Diagnostic value of MR-DWI technique in the diagnosis and staging of Hodgkin and non-Hodgkin lymphoma: comparison with PET-CT methods

Poster No.: C-2106  
Congress: ECR 2015  
Type: Scientific Exhibit  
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Keywords: Haematologic, Lymph nodes, MR, MR-Diffusion/Perfusion, PET-CT, Contrast agent-intravenous, Cancer, Lymphoma  
DOI: 10.1594/ecr2015/C-2106 

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Aims and objectives

Introduction

Lymphoid malignancies include distinct pathological entities, often characterized by a neoplastic clone, phenotypically resembling normal lymphocytes at a particular stage of differentiation, by which it is possible to establish a diagnosis of lymphoid neoplasia associated with a specific classification. Lymphomas, Hodgkin's lymphomas (HL) and non-Hodgkin's lymphomas (NHL) comprise approximately 5-6% of all malignancies and they are the fifth most common type of cancer in the United States. The last classification of hematopoietic and lymphoid tissue’s malignancies of the World Health Organization (WHO), published in 2001 and updated in 2008, is a global agreement on the diagnosis of these tumors, adopted in the current use of pathologists, clinicians and scientists [1]. The first major division is between Hodgkin lymphoma, non-Hodgkin lymphomas and plasma cell neoplasms. NHLs account for 4-5% of incident cases of cancer in the male and female population, and are the ninth leading cause of cancer death in men and the sixth one in women. The Hodgkin's Lymphoma (HL) is a form of malignant lymphoma characterized by the proliferation of neoplastic cells derived from B-lymphocyte cells (Reed-Sternberg, RS). The HL constitutes about 16% to 30% of malignant lymphomas and 1% of all cancers in Western countries (incidence: 2.5 cases per 100,000 inhabitants) with a higher incidence in males [2]. The incidence of HL is bimodal, with a peak towards the end of the second decade, and thereafter, a progressive increase starting from 40-45 years. The majority of cases occur, in total, between the second and the fourth decade [3]. Once the diagnosis of HL or NHL is made with a biopsy, the determination of disease extent (staging) is important for therapeutic planning and for determining the prognosis [4]. Furthermore, an accurate revaluation at the end of therapy it is fundamental to document the complete remission. The specific staging of HL and NHL is based on the Ann Arbor classification [5]:

- Stage I indicates that the cancer is located in a single lymph node region, usually one lymph node and the surrounding area.
- Stage II indicates that the cancer is located in two separate lymph node regions, an affected lymph node or organ and a second affected area, and that both affected areas are confined to one side of the diaphragm, above or below.
- Stage III indicates that the cancer has spread to both sides of the diaphragm.
- Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs.
Staging of HL and NHL is usually performed with total body Computed Tomography (CT) and Positron Emission Tomography fused with CT imaging (PET-CT, actually gold standard), according to international guidelines [6]. Unfortunately both examinations need to be repeated several times during the treatment and the follow up, with a relevant cumulative radiation dose, particularly with regard to younger patients.

In a recent report from the National Cancer Institute, it was pointed out that there was "a great opportunity [for the diffusion-weighted magnetic resonance imaging (MR-DWI)] to evolve into a clinically relevant imaging tool" [7]. The biggest advantages of MR-DWI include the total absence of exposure to ionizing radiation, radioisotopes and, eventually, even without intravenous contrast media.

It should be noted that investigations with whole-body MR-DWI are nowadays executable in a reasonably short acquisition time, allowing whole-body DWI studies to be incorporated into clinical practice [8] Furthermore, the information obtained can be quantified on parametric maps, allowing the analysis of the spatial heterogeneity of normal and tumor tissues before and in response to treatment. The apparent diffusion coefficient (ADC) obtained by diffusion-weighted imaging allows a quantitative evaluation of lesions, which is independent from the observers and from the intensity of the magnetic field. The quantitative analysis of the lesions in DWI is somehow similar to the quantitative assessment of the SUV in PET-CT. Moreover, the relative simplicity of data acquisition in DWI facilitates multicentric and longitudinal studies [9].

The purpose of our study was to compare the sensibility, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of MR-DWI with PET-CT in patients with malignant lymphomas, before or during treatment. In particular, we aimed to compare both qualitative and quantitative results obtained by the two different diagnostic modalities.
Methods and materials

From January 2013 until September 2013, we performed a prospective study on patients with known lymphoproliferative disease followed at the Hematological Clinic of the Policlinico Umberto I University Hospital of Rome, both at the onset and during therapy or follow-up. Selected patients underwent evaluation with both PET / CT and RM-DWI within a short period of 15 days interval. Main inclusion criterion was that these patients were scheduled for PET / CT for the diagnosis and staging of their lymphoproliferative disease. All patients had to undergo also a MR-DWI investigation in a short term from the PET / CT.

Other inclusion criteria were:

1. Accessibility to PET / CT images and report.

2. Willingness to perform MRI-DWI within 1-3 weeks of the PET-CT.

3. Volunteers patients, or parents / guardians of children patients, able to understand and sign an informed consent form showing that:
   a) the examination which underwent was not essential, but in the future could help to understand or stage the disease;
   b) the awareness of being subjected to an examination without ionizing radiation exposure.

4. Absence of contraindications to the performance of MR, signing the appropriate questionnaire.

5. MR programmed to not more than 1-3 weeks away from the survey of nuclear medicine; patients considered candidates for the study but who, for various reasons, had carried out the survey MR-DWI after this time limit, were considered unsuitable.

6. Patients with lympho-proliferative disease clinically and histologically diagnosed and staged according to the criteria of Ann Arbor and amended in accordance with Cotswold, at the onset, during or out of treatment.

Exclusion criteria:

1. Low quality of PET/CT or unavailable PET/CT DICOM images.
2. Time interval longer than 3 weeks between PET/CT and MR-DWI.

Twelve patients were selected according to the above criteria (5 males and 7 females) aged between 12 and 63 years, with an average of 31.5 years; 11 patients had a diagnosis of classical LH nodular sclerosis variant (NS), whereas one patient had a MALT-type B lymphoma.

**Technical data**

All MRI examinations were performed in the Department of Radiological Sciences at Policlinico Umberto I Hospital. Patients were studied with a superconducting MRI equipment at 1.5T and 3T. After a scouting sequence, conventional DWI sequences and DWI sequences were acquired with background body signal suppression (DWIBS) on axial and coronal planes, repeated several times to cover all anatomic regions of interest, in order to replicate the coverage of the PET / CT examination. Ten different sites were assessed in each patients in the cervical, thoracic, abdominal, inguinal and extra-nodal regions.

The DWI sequences were performed at three different b-values: \( b = 50, b = 500, \) and \( b = 1000 \) mm\(^2\) / s.

Moreover, conventional T1 and T2-weighted turbo spin echo (TSE) sequences, with and without contrast medium, were acquired at completion of the survey for the morphological characterization of the disease.

The PET / CT exams were performed outside of our institution and performed according to the standard total body technique. Only tests with comprehensive report of SUV max values and available DICOM PET and CT images were taken into account.

PET examinations were performed with a hybrid scan, 60 minutes after i-v injection of \(^{18}\)F-fluorodesoxigluucose with a total activity of 400Mbq. Images of tracer distribution were acquired for a period of approximately 30 minutes ; 4,25 mm thickness reconstructions on axial coronal and sagittal planes were finally obtained.

**Image analysis**

**Per patient analysis** : it was performed in all patients reporting a final evaluation of remission (score 0) low activity (score 1) high activity (score 2) according to the final report and related SUV values in the diseases areas.

**Per site analysis:**
a. **Qualitative analysis**: it was performed at the level of 9 main body lymph node stations: 2 in the cervical region (cervical and supraclavicular lymph nodes); 2 in the chest (mediastinal hilar and axillary lymph nodes); 4 in the upper and lower abdomen (para-aortic lymph nodes above and below the transverse mesocolon, mesenteric and common iliac, internal and external lymph nodes), and inguinal lymph nodes. Extra-nodal localizations (liver, spleen and bone marrow) were also evaluated. To each one of the 10 regions above described a 0-2 score (0 =normal, 1 =low activity / partial remission, 2 = activity) was assigned based on a qualitative analysis of PET / CT images.

b. **Quantitative analysis**: it was conducted at the level of the lesions where specific SUV values of were available, which were thus considered as "target" lesions, in order to calculate the ADC values in the same lesions on the corresponding MR images. It was arbitrarily considered as positive a SUVmax value above 3.5 (active lesion), below 0.5 as negative, and as border-line a SUV max between 0.5 and 3.5.

After acquisition the original MRI images were subjected to post-processing. In particular, b-1000 images were evaluated using a reversed gray scale, so that on a white background (areas with no signal) diseased lesions were identified as images with different intensities of gray (from light gray to black), in order to obtain a qualitative optical visualization most directly comparable to PET / CT.

In all MR images, information and personal data were removed.

Reporting sessions were conducted independently by two radiologists experienced in MR, blind of the results of PET / CT and clinical data.

**Per patient analysis**: for each MR examination a global judge of activity or inactivity or partial remission (score 0-1-2) was reached. For the statistical evaluation, score 1 and 2 were both considered as activity.

**Per site analysis**:

a. **Qualitative analysis**: The two radiologists independently filled an excel sheet in which they reported, blind of the PET-CT results, MRI data observed at the level of 9 main lymph node body regions: 2 in the cervical region (cervical and supraclavicular lymph nodes); 2 in the chest (mediastinal hilar and axillary lymph nodes); 4 in the upper and lower abdomen (para-aortic lymph nodes above and below the transverse mesocolon, mesenteric and common iliac, internal and external lymph nodes), and inguinal lymph nodes. Extra-nodal localizations (liver, spleen and bone marrow) were also evaluated. To each one of the 10 regions above described a 0-2 score (0 =normal, 1 =low activity / partial remission, 2 = activity) was assigned based on a qualitative analysis of PET / CT images (Figure 6).
b. Quantitative analysis: The ADC values of the target lesions were measured in a second reading session, at the level of target lesions reported in to the PET / CT, after taking vision of the target lesions of the PET but blind of the SUVmax values reported. The target lesions were identified on morphological MR images, and then directly on the parametric ADC map. A region of interest (ROI) was placed manually on the target lesion at the level of the regions that showed the lowest signal intensity in the ADC map, particular in the case of inhomogeneous lesions, or at any point of the lesion in the case of homogeneous signal. To ensure proper placement of the ROI on ADC maps, the corresponding T2-weighted images and contrast enhanced T1-weighted images were evaluated in comparison. We considered two possible cut-off values for activity and inactivity, since definitive values are not yet established. We considered these two different ADC cut-off values: higher than 1.7 or higher than 1.5 (x 10-3) mm2 / s, assessing, in both cases the correlation with the values of SUVmax. In the first case, were considered as inactive (score 0) lesions above 1.7 (x 10-3) mm2 / s, slightly active (score 1) lesions between 1.5 and 1.7 (x 10-3) mm2 / s frankly active (score 2) lesions under 1.5 (x 10-3) mm2 / s. In the second case, lesions above 1.5 (x 10-3) mm2 / s were considered inactive (score 0), lesions between 1.3 and 1.5 (x 10-3) mm2 / s as slightly active (score 1) and lesions under 1.3 (x 10-3) mm2 / s as frankly active (score 2).

Comparative analysis DWI / PET / CT

The diagnostic accuracy, sensitivity and specificity of DWI with positive and negative predictive value (NPV and PPV), considering the PET / CT as the gold-standard, were calculated both per-patient and per-site. Comparative evaluations of the quantitative data obtained from PET / CT and MR-DWI were then carried out.

Qualitative and quantitative data were statistically compared by Pearson's correlation.
Results

A total of 15 DWI examinations were compared with as many PET / CT exams in the 12 selected patients; 3/12 patients performed two examinations with both methods at different stages of the disease, therefore they were considered as different examination.

1. MRI-DWI qualitative analysis results (per patient):

Results of DWI were expressed as three different qualitative scores (0: inactivity, 1: partial remission; 2 activity). In 11 patients DWI showed active disease (score = 2) while in 2 patients a moderate disease activity or partial regression for incomplete response to therapy (score = 1) in full agreement with PET / CT (True Positive [TP] = 13 ); 2 exams were negative for both PET / CT and MR-DWI (True Negative [TN] = 2).

Sensitivity, specificity, PPV, NPV and accuracy diagnostics of DWI on a per-patient analysis were 100% (full correlation between MR-DWI and PET / CT. Figure 1.
### Table showing activity score for each patient in both MRI-DWI examination and PET/CT

<table>
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<tr>
<th>Per-patient (examination) global result</th>
<th>MR-DWI</th>
<th>PET/CT</th>
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**Fig. 1:** Table showing the activity score (0: inactivity, 1: partial remission; 2 activity) for each patient in both MRI-DWI examination and PET/CT. For the statistical evaluation, score 1 and 2 were both considered as activity.

**References:** Department of Radiology, Sapienza, University of Rome - Rome/IT

2. **MR-DWI qualitative analysis (per-site):** A total of 150 locations were assessed at the level of the interest regions in the 15 MR-DWI and PET/CT examination, considering 9 lymph nodal regional and one extra-nodal site. Out of these 150 sites, at DWI 21 were positive for active disease (score 2), 6 for low activity or partial response to therapy (score 1) in full agreement with PET/CT; 3 sites showed low activity at DWI (score = 1) but were still frankly positive at PET/CT (score = 2); these findings, however, were considered...
simply positive in the final qualitative per-site comparative evaluation. Thus, a total of 30 positive lesions were observed on both examinations (TP = 30). Out of 150 sites, 119 were negative, because of the absence of disease or for total remission following treatment (score 0) both on DWI and PET / CT (TN = 119). One site resulted as false negative on DWI in comparison with PET / CT (FN = 1). Figure 2, 3.

At a per-site analysis. DWI showed 96%, sensitivity, 100%, specificity, 100%, positive predictive value, 99% negative predictive value (NPV), with a 99.3% diagnostic accuracy.

Fig. 3: Graphic showing the activity score (0: inactivity, 1: partial remission; 2 activity) for each disease site in both MRI-DWI examination and PET/CT. For the statistical evaluation, score 1 and 2 were both considered as activity.

References: Department of Radiology, Sapienza, University of Rome - Rome/IT
Fig. 2: The figure shows the main body disease localizations considered in our study for each patient.

References: Department of Radiology, Sapienza, University of Rome - Rome/IT

3. Quantitative analysis on specific target lesions: a total of 26 target lesions with available SUVmax values were assessed in PET / CT and compared with MR-ADC values, according to the predetermined cut-off values for activity and inactivity (respectively 1.5 and 1.7 $10^{-3}$ mm$^2$/sec). At CT-PET the SUV-max was considered as active when > 3.5. For cut-off value of 1.7 $10^{-3}$ mm$^2$/sec the correlation between SUVmax and ADC values was 44%, while for cut-off value of 1.5 $10^{-3}$ mm$^2$/sec the correlation was of 24%. Figure 4, 5.
Fig. 4: Correlation of 44 % between SUVmax and ADC values for a cut-off value off a 1.7 mm2/s.

References: Department of Radiology, Sapienza, University of Rome - Rome/IT
Fig. 5: Correlation of 24 % between SUVmax and ADC values for a cut-off value of 1.5 mm2/s

References: Department of Radiology, Sapienza, University of Rome - Rome/IT

CASE 1.
**Fig. 6**: The axial images focus on a mediastinal lesion in Patient affected by LH-SN with in a partial regression of pathology. Functional assessment by PET / CT and DWI has identified a small lesion in the context of the mass outbreak of residual disease. DWI sequences acquired at two different b-values (0-1000) also allow to distinguish this lesion from the background thanks to the "shine through" effect.

**References:** Department of Radiology, Sapienza, University of Rome - Rome/IT

CASE 2.
Fig. 7: Coronal T2-weighted MR image showing a large mesenteric lymphadenopathy of about 2 cm (A). Axial DW-MR image at high b-value of 1000 showing the lymphadenopathy as an hyperintense lesion (B). The lesion is even more evident in ADC map as an hypointense area (C). The axial PET-CT fusion image (D) show how the lesion detected by MR-DWI is perfectly corresponding to the result of PET / CT investigation.

References: Department of Radiology, Sapienza, University of Rome - Rome/IT
Conclusion

Our study highlights the reliability of MR-DWI as a diagnostic alternative tool to PET / CT in the pre-therapeutic assessment, as well as in the staging and restaging of lymphoproliferative disorders. Our results are still preliminary, being based on a small number of patients and on data collected in a single center, requiring further confirmation on larger series. However, if confirmed, these results could change the management of patients affected by lymphoma, leading to the inclusion of MR-DWI in the diagnostic protocol, in order to limit the use of CT and PET / CT. A multicenter study to validate these results and relevance that the MR-DWI would be highly desirable. Our study confirms the emerging role of MR-DWI, which is developing as a concrete alternative to PET / CT, with the added advantage of being a diagnostic "radiation free" tool in the clinical management of frequently young onco-hematology patients. Hopefully, in the next year a large part of the diagnostic work up of these patients, which is currently based on PET-CT, will be substituted by MR-DWI, a radiation free examination.
References


