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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Comparison of diffusion weighted MRI parameters of mediastinal lymph nodes with PET/CT in lung cancer patients

Akciğer kanserli hastalarda mediastinal lenf nodlarının difüzyon ağırlıklı MRG ile değerlendirilmesi ve PET/BT ile karşılaştırılması

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ABSTRACT

Objective: We have compared diffusion-weighted magnetic resonance imaging (DW-MRI) properties of mediastinal lymph nodes in lung cancer patients with positron emission tomography/computed tomography (PET/CT) findings.

Patients and Methods: Twenty-one consecutive untreated patients with lung cancer were included. DW-MRI was performed on a 1,5T scanner with b values of 50, 500 and 1000. Additional MR imaging was performed for anatomical correlation.

Results: A total of 47 lymph nodes were analyzed. While no correlation was found between minimum apparent diffusion coefficient (ADC) values (ADCmin) of lymph nodes and their maximum standardized uptake values (SUVmax) on PET/CT, ADCmin ratios of lymph nodes to main lesion (ADCmin Node/Lesion) ($r = - 0.407$; $p = 0.005$) and lymph node to cerebrospinal fluid (ADCmin Node/CSF) ($r = - 0.364$; $p = 0.012$) were correlated with SUVmax. Cutoff values for DW-MRI parameters were determined using ROC analysis. Six lymph nodes were histopathologically examined. Both methods correctly identified one metastatic and two metastasis negative lymph nodes, while staging one lymph node with granulomatous change as metastasis positive. Two metastasis negative lymph nodes, reported as suspicious on PET/CT, were correctly staged on DW-MRI.

Conclusion: Our findings indicate that DW-MRI could be at least as valuable as PET/CT in mediastinal staging of patients with lung cancer.

Key words: Diffusion magnetic resonance imaging, Positron-emission tomography/Computed tomography, Lung neoplasms, Lymph nodes, Mediastinum

ÖZET

Amaç: Akciğer kanserli hastalarda mediastinal lenf nodu tutulumunun değerlendirmesinde difüzyon ağırlıklı manyetik rezonans görüntüleme (DA-MRG) bulguları ile pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) bulguları arasındaki ilişkiyi incelemek.

Hastalar ve Yöntem: Tedavi almamış, ardışık 21 akciğer kanserli hasta çalışmaya dahil edildi. DA-MRG 1,5T alan gücüne sahip cihaz ile b 50, 500 ve 1000 değerlerinde yapıldı. Anatomik korelasyon amaçlı ek incelemeler yapıldı.

Bulgular: Toplamda 47 lenf nodu değerlendirildi. Lenf nodlarının minimum göreceli difüzyon katsayı (ADCmin) değerleri ile PET/BT' de ölçülen maksimum standardize tutulum değerleri (SUVmax) arasında anlamlı ilişki saptanmazken, ADCmin değerlerinin ana kitle ve beyin omurilik sıvısının ADCmin değerlerine oranlandığında elde edilen oranlar ile SUVmax değerleri arasında ilişkili bulundu (sırasıyla $r = - 0,407$; $p = 0,005$ ve $r = - 0,364$ ve $p = 0,012$). ROC analizi kullanılarak metastaz için eşik değerler belirlendi. Altı lenf nodu histopatolojik olarak değerlendirildi. PET/BT ve DA-MRG bir metastaz pozitif ve iki metastaz negatif lenf nodunu doğru evrelerken, her ikisi de granülomatöz değişiklik barındıran bir lenf nodunda yanlış pozitif sonuç verdi. Histopatolojik olarak metastaz negatif olan iki lenf nodu PET/BT'de şüpheli sonuç verirken, DA-MRG bu lenf nodlarını doğru evreledi.

Sonuç: DA/MRG, akciğer kanserli hastalarda mediastinal lenf nodlarının değerlendirilmesinde en az PET/BT kadar başarılı olabilir.

Anahtar kelimeler: Difüzyon manyetik rezonans görüntüleme, Pozitron-emisyon tomografi/Bilgisayarlı tomografi, Akciğer tümörleri, Lenf nodları, Mediasten

Introduction

Lung cancer is the leading cause of cancer related deaths in the world. Treatment is given according to the stage of the disease. Early stage lung cancer, having the possibility of cure, is treated surgically, while advanced stages are not. Lymph node involvement is an important factor affecting the stage of the disease [1].

Positron emission tomography (PET), or more commonly, positron emission tomography/computed tomography (PET/

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CT) is the method of choice in the assessment of nodal involvement.

PET/CT requires the administration of the radioactive substance^{18} F-2-flouro-2-deoxy-D-glucose (FDG). The relative unavailability of PET and PET/CT scanners and difficulties in the production, acquisition, and transport of FDG are limiting factors for the method.

Diffusion weighted magnetic resonance imaging (DW-MRI) of lymph nodes has been studied in various anatomical regions, especially in the head and neck. Previous studies have yielded promising results in the discrimination between benign and malignant lymph nodes [2, 3]. Mediastinal lymph nodes have also been studied with DW-MRI [4-7]. Authors have used different and sometimes cumbersome methods and parameters in their studies, which are not useful for day-to-day practice.

The aim of this study is to search for practical and reproducible parameters in the assessment of mediastinal lymph nodes in patients with lung cancer using DW-MRI and imaging relationship with PET/CT.

Patients and Method

This prospective study was carried out between September 2009 – June 2010 on 21 consecutive patients with a pathologically confirmed diagnosis of lung cancer, who were submitted to our Nuclear Medicine Department for staging purposes. Patients had not received any treatment before imaging. DW-MRI was carried out before or after the PET/CT scan, but prior to any treatment, with no more than 1 month between both studies. Our study was approved by Marmara University, School of Medicine Ethics Committee and written informed consent was obtained from all patients.

All MR imaging studies were performed on a 1,5T scanner (Magnetom Vision, Siemens, Erlangen, Germany) using a surface coil. Patients were scanned from the thoracic inlet superiorly to the cardiac apex inferiorly. Diffusion weighted images were obtained in three orthogonal planes using a non-breathold, single shot echo planar trace method with chemical shift selective fat suppression with b values of 50, 500, and 1000, TR/TE: 4600/88 ms, FOV: 400 mm, Slice Thickness: 5 mm, Interslice Gap: 1mm, NEX: 4. T2 weighted gradient echo (TRUFI; TR/TE: 3,79/1,56 ms, Flip Angle: 60°, FOV: 400mm, Slice Thickness: 5 mm, Interslice Gap: 1mm, NEX: 1), T1 weighted spin echo (TR/TE: 289/4,76 ms, Flip Angle: 70°, FOV: 400mm, Slice Thickness: 5 mm, Interslice Gap: 1mm, NEX: 1) and T2 weighted turbo spin echo images with chemical shift fat suppression (TR/TE: 4300/103 ms, Flip Angle: 170°, FOV: 400mm, Slice Thickness: 5 mm, Interslice Gap: 1mm, NEX: 1) were obtained for anatomical correlation. All scans were performed in the axial plane. Total imaging time was between 5-6 minutes.

Images were evaluated on a Leonardo workstation (Siemens, Erlangen, Germany). ADC maps were automatically generated from b50 and b1000 diffusion weighted images. A freehand region of interest (ROI) was drawn on the the image with the maximum diameter of a lymph node. Minimum and average ADC values (ADCmin and ADCavg) were recorded.

PET/CT imaging was performed on a Discovery STE (General Electric, Milwaukee, Wisconsin, US) scanner with 16 channel CT and Bismuth-Germanium oxide (BGO) crystal PET equipment. Every patient fasted for at least 6 hours before the exam. FDG was administered at a dose of 2,5 MBq/kg of body weight. Patients rested for approximately one hour for the metabolic distribution of FDG, after which they were scanned from the skull base to the midthigh. CT scanning was performed with the following parameters: kVp 120, mA/s: 110, slice thickness 3,8 mm, Pitch: 1,5. PET imaging was performed three dimensionally with 3-4 minutes of imaging time per bed position and a total imaging time of 15-20 minutes. Volumetric regions of interest (VOI) were drawn on each lymph node to determine its standardized uptake value (SUVmax). An SUVmax of ≥2,5 was considered positive for malignancy. Lymph nodes without any FDG uptake were given a SUVmax value of 1.

To minimize possible artifacts, ratios between ADCmin values of lymph nodes and those of the primary lesion (ADCmin Node/Lesion), of CSF (ADCmin Node/CSF), and spinal cord (ADCmin Node/SC) were calculated. ADCmin values of the primary lesion were measured at the level of its maximum diameter. ADCmin values of the spinal cord were recorded at the level of the given lymph node. ADCmin value of the cerebrospinal fluid was measured at the widest space available, irrespective of its level. Care was taken not to include any surrounding tissue while placing ROIs for measurements. These ratios, as well as the ADC values of lymph nodes, were then compared to the SUVmax values of lymph nodes for any relationship.

Patients were followed up for any surgical intervention in order to obtain histopathological results for any given lymph node.

Statistical analysis (except ROC analysis) was performed using SPSS v17 software for Windows. Relationships between DW-MRI parameters and SUVmax were evaluated using correlation analysis and the Spearman correlation coefficient was computed. Any significant difference in DW-MRI parameters between the PET/CT positive and negative groups were studied using the Student

t-test, with p values of <0.05 being considered as significant. Threshold values of DW-MRI parameters for PET/CT positivity were calculated using the receiver operating characteristic (ROC) analysis with MedCalc v12 software for Windows.

Results

Eighteen of the twenty-one patients were male and three were female with an age range of 40-81 (Mean 63.52 ± 10.62). A total of 48 lymph nodes were found in 21 patients, 39 were PET/CT positive (81.2%) and 9 were PET/CT negative (18.8%). One PET/CT positive lymph node was excluded from final analysis because it was outside of our imaging area in DW-MRI.

The final analysis group consisted of 47 lymph nodes. Lymph node sizes were between 4.5 – 23 mm (mean 11 mm ±4.9 mm). Minimum ADC values of lymph nodes ranged between 0.14 -1.59x10^{-3} mm^2/s (mean 0.6 ± 0.26 x10^{-3} mm^2/s) and SUVmax values ranged between 1-24.3 (mean 6.23 ±5.05). Mean time between the PET/CT and MRI scans was 5.51 (±6.5) days (Range 0-28 days).

The most significant relationship was found between SUVmax and ADCmin Node/Lesion (Spearman' s Rho r = - 0.407 and p = 0.005). There was also a significant relationship between ADCmin Node/CSF (r = - 0.364 and p=0.012). There was no significant relationship between ADCmin (r = - 0.235 and p = 0.112), ADCavg (r = - 0.122 and p = 0.416), and ADCmin Node/SC values (r = - 0.248 and p = 0.092) and SUVmax of lymph nodes.

DW-MRI parameters significantly different between PET/CT positive and negative groups were: ADCmin Node/SC (PET (+) M=0.6 SD=0.34; PET (-) M=0.954 SD=0.337; p=0.015), ADCmin Node/Lesion (PET (+) M=1.167 SD=0.469; PET (-) M=2.743 SD=1.598; p=0.018), ADCmin (PET (+) M=44.973 SD=16.074; PET (-) M=81.111 SD=42.348; p=0.034), and ADCmin Node/CSF (PET (+) M=0.32 SD=0.16; PET (-) M=0.786 SD=0.549; p=0.035). DW-MRI parameters were significantly lower in the PET/CT positive group.

After the ROC analysis, the Youden Index method revealed a threshold value of ≤1.57 for ADCmin Node/Lesion ratio (AUC = 0.846; CI(95) = 0.712-0,935; p<0,001). It had 84% sensitivity, 78% specificity for PET/CT positivity. Values ≤2.149 had 95% sensitivity, while values ≤1.057 had 95% specificity for PET/CT positivity.

Five patients underwent surgery and six lymph nodes were histopathologically evaluated. One lymph node harbored a metastatic focus (Figure 1), five were metastasis negative. PET/CT was positive for the metastatic lymph node and the ADCmin Node/Lesion ratio was 1.21.

Of the five metastasis negative lymph nodes, one contained granulomatous change which was PET/CT positive (false positive), and the ADCmin Node/Lesion ratio was also found to be 1.21 (Figure 2). Two lymph nodes with SUVmax values of 2.1 and 2.6 were reported as "suspicious" on PET/CT. Their ADCmin Node/Lesion ratios were 2.25 and 5.58 respectively. The remaining two lymph nodes were PET/CT negative and their ADCmin Node/Lesion ratios were 1.62 and 3.38.

Discussion

Computed tomography (CT) is the most widely used method for the evaluation of lymph nodes, because of its wide availability and repeatability. It is not, however, valuable in the detection of lung cancer metastases with sensitivities of 52-64% and specificities of 62-69% [8, 9].

The superiority of FDG-PET over CT in the evaluation of mediastinal lymph nodes has been proven in meta-analytic studies [10, 11]. In a prospective study with 102 patients, the sensitivity and specificity of FDG-PET in the detection of mediastinal lymph node metastases was found to be 91% and 86% respectively [12]. The main advantages of FDG-PET are its ability to detect metastatic lypmh nodes smaller than 1 cm in size and its high negative predicitive value [13, 14].

In PET/CT, metabolic data of FDG-PET are fused with anatomic images of CT. This method was found to be superior to FDG-PET alone [15]. Antoch et al. compared PET/CT to FDG-PET in their study on non small cell lung cancer patients and found that PET/CT changed tumor stage in 26% and the choice of treatment in 15% of their patients [16].

The main disadvantage of FDG-PET, and thus PET/CT, is its high rate of false positivity [17, 18]. The main factors causing false positivity in FDG-PET are inflammatory and granulomatous diseases [11, 14, 19, 20]. Al-Sarraf et al. have found that, even when not in its active stage, exposure to tuberculosis led to an 8 fold increase in false positivity [20]. On the other hand, the low spatial resolution of the camera (low sensitivity for objects under 7 mm) and diabetes may lead to false negativity [11, 20]. Additionally, PET/CT is still not as widely available as CT or MRI. Patients receive injections of FDG, a radioactive material, and have to rest for approximately one hour after the injection.

With the development of fast imaging methods like echo planar imaging (EPI), DW-MRI has also been used on body imaging. Characterization of lymph nodes with DW-MRI has been studied especially in the cervical and pelvic regions, with promising results in the discrimination between benign vs. malignant lymph nodes [21-24]. DW-MRI of mediastinal lymph nodes however, is a less

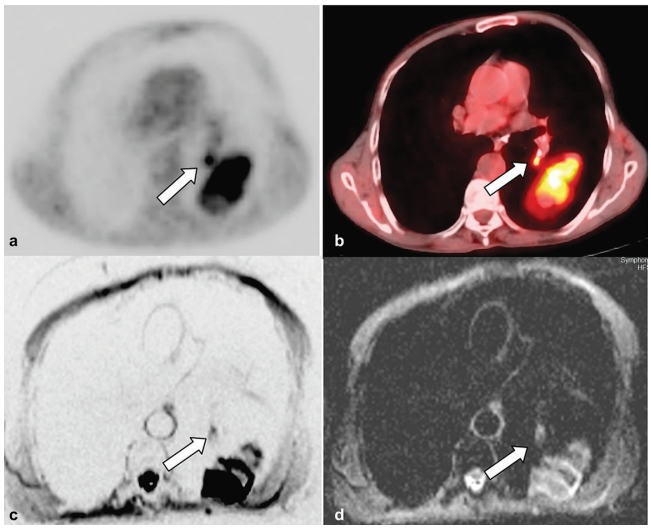

Figure 1. Histopathologically confirmed metastasis positive lymph node (Arrows). Main lesion and the metastatic lymph node appear bright on DW-MRI. The inverted DW-MRI image is shown because of its similarity to PET. (a) PET, (b) PET/CT, (c) inverted DW-MRI and (d) ADC map images.

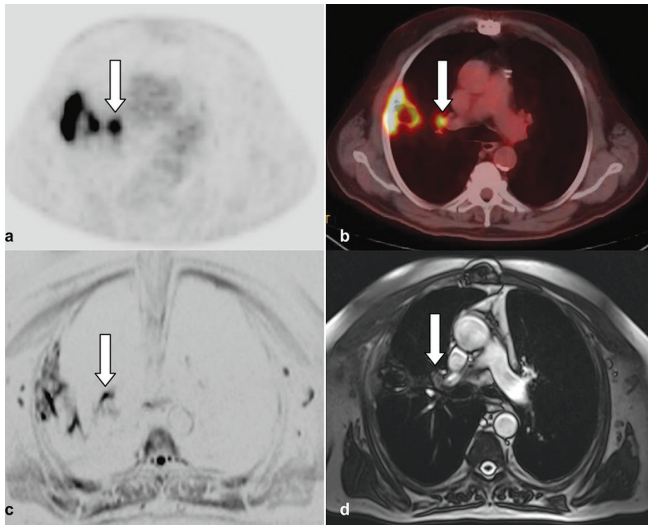

Figure 2. Metastasis negative lymph node containing granulomatous change (Arrows). It was incorrectly staged as positive on PET/CT. It also had a low ADCmin Node/Lesion ratio, indicating false positive staging on DW-MRI, too. (a) PET, (b) PET/CT, (c) inverted DW-MRI and (d) T2 weighted gradient echo images.

studied area probably due to respiratory and cardiac motion artifacts, which interfere with ADC measurements [25].

We used DW-MRI parameters as suggested by previous authors [25, 26]. To increase patient cooperation, a non-breathold method without cardiac gating was used. ADC figures were calculated using b 50 and b 1000 values. DW-MRI at b 50 values is less prone to signal changes related to capillary perfusion than imaging at b 0 [25].

There are no standardized criteria for the evaluation of lymph nodes on DW-MRI. When evaluating diffusion weighted images, hyperintense lymph nodes should not be assumed to be malignant because lymph nodes have varying signal properties even at high b values [7, 25]. Some investigators have used multiple ROI measurements with minimum pixels and averaged the results (ADCavg) on ADC maps, while others have placed the ROI on hyperintense areas of the b1000 diffusion images and copied this ROI onto the ADC map [25, 27]. deBondt et al. suggest that if ADCavg values are to be used, necrotic areas of lymph nodes on conventional images should be excluded [22].

We based our measurements on minimum ADC values, since using average ADC values would require multiple measurements to exclude necrotic areas and would conflict with our goal: to search for parameters that are easy to use. It was also our opinion that using multiple ROIs could decrease our sensitivity for detecting small metastatic foci. Since none of the lymph nodes we studied showed necrotic changes, we chose to include ADCavg results (using only one ROI) into our analysis. When using ADCmin values however, special care must be taken not to include the surrounding tisse while placing ROIs.

There are some inherent pitfalls to be kept in mind in the evaluation of lymph nodes with DW-MRI [25]. Lymph nodes less than 2-4 mm in size may be too small for evaluation. Reactive changes and lymphomas may lead to a decrease in ADC values. Partial volume effects, blood products (after biopsy), image noise, and motion artifacts may interfere with measurements. Micrometastases may not cause detectable diffusion restriction.

Another issue is reproducibility of measurements. Kwee et al. studied intra and interobserver reproducibility of ADC measurements of lymph nodes in healthy volunteers and reported that measurements were only moderately repeatable [27]. They noted that differences between ADC measurements often exceeded previously reported threshold values for benign vs malignant lymph nodes. In the same study, Kwee et al. noted that studies for the same pathology and lymph node region resulted in different ADC threshold values and pointed at the aforementioned differences in measurement, hardware, software, and patient artifacts.

Threshold ADC values of mediastinal lymph nodes also differ between studies. Usuda et al. based their measurements on average ADC values and reported a threshold value of ADCavg as $1.7x10^{-3}mm^2/s$ [4]. Koşucu et al., on the other hand, also used average ADC values and reported $1.012\pm0.025x10^{-3}mm^2/s$ as the threshold value with a range between $0.720\text{-}1.125x10^{-3}mm^2/s$ [7]. Nomori et al., using imaging parameters similar to those of our study, reported an ADCmin threshold value of $1.6x10^{-}$

$^{3}mm^{2}/s$ [5], while the highest ADCmin value in our study was $1.59x10^{-3}mm^{2}/s$.

One way to minimize these differences may be to use relative ADC values by comparing them to other tissues [25, 28]. The place to start is the primary lesion, which is the source of the metastasis. While there was no significant relationship between ADC values of lymph nodes and SUVmax in our study, a highly significant relationship was found between the ADCmin Node/Lesion ratio and SUVmax. This indicates that patient related imaging artifacts greatly influence DWI measurements.

Uto et al. [29] found that the ratio of the signal intensity for the lesion relative to the spinal cord on high b-value DWI was useful in differentiating between malignant and benign lung nodules. In our study, however, there was no significant relationship between ADCmin Node/SC and SUV max. This might be due to variations of ADC values of the spinal cord at different levels and in different age groups [30].

We could not find any study exploring the normal range of ADC values of CSF in normal subjects or its variation with age and sex. The fact that we found a significant relationship between the ADCmin Node/CSF ratio and SUVmax indicates that it does not differ significantly between individuals and can potentially be used as a reference for signal intensity in diffusion weighted imaging.

Except for ADCmin Node/Lesion and Node/CSF, the significant differences in DW-MRI parameters between PET/CT positive and negative groups might be attributed to our small sample size, especially in the PET/CT negative group.

ROC analysis revealed a threshold ADCmin Node/Lesion value of 1.57 for PET/CT positivity. The metastasis positive lymph node (Figure 1), as well as the lymph node with granulomatous change (Figure 2), which was PET/CT positive, had a ratio of 1.21. Nomori et al [5] reported that granulomatous change caused false positive findings in DW-MRI in their study. Two metastasis negative lymph nodes, reported as suspicous on PET/CT, had ADCmin Node/Lesion ratios of 2.25 and 5.58.

The limiting factors of our study were small sample size and the low number of lymph nodes with a pathologically confirmed diagnosis. Thus, we could not establish the true value of our parameters. Previous studies have reported DW-MRI to be a useful method with accuracies superior to PET/CT [4-7]. The relationship we found between ADCmin Node/Lesion, ADCmin Node/CSF and SUVmax indicates similar accuracy values to PET/CT.

Because of the limitations mentioned above, our study should be regarded as preliminary work. Our measurements were practical enough to be used in a clinical setting and our findings were promising, warranting further studies with larger sample sizes to verify our findings.

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