic lung regions were excluded by reference to T2-weighted images and contrast-enhanced images. Regions of interest (ROI) of different sizes were placed in such a way as to cover at least 2/3 of the solid parts of the lesion. ADC measurements were taken with ROI placed on five different areas of the lesion. The mean of the five separate ADC values obtained from the lesions was recorded as the mean ADC (mADC); mADC values were calculated for lesions before and after chemotherapy. Changes in mass ADC and mass dimensions before and after chemotherapy were compared. The response to chemotherapy was evaluated separately in two subgroups, as SCLC and NSCLC, according to their histopathology.

Clinical treatment, assessment of tumour response and follow-up

Ten patients (31.2%) received cisplatin+etoposide therapy, five (15.6%) carboplatin+gemcitabine, four (15.6%) cisplatin+vinorelbine, five (15.6%) carboplatin+etoposide, five (15.6%) cisplatin+gemcitabine and three (9.37%) carboplatin+ paclitaxel.

Lesion sizes were measured before and after chemotherapy. Post-treatment tumour responses were assessed according to RECIST 1.1[1]: (1) Loss of all lesions was defined as a complete response; (2) ≥30% reduction in the sum of the maximum diameters of the target lesion was defined as a partial response (PR); (3) The maximum diameter change of the target lesion between PR and progressive disease (PD) was defined as stable disease (SD); (4) ≥20% increase in the sum of the maximum diameters of the target lesion and the emergence of new lesions was defined as PD. Patients underwent diffusion MRI and chest MRI with 3T MRI one week before and three weeks after chemotherapy.

Statistical analysis

All collected data were analyzed using the SPSS 23.0 (Statistical Package in the Social Sciences for Windows, Version 13.0, SPSS Inc., Chicago, IL, U.S., 2018) software packages. The normal distribution characteristics of the research data were analyzed using the Kolmogorov-Smirnov test. Normally distributed quantitative data were presented as mean ± standard deviation (SD) values and compared using the student's t-test. Categorical variables were presented as numbers (n) and percentage (%) values. Comparisons between two dependent groups were performed using the paired t test when normal distribution conditions were established and the Wilcoxon test when normal distribution was not established. Spearman's correlation test was used to

determine correlation of constant variables. The power analysis of the study was found to be 81.67%. A p value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic features. The mean age of the study group was 63.8 (18-95) years. Among 32 cases, 7 (18.5%) were in the progression group, and 25 (81.5%) were in the RG. There was no statistically significant difference between the ages in the regression and progression groups (p>0.05). Mean size in the regression group was 59.1±23 mm pre-chemotherapy and 31.6±14.4 mm post-chemotherapy. Mean size in the progression group was 37.5±18 mm pre-chemotherapy and 59.4±22.6 mm post-chemotherapy. There was a statistically significant difference in the change of tumor size in the PG and RG (p<0.041).

ADC values according to regression and progression group and tumor type are summarized in Table 2. There was a statistically significant difference in mADC values in regression and progression groups and different histologic types (p<0.046) (Figure 1, 2).

The changes in ADC values in the regression and progression groups of different histological types are summarized in Table 3. There was no statistically significant difference in mADC values pre and post-chemotherapy in SCLC tumor type in the progression group (p>0.05). There was a statistically significant difference in mADC values pre and post-chemotherapy in SCLC and NSCLC tumor types in the regression group and NSCLC tumor type in the progression group. (p<0.043)..

Table 1. Demographic features

Variable		N (%)
Age		63.8 years (range 44-84).
Gender*	Male	31(96.9)
	Famele	1 (3.1)
Pathologic Type*	SCLC	11 (34.3)
	NSCLC	21 (65.7)
	Adenocarcinoma	11 (34.3)
	Squamous cell cancer	9 (28.1)
	Large cell cancer	1 (3.1)
TNM stage*	IIIA	9 (28.1)
	IIIB	12 (37.5)
	IIIC	6 (18.7)
	IVA	5 (15.6)
Maxiumum tumor diameter treatment, cm, mean ± SD	Before	54.4±23.6
	After	37.7±19.9
ADCmean, 10^{-3} mm /s, treatment	Before	0.95±0.31
	After	1.12±0.30

ADC = apparent diffusion coefficient; SCLC = small cell lung cancer. NSCLC = non-small cell lung cancer.
*n(%)

Table 2. ADC values in regression and progression group and between different histologic types

Parameter	ADC_{pre}, 10^{-3}mm /s	ADC_{post}, 10^{-3} mm /s	p value	
Regression Group	0.92±0.27	1.2±0.26		<0.001
Progression Group	1.06±0.43	0.85±0.24		0.018
SCLC	0.82±0.32	1.03±0.31		0.046
NSCLC	1.02±0.28	1.26±0.29		0.044

ADC = apparent diffusion coefficient; ADCpre = average apparent diffusion coefficient value before treatment; ADCpost = average apparent diffusion coefficient value after treatment; SCLC = small cell lung cancer. NSCLC = non-small cell lung cancer.a p<0.05

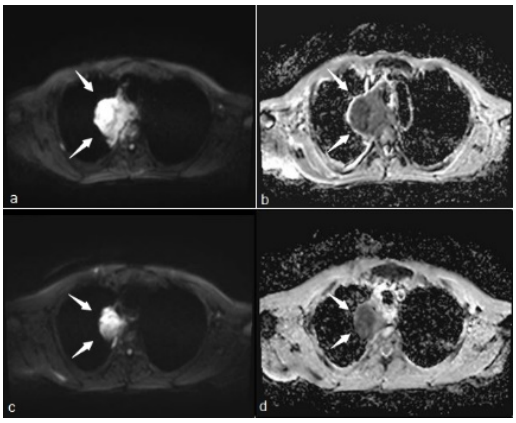

Figure 1 Transverse images in a 60 -year-old-man with squamos cell carcinoma a) pre-chemotherapy Transverse diffusion-weighted echo-planar MRI shows mass at the upper right lobe (arrows). b) pre-chemotherapy ADC map showing that mass is hypointense; ADCmean:0.735x 10^{-3} mm^2/sec. c) Post-chemotherapy Transverse diffusion-weighted echo-planar MR image shows decrease of volume of mass at the upper right lobe (regression). d) Post-chemotherapy ADC map; ADCmean:0.655x $10^{-3}mm^2$/sec.

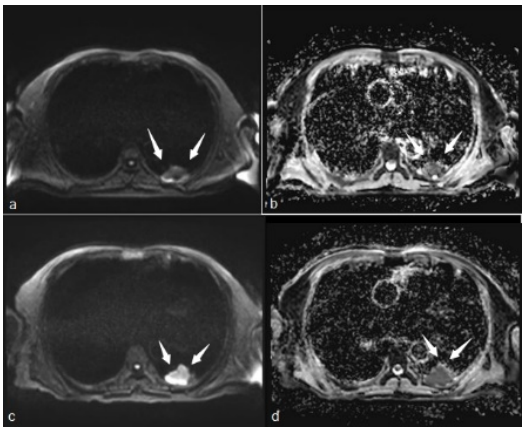

Figure 2. Transverse images in 84-year-old men with adenocarcinoma a) Pre-chemotherapy Transverse diffusion-weighted echo-planar MRI shows mass at the upper left lobe (arrows). b) Pre-chemotherapy ADC map showing that mass is hypointense; ADCmean:0.980x $10^{-3}mm^2$/sec. c) Post-chemotherapy Transverse diffusion-weighted echo-planar MR image shows increase of volume of mass at the upper Left lobe (progression). d) Post-chemotherapy ADC map; ADCmean:0.712x 10^{-3} mm^2/sec.

Table 3. ADC values in regression and progression groups of different histological types

Parameter	Regression Group		p value	Progression Group		p value
	ADCpre, 10-3mm /s	ADCpost, 10 -3 mm /s		ADCpre, 10-3mm /s	ADCpost, 10 -3 mm /s	
SCLC	0.85±0.35	1.13±0.26	p=0.028	0.69±0.2	0.62±0.18	p>0.05
NSCLC	0,98±0.2	1.3±0.24	p=0.021	1.21±0.43	0.91±0.27	p=0.043

ADC = apparent diffusion coefficient; ADCpre = average apparent diffusion coefficient value before treatment; ADCpost = average apparent diffusion coefficient value after treatment; SCLC = small cell lung cancer . NSCLC = non-small cell lung cancer.a $p<0.05$

Pre-chemotherapy ADC values in the regression group were lower than those of the progression group. However, no statistically significant difference was determined between the two groups ($p>0.05$).

DISCUSSION

The change in mADC values post-chemotherapy in our study differed between the regression and progression groups. A highly significant increase in ADC values was determined following treatment in the regression group, while in the progression group ADC values decreased significantly. However, no statistically significant difference was determined between the two groups. An increase in ADC values may be anticipated in malignant tumors responding to treatment. The increase in ADC is associated with increased water diffusion inside the tumor after treatment. Cytotoxic edema and fibrosis are implicated in the increase in diffusion[13]. In contrast, cellularity increases and diffusion is restricted in malignant tumors refractory to treatment. ADC values will therefore be expected to decrease[5].

Various studies have investigated the role of diffusion MRI in malignant masses after treatment. In increase in ADC values in patients responding to chemotherapy compared to pre-treatment levels was

reported as a common finding of three separate studies investigating ADC values following chemotherapy in patients with squamous cell cancer[14-16]. A few studies have investigated ADC values in parallel to a decrease in mass size together with treatment in lung cancer patients. Two studies involving diffusion MRI reported that, despite low patient numbers, ADC values increased in masses that decreased in size following chemotherapy, while ADC values decreased in masses that increased in size[9, 11]. In our study, ADC values increased in the group that responded to treatment in the form of regression, and decreased in the group responding in the form of progression. In other study of 28 patients with NSCLC, Yabuuchi. et al.[17] reported that the decrease in mass size with treatment in patients responding to treatment in the early stage and the increase in ADC values were seen to be significant. Xu et al. found a statistically significant inverse correlation between tumor regression rate and ADC rates in patients with NSCLC treated with chemoradiotherapy.[18] Similarly in our study, a statistically significant increase was determined in ADC values after treatment compared to before treatment in the NSCLC group.

Response to treatment is evaluated at the cellular level by determining tumor cellularity levels with ADC values before and after chemo/radiotherapy. Cellular activity capable of determining prognosis can thus be assessed without exposure to ionizing radiation. Presence or absence of response to treatment and an estimation of prognosis can be predicted by measuring ADC values before treatment[19]. We also compared pre-treatment ADC values in terms of evaluating prognosis between the regression and progression groups. Lower ADC values were observed in the regression group. Our results provide evidence that DWI provides promising results in evaluating the efficacy of chemotherapy in the treatment of patients with inoperative lung cancer. We think that further studies with wider patient groups are now needed on this subject.

The main limitations of our study are the low patient number, and the difference in patient numbers between the groups. Another limitation is the absence of a 'stable group' with no significant change in lesion dimensions after treatment. A further limitation is the numerical inhomogeneity of the subgroups established on the basis of cell types. Parallel results were not achieved in all subgroups. We think that the main reason for this is the lack of sufficient numbers of patients with different cell types.

In conclusion, measurement of ADC values with DWI can be used to evaluate treatment efficacy in malignant lung tumors with or without size change. We did not study tumor response using PET with DWI, as none of the patients underwent positron emission tomography (PET) examination before and after treatment. Therefore, further studies are needed in inoperative lung cancer patients undergoing PET scan before and after treatment to better determine the role of DWI in evaluating response to chemotherapy.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EB, PK; Veri toplama: EB, IMC, ACB; Veri analizi ve yorumlama: PK, HK, TO; Yazı taslağı: EB, PK; İçeriğin eleştirel incelenmesi: MK, ACB; Son onay ve sorumluluk: EB, PK, TO, MK, HK, IMC, ACB; Teknik ve malzeme desteği: TO, HK, MK; Süpervizyon: EB, MG, TO; Fon sağlama (mevcut ise): yok.
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