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MRI versus CT and PET/CT in the Preoperative Assessment of Hodgkin and Non-Hodgkin Lymphomas

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Abstract: (1) Background: The purpose of this study is to retrospectively compare CT, MRI, and PET/CT in detecting lymphadenopathies and extra-nodal lesions in lymphoma and in disease staging. (2) Methods: Inclusion criteria were the availability of TB (Total Body) CT and/or PET/CT performed before treatment; MRI performed no later than 2 weeks after TBCT; histological confirmation of lymphoma; clinical-diagnostic follow-up. Using these criteria, we included 64/353 patients with TBCT and MRI performed at our hospital; 20/64 had PET/CT performed in other hospitals. Histology and follow-up were gold standard. (3) Results: The sensitivity, specificity, and accuracy in lymph nodes detection was 84.5%, 94.4%, and 91% for CT and 95%, 98.9%, and 95.6% for MRI. High agreement was observed between CT and MRI regarding the number and size of positive lymph nodes and for disease staging. MRI identified eight more extra-nodal lesions than CT. In the subgroup of 20 patients, PET/CT did not show a significant superiority in sensitivity, specificity, accuracy, and staging ability than CT and MRI. (4) Conclusions: Our study demonstrates a mild superiority of MRI over CT in lymphoma staging. Although PET/CT remains the reference standard, MRI demonstrated a similar diagnostic accuracy, with the added value of being radiation-free.

Keywords: diffusion weighted imaging; MRI; PET/CT; CT; Hodgkin lymphoma; non-Hodgkin lymphoma; staging

1. Introduction

Lymphomas include a wide spectrum of pathologies with heterogeneous clinical manifestations and localizations, with more than 50 subtypes, which differ in terms of molecular and genetic characteristics, histocytopathology, response to pharmacological treatment, and autologous transplantation, as well as for prognosis [1]. Worldwide, it is the most common hematologic malignancy, accounting for approximately 3% of all malignancies [2]: 14.4% are Hodkin's lymphomas (HL), while 85.6% are non-Hodgkin's lymphomas (NHL) [3]. Despite an overall increasing trend in lymphoma incidence, there is also an increasing trend in survival rate, due to both the development of targeted therapies and the evolution of imaging.

For a long time, CT has been the main imaging modality for both staging and follow up during and after therapy [4]. Obtaining a correct estimate of the extension of the

pathology is fundamental to tailor the proper pharmacological and radiotherapy treatment to the patient's needs, thus reducing as much as possible the morbidity associated to the treatment. However, compared to PET/CT and MRI, CT has a reduced overall sensitivity, since it cannot provide functional or metabolic information regarding the activity of lymph nodes or extra nodal localizations of disease [5–7]. CT staging of disease is based on morphological and dimensional criteria only. The most recent guidelines (Lugano classification) recommend a 15 mm largest diameter cut-off to consider a lymph node as pathological and 10 mm diameter for extra-nodal lesions. This does not exclude the possibility that smaller lymph nodes may also be affected by disease, which is a phenomenon that can be recognized in subsequent CT exams only, if lesions grow in size, or that larger lymph nodes may be inflammatory and therefore disease free, if unchanged at follow up [8]. In addition, CT has a particularly low sensitivity for determining the extent of bone marrow disease [9].

Due to these CT limitations, positron emission tomography (PET) associated with CT (PET/CT) is currently the method of choice for staging aggressive lymphomas, because it exploits the high metabolic activity of malignant lymphoproliferative tissue and the subsequent uptake of marked glucose [10]. PET/CT has a reported staging accuracy of 98% [11]. Since FDG avidity may change in lesions that have responded to treatment, PET/CT is also critical in the evaluation of lesions response during chemotherapy [12].

The main factor limiting the application of PET/CT is the high radiation doses to which the patients are exposed [13], especially considering that usually, they must undergo PET/CTs several times during their treatment; the cost and difficulty of accessing the equipment; and finally, the non-specific uptake of FDG in some avid tissues that may reduce the specificity of the examination. Furthermore, PET/CT does not exclude the need to undergo contrast-enhanced total body CT (TBCT) for most patients, since the morphological evaluation of most abdominal organs, mediastinal structures, and brain cannot be achieved with the use of PET/CT without intravenous injection. In addition, some lymphoma subtypes, such as MALToma, are less FDG avid; in these cases, the functional assessment of PET/CT becomes less sensitive, making this exam not recommended, as under-staging could lead to a wrong therapeutic pathway [14]. Therefore, currently, most of the lymphomas are staged by the association of contrast-enhanced TBCT examinations and PET/CT scans, which are periodically repeated.

MRI has an enormous advantage over the other imaging methods described, as it is the only one that does not use ionizing radiation, which is why it is gaining more and more clinical interest. The standard protocol of an MRI examination for lymphoma consists of T1 and T2 weighted morphological sequences, with and without suppression of fat tissue signals, with subsequent injection of intravenous paramagnetic contrast agents. The disease-staging ability of morphological and dynamic MRI sequences is comparable to that of a standard CT examination [7]. Recently, the addition of Diffusion Weighted Imaging (DWI) sequences to this protocol allows the non-invasive study of the natural diffusion of water molecules in body tissues, which is usually highly reduced in high cellularity tissues, such as lymphomas, including indolent non-FDG avid lymphomas [15,16]. Furthermore, DWI results can be quantified with the ADC (Apparent Diffusion Coefficient) map, similarly to the SUV max (Standard Uptake Value) in PET/CT; as opposed to SEV values, low (rather than high) ADC values are indicative of high cellularity and high lymphomas activity.

In the literature, there is emerging evidence that an increase in ADC values after and during treatment is an objective indicator of complete response, even in lesions that do not present morphological changes [17–19]. Despite these preliminary promising results, PET/CT still remains the gold standard in lymphoma staging.

The purpose of this study is to compare the diagnostic performance DWI-MRI versus contrast-enhanced TBCT and PET/CT in the staging of lymphomas including both HL and NHL.

2. Materials and Methods

A total of 353 CT and MRI examinations performed at the Department of Radiological Sciences of our institution for the diagnosis and staging of lymphoma between January 2014 and June 2020 were retrospectively reviewed. Inclusion criteria were the following: (a) contrast-enhanced TBCT and/or PET/CT before treatment; (b) MRI performed no later than 2 weeks after TBCT; (c) MRI performed at the level of the same body regions of TBCT (total body MRI); (d) histological analysis and contrast-enhanced TBCT and/or PET/CT follow-ups.

This is a retrospective observational study; only existing information collected from human participants was used, and there are no identifiers linking individuals to the data/samples. Institutional Review Board approval was obtained. All methods and procedures complied with institutional and research committee ethical standards and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

A total of 64 patients were finally included in the study, and their contrast-enhanced TBCT and MRI examinations were reviewed retrospectively. Of the 64 patients included in the study, 20/64 patients underwent 18 F-FDG PET/CT examinations in other hospitals, which were performed with a standard technique and included in the retrospective review.

2.1. Imaging Protocols

CT and MRI images were retrieved from the Hospital Picture Archiving and Communication System (PACS). CT scans of the skull, neck, chest, abdomen, and pelvis were performed on 32- (Optima CT520; GE Healthcare, Milwaukee, WI, USA), 64- (Somatom Definition; Siemens Medical Systems, Erlangen, Germany), and 128-slice (Ingenuity CT; Philips Healthcare, Best, The Netherlands) CT scanners. Scans were performed both before and after the administration of an intravenous iodinated contrast agent (70–130 mL); 13 patients ingested an oral contrast agent before performing the examination (Diatrizoate Meglumine, Gastrografin®). Layer thickness was 1–2 mm in all exams, and multiplanar 3-mm axial, coronal, and sagittal reconstructions were obtained in all patients. Automatic care dose systems were used, and only post-contrast images (portal venous phase) were acquired in all patients for radiation protection purposes. In adults, the X-ray tube voltage and tube current ranges were 100–120 kV and 130–200 mAs, respectively; in pediatric patients, the X-ray tube voltage and tube current ranges were 80–100 kV and 50–80 mAs, respectively, depending on the patient's weight and height.

MRI examinations were performed with a 3 Tesla (Discovery 750; GE Healthcare, Milwaukee, WI, USA) or 1.5 Tesla (Magnetom Avanto; Siemens Medical Systems, Erlangen, Germany) system. In patients with lymphomas, the MRI protocol routinely included evaluation of the neck, chest, abdomen, and pelvis (Total Body MRI). The brain was scanned only in selected cases, upon clinical request. After localization scans, images were acquired in three orthogonal planes, using the following protocol:

- Axial and coronal T2-weighted single shot fast spin echo sequence before and after fat suppression;
- Axial single shot fat suppressed echo-planar diffusion-weighted sequence with diffusion-sensitizing gradient applied along the x, y, and z axes and with a b-value of 50, 500, and 1000 s/mm^2. Using DWI sequences, parametric ADC maps were automatically generated.
- Axial T1-weighted 3D dynamic gradient echo fat suppressed sequence, before and after contrast administration (at 60–180 s delay). The contrast medium used was always a cyclic chelate of gadolinium, including gadoteridol (Prohance®), gadoterate (Dotarem®), and gadobutrol (Gadovist®) administered in a concentration of 0.1 mmol/kg and injected through a 20 G intravenous cannula at the rate of 2 mL/s using an automatic injector, followed by infusion of 15 mL saline solution at the same speed.
- Coronal T1-weighted gradient echo fat suppressed sequence.

The 18 F-FDG PET/CT exam was performed following EANM guidelines [20]. A CT contrast agent was not administered.

2.2. Imaging Data Analysis

The selected examinations were retrospectively reviewed by two radiologists, one (F.M.) with more than 20 years of experience in CT-MRI, one (M.L.) with five years' experience, and by a third-year resident (A.Ca.). The reading was performed without access to the other examinations or original reports, and with random distribution of examinations among the three readers. The inter-observer agreement among the three readers was calculated for both CT and MRI examinations; the intra-observer agreement between the new report of the senior radiologist and the previous original report was also evaluated. Discordant cases were reviewed, and a final agreement was reached by consensus.

PET/CT examinations were interpreted by a nuclear medicine physician with more than 15 years of experience (G.C.), independently of the radiologists, without knowing the other diagnostic imaging results or bone marrow (BM) biopsy data but having information regarding the morphological type of lymphoma.

MRI and CT reading criteria: based on the Lugano classification, lymph nodes with the longest diameter greater than 15 mm and extra-nodal lesions greater than 10 mm were considered pathologic. Lymph nodes with the longest diameter greater than 15 mm but with non-suspicious morphology (presence of fatty hilum, thin cortex) were excluded. Lymph nodes with the longest diameter shorter than 15 mm but with suspicious morphology (round shape, absence of fatty hilum or grouped) or localized in atypical regions were included. We considered 13 lymph node stations (reported on Table 1) and 5 extra-nodal areas of interest (spleen, liver, intestine, bone marrow, lung). For each patient, we assessed on CT and MR: patient stage, the overall number of positive and negative lesions per-patient, the diameter of the largest lymph node and extra-nodal lesions, and the corresponding anatomic region.

Table 1. Pathological lymph nodes detected by CT, and MRI classified by anatomic region.

Anatomic Region	CT	MRI
Waldeyer's Ring	4	6
Laterocervical	45	66
Infraclavicular	13	14
Axillary/Pectoral	36	42
Mediastinal	124	134
Hilar	34	26
Epitrochlear	0	0
Paraortic	87	93
Spleen	12	12
Mesenteric	45	47
Iliac	23	20
Inguinal–Femoral	15	18
Popliteal	0	0
	438	478

When available, biopsy results were used as a gold standard to define the positivity of lymph nodes and extra-nodal sites. Since lymph nodes biopsy was available in a very limited number of lesions, whenever the diagnosis was doubtful, PET/CT scans or follow-up studies were used as the gold standard. Disease sites that decreased in size during or at the end of chemo- or radiotherapy, or that increased in size, as well as those that remained stable during or after treatment, were defined as true positive. Lymph nodes of normal size remaining stable during and after treatment were considered as negative. Lesions that

were stable or increased in size during treatment were followed up for at least 12 months to exclude different diseases.

PET reading criteria: Both attenuation-corrected (AC) and non-attenuation-corrected (NAC) PET images were analyzed for interpretation and abnormal focality identified on AC-PET images were evaluated on the NAC-PET images, particularly when adjacent to highly attenuating materials. Images were evaluated using software capable of merging and displaying PET and CT data and using an SUV scale. To interpret the PET/CT image, the LNs were considered involved when FDG uptake was greater than the background or mediastinal pool radioactivity; instead, spleen and BM were involved when their uptake was greater than the liver. SUV-bw were calculated automatically using VOI analysis and the Deauville score.

2.3. Statistical Analysis

Sensitivity, specificity, and accuracy values were calculated for TBCT and MRI, taking into account the reference standards described above. An exact McNemar's test determined that there was a statistically significant difference for both modalities ($p < 0.01$). Correlation of lesion size and number of lesions obtained in CT and MRI were calculated with the Spearman's correlation test. Cohen's κ was used to determine intermodal agreement regarding Ann Arbor stage (CT vs. MRI). Intraclass coefficient (ICC), two-way mixed, absolute agreement was used to determine inter-observer agreement between the three radiology readers (CT and MRI) and between the nuclear physician's reports and those performed in other hospitals, and intra-observer agreement for the senior radiology reader. Referring to Cicchetti's interpretation guidelines, a Cohen's κ value or ICC value in the range 0.60–0.74 indicates good agreement, while the range 0.75–1.0 indicates excellent agreement.

Sensitivity, specificity, and accuracy for CT vs. MRI vs. PET/CT were calculated in a subgroup of 20 patients.

Statistical significance was set at $p < 0.05$. All data analyses were processed using SPSS (IBM statistical software program), version 25.0.

3. Results

3.1. Patients' Data

CT and MRI scans were retrospectively reviewed and compared in 64 Patients. The mean age of the study group was 45.3 years (range: 9–85); 36 were male, and 28 were female. Lymphoma types included were 15 Hodgkin's lymphomas, 40 diffuse large B-cell lymphoma (DLBCL), 2 follicular lymphomas, 2 nasal-type lymphomas, 2 Burkitt's lymphomas, and 1 mixed DLBCL and follicular lymphoma.

3.2. CT vs. MRI: Lymph Nodes

CT identified 438 lymph node stations as suspicious for disease out of a total of 1282 lymph nodes identified (34.1%), whereas MRI identified 478 out of a total of 1316 lymph nodes (36.3%). The inter-observer agreement among the three readers for CT and MRI studies was 0.825 and 0.898, respectively ($p < 0.001$); intra-observer agreement was greater than 0.9 for both modalities ($p < 0.001$).

Pathological lymph nodes were classified by anatomic region as reported in Table 1. The number of false positives and false negatives was 12 and 78 for CT and 9 and 23 for MRI, respectively. The resulting sensitivities, specificities, and accuracies were 84.5%, 94.4%, and 91% for CT and 95%, 98.9%, and 95.6% for MRI. The intermodality agreement between CT and MRI in the assessment of positive lymph nodes was high ($r_s = 0.951$, $p < 0.001$) as well as the assessment of the size of lymph nodes assigned as positive ($r_s = 0.984$, $p < 0.001$).

3.3. CT vs. MRI: Extra-Nodal Lesions

MRI proved to be more accurate in identifying extra-nodal localizations, allowing the identification of 92 extra-nodal lesions compared with 84 extra-nodal lesions visualized by

CT (as reported in Table 2). The standard reference system (biopsy, PET/CT, and follow up) allowed the identification of a total of 98 extra-nodal lesions. The most common anatomic site of extra-nodal disease involvement was bone/bone marrow, which was observed in 14 cases, including eight in which bone marrow was the only site of disease. There were two cases of primary hepatic lymphoma and six in which liver involvement was secondary (including two with spleen disease). In six cases, there was involvement of the the gastro-intestinal tract, including two gastric Burkitt's lymphomas, two small bowel lymphomas, and two large bowel lymphomas. There was an excellent intermodality agreement between CT and MRI in the number ($r_s = 0.995$, $p < 0.001$) and size assessment of extra-nodal lesions ($r_s = 0.972$, $p < 0.001$). The inter-observer agreement among the three readers for CT and MRI studies was 0.876 and 0.915, respectively ($p < 0.001$); intra-observer agreement was greater than 0.9 for both modalities ($p < 0.001$).

Table 2. Extra-nodal lesion detected by CT and MRI classified by localization.

Anatomic Region	CT	MRI
Lung	0	0
Liver	28	29
Spleen	16	17
Focal bone/bone marrow	32	38
Intestine	8	8
	84	92

3.4. CT vs. MRI: Staging

MRI and CT stages were assessed and compared for all patients according to Ann Arbor criteria. Of the 64 patients, CT assigned the correct stage in 62 (97%) and MRI in 64 (100%).

CT and MRI were assigned to the same stage in 62 patients. The Cohen's κ agreement was excellent between CT and MRI ($\kappa = 0.955$, $p < 0.05$). One case was discordant between the two modalities because of the presence of a positive lymph node station not recognized by CT and detectable only by DWI-MRI, bringing the stage from 2 to 3. Another case was discordant because CT did not detect bone disease, while MRI revealed a diffuse bone marrow involvement.

3.5. CT vs. MRI vs. PET/CT

In the subgroup of 20 patients where a direct comparison between CT, MRI, and PET/CT was available, CT identified 128 lymph node stations as suspicious for disease out of a total of 365 identified lymph nodes. Meanwhile, MRI identified 152 out of a total of 394 lymph nodes, and PET/CT identified 160 out of a total of 398. The number of false positives and false negatives were eight and 25 for CT, seven and six for MRI, and two and four for PET/CT, respectively. The resulting sensitivities, specificities, and accuracies were 83.7%, 96.2%, and 90.6% for CT, 96.2%, 97.0%, and 96.7% for MRI, and 97.6%, 99.2%, and 98.5% for PET/CT (see Table 3).

Table 3. Diagnostic performance for the detection of pathological lymph nodes in CT vs. MRI vs. PET/CT.

Modality	Sensitivity	Specificity	Accuracy
CT	83.7% (95% CI [76.8%, 89.1%])	96.2% (95% CI [92.7%, 98.4%])	90.6% (95% CI [87.5%, 93.7%])
MRI	96.2% (95% CI [91.9%, 98.6%])	97.0% (95% CI [94.0%, 98.8%])	96.7% (95% CI [94.4%, 98.2%])
PET/CT	97.6% (95% CI [93.9%, 99.3%])	99.2% (95% CI [97.0%, 99.9%])	98.5% (95% CI [96.8%, 99.4%])

MRI, CT, and PET/CT stages were assessed and compared according to Ann Arbor criteria. Of the 20 PET/CT examinations available, the stage was correct in all 20 patients (100%); no patients received an incorrect higher or lower stage after PET/CT. CT assigned the correct stage in 19 (95%) and MRI assigned the correct stage in 20 (100%). CT incorrectly assigned a lower stage in one exam (5%).

Inter-observer agreement between the nuclear physician's reports and those performed in other hospitals was excellent (0.915, $p < 0.001$).

4. Discussion

Determining the correct pre-treatment stage of lymphoma is critical for therapeutic planning. For many years, CT has been the only reliable imaging modality for staging lymphoma. Advances in nuclear medicine technologies have allowed PET/CT to supplant CT as the diagnostic modality of choice for staging and assessment of ongoing and post-treatment response. The main limitation affecting both methods is the significant patient exposure to ionizing radiation. The increasing use of diagnostic modalities associated with ionizing radiation exposure has corresponded to a more than seven-fold increase in the average radiation dose of the general population over the past three decades. When considering that lymphomas currently have an excellent 5-year survival rate (>80%) with a long life expectancy; that lymphomas frequently occur in pediatric or young adult patients; that CT and PET/CT are the imaging modalities of choice for diagnosis, staging, and follow-up and therefore these examinations are repeated several times a year; it emerges that the total radiation dose accumulated by patients and the risk of overexposure to radiation is an issue that must be strongly addressed [21,22]. Moreover, some organs are particularly radiosensitive, especially in younger patients, such as the breast and thyroid, and several studies have already shown that overexposure, especially at a young age, is a strong risk factor for thyroid disorders and breast cancer [23,24].

In contrast, MRI is an ideal diagnostic method since it does not use ionizing radiation. The main disadvantages of MRI are patient refusal (claustrophobia), the presence of intra-body devices that are not compatible with MRI, the high cost and low accessibility (similar to PET/CT), the length of the examination, and the heterogeneity among MRI systems, MRI software, and examination protocols. Recently, Whole Body Diffusion MRI (WB-DW MRI) has been proposed as a possible alternative to PET/CT [25,26]. It has also been demonstrated that WB-DW MRI is less histology dependent than PET/CT and thus is likely to become the imaging test of choice for staging indolent lymphomas with low FDG avidity in a short time frame [27–29].

Our retrospective study was conducted on 64 patients to compare the diagnostic and staging capabilities of CT, MRI, and PET/CT in the evaluation of lymphoma. Our study demonstrated that CT and MRI have similar efficacy in assessing both lymphadenopathies and extra-nodal lesions, with great agreement in both assessing the number and size of lesions. However, MRI showed slightly greater sensitivity, specificity, and accuracy than CT but substantially overlapping with PET/CT. Our observations confirm the diagnostic value of MRI already known in the literature, where reported sensitivity and specificity ranged from 90% to 98% and 94% to 99% for the evaluation of lymph nodes and from 79% to 100% and 99% to 100% for the evaluation of extra-nodal areas [25].

In our study, MRI allowed the detection of more pathological lymph nodes and extra-nodal areas than CT, which was mainly due to the use of diffusion-weighted sequences. As a matter of fact, significant hypercellularity in lymphoproliferative pathologic tissues results in a very strong reduction in diffusivity in pathologic lesions. Lymph nodes that were undetectable or more difficult to recognize on MRI than on CT or PET/CT were those that were located in regions affected by respiratory motion artifacts, such as the hilar lung region. On the other hand, MRI is more efficient than CT in staging the extent of disease in the bone marrow, whereas PET/CT is more efficient in diagnosing lymph nodes that have not increased in size (but have been defined as positive on histological analysis or in subsequent controls) or in assessing splenic involvement, as described previously by

Kharuzhyk et al.; MRI is potentially less effective in the diagnosis of spleen involvement because of the physiologic restriction of DWI in the spleen and the relatively low specificity of the size criteria (sagittal diameter greater of 13 cm) [25], although in our experience, no difference between modalities has been noted in the evaluation of splenic lesions, in part because of the use of endovenous contrast, which facilitates the identification of splenic lesions.

In this study, we did not analyze or compare quantitative ADC values related to DWI because there are currently no validated single cut-off values to differentiate positive from negative lymph nodes, although lower values have been positively correlated with malignancy, whereas higher values indicate normal histology [25,30]. Future comparative studies between SUV max and ADC values could clarify the correlation (that we expect to be negative or inverse) between the quantitative data offered by these two imaging modalities in the characterization of malignant lymph nodes [31].

Our study has several limitations. The patient's population size is small because of restrictive selection criteria. With a small population, in which the majority of cases are, as per the literature, composed mainly of LH and DLCBLs, it was not possible to divide the patients into subgroups according to histological type, so we had less information about the rarer subtypes, some of which (such as small lymphocytic lymphomas) are not represented in our population. In addition, it was not possible for obvious reasons to obtain histological analysis of all lymph node stations and extra-nodal lesions examined, so we considered PET/CT examination, which is not 100% accurate, as one of the main reference standards. Furthermore, we did not divide the cases between FDG avid and non-FDG avid lesions, although Mayerhoefer et al. already demonstrated the superiority of DW-MRI over PET/CT in non-FDG avid lymphomas [15]. Finally, although TBCT and MRI examinations were available in a relatively large group of patients, PET/CT were available in a smaller group, approximately one-third of the total.

In conclusion, our study demonstrates high agreement in determining the number and size of lesions between CT and MRI, with a slight superiority of MRI in the evaluation of bone marrow involvement. Both modalities showed a per-lesion sensitivity and staging accuracy comparable to PET/CT, which still remains the gold standard in international diagnostic guidelines. Considering the numerous CT and PET/CT examinations routinely required in patients with lymphoma, an increasing use of MRI, which has the great advantage of being radiation-free, is therefore highly recommended, particularly in the evaluation of pediatric and younger patients. This calls for an update of the diagnostic guidelines for hematologic diseases, which at the time of this study do not consider DWI-MRI yet.

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