Utility of ADC Measurements in the Discrimination between Benign and Lymphomatous Abdomino-Pelvic Lymph Nodes

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Abstract

Background: Contrast-enhanced Computed Tomography (CT) has been the most commonly used imaging technique for staging of lymphoma as well as its follow-up for a long time. However, it does not provide metabolic or functional information and this may compromise the identification of the disease in non enlarged lymph nodes. 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) has been recently considered as the functional imaging method of choice for lymphoma as it depends on the identification of elevated glucose metabolism in lymphomatous lesions. However, not many institutions have this facility; it is expensive and carries the risk of exposure to radioactive material and ionizing radiation. It has been proposed recently that diffusion-weighted magnetic resonance imaging (DWI) may be a possible radiation-free alternative to FDG-PET/CT for the staging of lymphoma. It is a functional MRI technique that depends on the restriction of water movement in highly cellular tumors due to narrowing of the extracellular space.

Aim of the Work: The purpose of this study is to investigate whether Apparent Diffusion Coefficient (ADC) measurements can help in the discrimination between lymphomatous and benign abdomino-pelvic lymph nodes with comparison to PET-CT.

Patients and Methods: Thirty participants were included in this study. 18 cases of lymphoma (11 males and 7 females) and the other 12 patients (8 males and 4 females) were free from lymphoma or other malignancies. Their ages ranged from 30 to 75 (average age is 52). The study was performed in the period from June 2013 till January 2015. Full clinical history was taken from all patients as well as their histopathological data, laboratory investigations, and previous imaging. Conventional and diffusion weighted MRI and PET-CT studies were done for lymph nodes assessment.

Results: The ADC values of lymphomatus lymph nodes (mean ADC value is 0.66±0.11 X 10⁻³ mm²/sec) were significantly lower than those of benign lymph nodes (mean ADC value is 1.27±0.15 mm²/sec) with p-value <0.0001. There was a statistically significant inverse relation between the SUV max values and the ADC values of the examined lymph nodes (p-value <0.0001) suggesting that the ADC value measurements can provide pathophysiological information similar to PET CT.

Key Words: Diffusion – MRI – Apparent diffusion coefficient – PET-CT – Lymph node – Abdomen – Pelvis – Lymphoma.

Introduction

MALIGNANT lymphomas, including the Hodgkin and non-Hodgkin types, comprise about 5.0% of all cancers and about 3.7% of all cancer deaths in the Western world [1].

Once malignant lymphoma is diagnosed by excision biopsy from a particular site, determination of the extent of the disease (staging) is essential for appropriate treatment planning and prognosis determination. The Ann Arbor staging system is the most frequently used staging system for malignant lymphomas. In this system, the patients are divided into four stages based on whether the patient has localized disease, multiple sites of disease on one side of the diaphragm or the other, lymphatic disease affecting both sides of the diaphragm and disseminated extranodal disease [2].

CT is the most common radiologic study currently used for staging of patients with malignant lymphoma, due to its widespread availability and scan speed. FDG-PET has an important role in the evaluation of response to therapy and in the detection of recurrent or persistent disease. Today, most FDG-PET studies are performed as part of combined FDG-PET/CT combination [3].

The main disadvantage of CT and FDG-PET is the patient's exposure to ionizing radiation, which can induce the development of other neoplasms later in life. This disadvantage is particularly
of interest in children. Children have rapidly dividing cells, which are more sensitive to radiation induced effects. Children also have more years ahead in which cancerous changes may occur [4].

In the present era, treatment strategies aim at maximizing the chance of cure and in the same time minimizing the late toxicity. Thus, the prevention of second neoplasms due to ionizing radiation exposure from medical imaging became a crucial issue [3].

A noninvasive technique that can be done to obtain physiological information about tumors is the diffusion-weighted magnetic resonance imaging (DWI). It exploits the random motion of the water molecules in order to detect relatively small changes in the tissue structure at the cellular level. The extent of the tissue cellularity and the presence of intact cell membranes affect the impedance of the water molecule diffusion and this can then be quantitatively evaluated using the Apparent Diffusion Coefficient (ADC) value [5].

DWI using the single-shot Echo-Planar Imaging (EPI) was a well-established method in the examination of the brain. However, DWI did not become of clinical standard in extracranial examinations because EPI was complicated by severe image distortion and magnetic susceptibility artifacts in the body. The recently introduced parallel imaging techniques and the development of multichannel coils and stronger gradients have largely helped to overcome this problem. Now DWI of good quality can be performed in the body and at high b-value [6].

Aim of the work:

The purpose of this study is to investigate whether Apparent Diffusion Coefficient (ADC) measurements can help in the discrimination between lymphomatous and benign abdomino-pelvic lymph nodes with comparison to PET-CT.

Patients and Methods

Thirty participants with enlarged abdominal and/or pelvic lymph nodes were included in this study. 18 participants were pathologically proven cases of lymphoma and the other 12 participants were free from lymphoma or other malignancies and had benign abdominal or pelvic lymph nodes. It was performed in the period from June 2013, till January 2015. Full clinical history was taken from all patients as well as their histopathological data, laboratory investigations, and previous imaging. Conventional MRI and DWI studies were performed for lymph nodes evaluation using high field system (1.0 Tesla) magnet units (Philips Intera) using a phased array coil.

The 18 cases of lymphoma were pathologically proven cases, all of which were of the Non Hodgkin type.

The conventional study included T1, T2 and T2 SPAIR weighted images. The DWI was performed using respiratory-triggered fat-suppressed single-shot echoplanar imaging and was performed in the transverse plane with tri-directional diffusion gradients using b-values of 0, 500 & 1000sec/mm². Blind detection and characterization of the lymph nodes was first performed, and then we reviewed the diffusion images and the ADC values. All imaging results were verified against a standard of reference.

We performed 18F-FDG PET-CT study was done for the patients. After the patients fasted for at least 4 hours, 18F-FDG (3.7Mbhq/kg) was administered intravenously to them. One hour after its administration, a transmission scan was acquired using CT for 90sec for anatomical imaging and attenuation correction. Non ionic water soluble contrast agent was administered intravenously (1mg/kg) for the CT portion of the PET/CT study. First blind characterization and detection of the lymph nodes was performed, then we measured the SUV max for each lymph node.

To calculate the SUV max of each lymph node, we drew ROI within the solid part of each lymph node at the slice in which the largest ROI could be drawn and including the highest uptake area. A lymph node was considered benign if its SUV max value was less than 2.5 and it was considered malignant if its SUV max was greater than 4.

The standard of reference for the benign lymph nodes from the other 12 non lymphoma patients was the FDG PET CT findings, where a lymph node was considered benign if its SUV max was less than 2.5.

Inclusion criteria:

For lymphomatous lymph nodes, we included only pathologically proven cases of lymphoma with enlarged abdominal and/or pelvic lymph nodes.

For benign lymph nodes, we included patients free from lymphoma or other malignancies with enlarged abdominal and/or pelvic lymph nodes.
Data assessment and interpretation:

We recorded the morphological features of each lymph node including its shape, size, margin, signal characteristics as well as their sites and number. Then we reviewed the diffusion images and the ADC maps.

For calculation of the ADC value of each lymph node, we drew a ROI directly on ADC map within each lymph node at the slice in which the largest ROI can be drawn.

To calculate the SUV max of each lymph node, we drew ROI within the solid part of each lymph node at the slice in which the largest ROI could be drawn and including the highest uptake area. A lymph node was considered malignant if its SUV max was greater than 4 and it was considered benign if the SUV max value was less than 2.5.

Results

This study included 18 cases of lymphoma (11 males and 7 females) and 12 non lymphoma patients (8 males and 4 females) with abdominal and/or pelvic lymph nodes detected in the conventional images. All lymphoma cases were of the Non Hodgkin type. Their ages ranged from 30 to 75 years (average age is 52 years).

There were 76 lymphomatous lymph nodes and 33 benign lymph nodes.

The sizes of the lymphomatous lymph nodes ranged from 0.7-5cm in their maximum short axes, while the sizes of the benign lymph nodes ranged from 0.5-2.5cm, also in their maximum short axes.

All lymphomatous lymph nodes showed diffusion restriction evidenced by an increase in their signal intensity in the diffusion images on increasing the \( b \)-values Figs. (1,2,4).

Of the 33 benign lymph nodes, 17 lymph nodes showed signal reduction in diffusion images on increasing the \( b \)-value. The other 16 lymph nodes showed no significant changes in their signal intensity on increasing the \( b \)-value Fig. (3).

Fig. (1): 43 years old male patient, a case of B cell lymphoma. (A) Axial T2 WI showing enlarged mesenteric lymph node. (B) DWI (b: 1000sec/mm\(^2\)) with the lymph node appearing hyperintense. (C) ADC map showing drop of signal of the lymph node. The ADC value of the lymph node is 0.79x10\(^{-3}\) mm\(^2\)/sec. (D) PET CT with the lymph node appearing hypermetabolic denoting malignant nature.
Fig. (2): 70 years old female patient, known case of lymphoma. (A,B) Axial T2 WI showing enlarged right common and external iliac lymph nodes (C,D) DWI (b: 1000sec/mm$^2$) with the enlarged lymph nodes appearing hyperintense. Their ADC values ranged from 0.61 to 0.90 X 10$^{-3}$ mm$^2$/sec.

Fig. (3): 57 years old male. (A) Axial T2 WI showing enlarged hepatic and precaval lymph nodes. (B) DWI (b: 1000sec/mm$^2$) with these lymph nodes appearing mildly hyperintense. (C) ADC map with these appearing of intermediate signals. The ADC value of the precaval lymph node was 1.27 X 10$^{-3}$ mm$^2$/sec while the ADC value of the hepatic lymph node was 1.18 X 10$^{-3}$ mm$^2$/sec. (D) PET CT showing no significant FDG uptake by these lymph nodes.
Fig. (4): 23 years old female patient, known case of lymphoma. (A) Axial T2 WI showing enlarged hepatic, celiac, pre caval, aorto caval and para aortic lymph nodes. (B) DWI (b: 1000 sec/mm$^2$) with these lymph nodes appearing hyper intense. (C) ADC map with these lymph nodes appearing of low intermediate signals. Their ADC values ranged from 0.52 to 0.87 X 10$^{-3}$ mm$^2$/sec.

The difference between the mean ADC values of the lymphomatous and the benign lymph nodes was statistically significant ($p<0.0001$).

The SUV max values of the benign lymph nodes were between 0 and 2.7 with a mean value of 1.5. The SUV max values of the lymphomatous lymph were between 7.5 and 29.0 with a mean value of 10.2. There was a statistically significant inverse relation between the SUV max values and the ADC values of the examined lymph nodes ($p$-value $<0.0001$).

**Discussion**

Imaging plays a critical role in the management of newly diagnosed patients with malignant lymphoma, as it can assess the disease extent (staging) in non-invasive means. Accurate staging is crucial for deciding the appropriate treatment plan and in determining prognosis [7].

Although PET/CT is now widely used in the management of malignant lymphomas, especially Hodgkin as well as aggressive non-Hodgkin lymphomas, it has some limitations. First, it is accompanied by a substantial radiation dose. This limitation is of particular concern in children, young adults and patients undergoing repeated studies.
for follow-up and detection of disease recurrence. Thus, a nonionizing imaging modality having similar functional imaging capacity would be of value in this setting particularly for follow-up scans. The second limitation is the high cost of PET/CT making it a substantial economic burden for the patients who will perform regular follow-up imaging. Moreover, low-grade subtypes of lymphoma show low uptake of FDG or even no FDG uptake, thereby limiting its clinical utility in these patients [8].

DWI is a nonionizing imaging modality that noninvasively detects the random microscopic motion of the water molecules in the body. It depends on the cellularity and the cell membrane integrity. In a densely cellular environment, the motion of the water molecules is impeded and with the presence of intact cell membranes (as in tumors), the cells and cell walls act as obstacles to the moving water molecules (ie, diffusion restriction). With breached cell walls and in less cellular environments, water molecules can move more freely (ie, free diffusion). So, the degree of diffusion restriction of water molecules is proportional to the degree of integrity of the cell membranes and the degree of tissue cellularity [9].

The purpose of this study is to investigate whether ADC measurements can help in the discrimination between lymphomatous and benign abdomino-pelvic lymph nodes.

In the current study, the ADC values (in 10^{-3} mm^2/sec) of the lymphomatous lymph nodes (with mean value of 0.66±0.11) were significantly lower than those of benign lymph nodes (with mean value of 1.27±0.15). The differences were statistically significant with p-value >0.0001. These results are in line with other previous studies. Kwee et al., [10] reported that the ADC values of lymphomatous lymph nodes were significantly lower than the ADC values of normal lymph nodes (mean ADC values of 0.70±0.22 vs. 1.00±0.15 respectively) with a p-value <0.0001. Sumi et al., [11] stated that the differences between the ADC values of lymphomatous lymph nodes and benign lymphadenopathies were statistically significant with a p-value <0.05 (mean ADC values 0.223±0.056 vs. 0.302±0.062 respectively). Also Abdel-Razek et al., [12] reported significantly lower ADC values for lymphomatous than benign lymph nodes with a p-value <0.04 (mean ADC values 0.97±0.27 vs. 1.64±0.16 respectively). Statistically significant differences between the ADC values of lymphomatous and benign lymphadenopathy were also recorded by Holzapfel et al., [13] [mean ADC values 0.64±0.09 vs. 1.24±0.16 respectively] and Salem et al., [14] [mean ADC values 0.60±0.09 vs. 1.70 respectively].

There is a wide variability in the reported ADC values by the different studies. This can be explained by differences in the ways of ADC measurements, for example, including the entire lymph node in the ROI will yield a higher ADC value than in case of excluding the necrotic areas from the measurement. Nevertheless, all these studies have reported generally lower ADC values for lymphomatous lymph nodes than those of benign lymphadenopathy.

In our study, we found that the best ADC threshold value for discriminating lymphomatous from benign lymph nodes was 1.05 X 10^{-3} mm^2/sec with sensitivity of 90.00% and specificity of 86.72%. This result is more or less comparable to that reached by Kwee et al., [10] who reached a slightly lower ADC threshold value of 1.00 X 10^{-3} mm^2/sec with a lower sensitivity 78.1% and higher specificity (100%). Abdel-Razek et al., [12] concluded a threshold value of 1.38 X 10^{-3} mm^2/sec with sensitivity of 98% and specificity of 88%. Holzapfel et al., [13] reached a threshold ADC value of 1.02 X 10^{-3} mm^2/sec with sensitivity of 100% and specificity of 87%. Salem et al., [14] reported a cut off value of 1.25 X 10^{-3} mm^2/sec with 95.4% sensitivity and 83.3% specificity.

In our study, we found a statistically significant inverse correlation between the PET CT SUV max values and the DWI ADC values of the lymphomatous lymph nodes. This finding suggests that DWI can provide additional pathophysiological information similar to PET CT. This conclusion was also reached by Regacini et al., [15] who reported an excellent agreement between whole body DWI and FDG PET CT and suggested that it can be a great alternative to PET CT in the management of lymphoma patients without the use of intravenous contrast agents or ionizing radiation. Also Stecco et al., [16] reported that whole body DWI can represent a radiation free alternative to PET CT in the staging of patients with gastrointestinal lymphoma and that it is of a comparable diagnostic value to PET CT.

Conclusion:

In conclusion, our results suggest that the ADC value measurements can provide pathophysiological information similar to PET CT and that it could be a highly specific tool for the differentiation between lymphomatous and benign lymph node.
References


