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The Role of Whole-Body MRI in Patients with Lymphoma: A Narrative Review

Benedetta Renzetti, MD[1,*], Arrigo Cattabriga, MD[1,2,*], Stefano Brocchi, MD[1], Caterina Gaudiano, MD[1], Marta Assenza[3], Cristina Nanni, MD[4], Alessandro Broccoli, PhD, MD[2,5], Antonio Basile, MD[6], PierLuigi Zinzani, PhD, MD[2,5], Stefano Fanti, MD[2,4], and Cristina Mosconi, MD[1,2]

Abstract

Lymphomas, including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), represent a significant proportion of malignancies affecting diverse age groups, including children and pregnant women. Traditional imaging modalities, such as 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) and contrast-enhanced CT, are standard for staging and monitoring but expose patients to ionizing radiation, increasing the risk of secondary malignancies. This review evaluates whole-body magnetic resonance imaging (WB-MRI) as a radiation-free alternative for assessing lymphoproliferative disorders. We examine its strengths, including the ability to detect disease and assess treatment response, as well as its limitations, such as challenges in visualizing small thoracic lesions. Recent studies demonstrate high concordance between WB-MRI and 18F-FDG-PET/CT, particularly for lymphomas with low or variable FDG avidity, making WB-MRI a promising modality for staging and follow-up, especially in young and pregnant patients.

Keywords

MRI, lymphoma, PET/CT, radiology, cancer detection, response assessment, nuclear medicine

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Introduction

Lymphomas are common malignant tumors that affect people of all ages, from children to the elderly, and account for approximately 5–6% of all cancers. Among these, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are the third most frequent types of cancer in children. Furthermore, Hodgkin lymphoma is notably one of the most commonly diagnosed cancers during pregnancy.[1]

Lymphoproliferative disorders encompass a range of histological subtypes, each with distinct prognoses and clinical characteristics. These disorders can be categorized into three main groups: Hodgkin lymphoma (HL), aggressive non-Hodgkin lymphomas (a-NHL), and indolent non-Hodgkin lymphomas (i-NHL).[1]

Hodgkin Lymphoma (HL) has two primary subtypes:

1. Classical HL: This subtype, which makes up over 90% of HL cases, is characterized by high 18F-fluorodeoxyglucose (18F-FDG) uptake on positron emission tomography/computed tomography (18F-FDG-PET/CT) and a more aggressive clinical course.

[1]Department of Radiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[2]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy
[3]Professional development and implementation of research in health professions unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[4]Nuclear Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[5]Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[6]Radiology I Unit, Policlinico Universitario G. Rodolico, Catania, Italy

*These authors contributed equally

Corresponding Author:
Arrigo Cattabriga, Department of Radiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.
Email: arrigo.cattabriga@unibo.it

2. Nodular Lymphocyte-Predominant HL: This form generally exhibits a slower progression and lower FDG uptake, indicating a more indolent nature.[2]

Aggressive Non-Hodgkin Lymphomas (a-NHL) are marked by rapid tumor growth and typically require immediate treatment. Key aggressive subtypes include:

- Diffuse Large B-Cell Lymphoma (DLBCL): The most common aggressive NHL, representing about 30% of all NHL cases, and noted for high FDG uptake.
- Mantle Cell Lymphoma
- Burkitt Lymphoma
- Peripheral T-Cell Lymphomas.[3]

Indolent Non-Hodgkin Lymphomas (i-NHL) are characterized by slow growth, a prolonged course, and often minimal symptoms. The most prevalent i-NHL is follicular Lymphoma, accounting for approximately 20% of NHL cases. In most cases, immediate treatment is not necessary, and a strategy of watchful waiting is commonly employed.[4]

Lymphoma imaging typically involves 18F-FDG-PET/CT and/or contrast-enhanced CT scans. 18F-FDG-PET/CT is utilized for FDG-avid lymphomas, while contrast-enhanced CT is preferred for non-FDG-avid subtypes.[1,5]

The current staging system for malignant lymphoma, known as the Cotswolds modification of the Ann Arbor staging system, is used for both HL and NHL. The Ann Arbor system takes into account the number of lesions and the extent of nodal and extranodal involvement; the Cotswolds modification enhances this approach by incorporating tumor burden as an additional factor, providing a more comprehensive assessment of the disease.[6,7]

As an alternative, the Lugano staging system has been specifically developed for staging HL. It defines four stages and further classifies each stage based on the presence (B) or absence (A) of symptoms, including fever, weight loss and profuse night sweats, as well as extranodal extension (E).[7,8]

While the improvement in overall survival for young lymphoma patients is encouraging, the repeated imaging required for staging and monitoring exposes them to high levels of ionizing radiation, which increases the risk of developing secondary cancers.[1,9,10]

To mitigate these concerns, whole-body magnetic resonance imaging (WB-MRI) has increasingly been considered a radiation-free alternative for assessing lymphoproliferative disorders.[1,9] This imaging technique enables the detection of disease regardless of the histological subtype, offering several additional advantages: it does not require contrast agents, it does not require specific preparation, and it has few contraindications, primarily limited to the presence of incompatible devices or issues related to claustrophobia.[11]

This paper aims to review the existing literature to clarify the current role of whole-body MRI (WB-MRI) in lymphoma management. By exploring its advantages and limitations, we will provide a comprehensive analysis of the state of the art of WB-MRI in the management of lymphoma patients.

Materials and Methods

This article represents a comprehensive review of current literature regarding the application of WB-MRI in the diagnosis, staging, and monitoring of lymphomas, including HL and NHL. A literature search was conducted using PubMed with keywords related to "whole-body MRI", "lymphoma", "Hodgkin lymphoma", "non-Hodgkin lymphoma" and "18F-FDG-PET/CT". The search was limited to articles published between 2007 and 2024, focusing on peer-reviewed studies, clinical trials, and meta-analyses relevant to the use of WB-MRI in lymphoma assessment.

Inclusion criteria were: (1) original studies involving at least 10 patients with histologically confirmed lymphoma (either Hodgkin or non-Hodgkin subtypes); (2) studies evaluating the diagnostic role of WB-MRI in one or more of the following clinical settings: initial staging, treatment response assessment, or post-treatment follow-up; (3) availability of diagnostic performance data, including sensitivity, specificity, accuracy, or concordance with other imaging modalities such as 18F-FDG-PET/CT or contrast-enhanced CT.

Exclusion criteria included: (1) case reports, small series with fewer than 10 patients, and conference abstracts without full-text availability; (2) studies not involving WB-MRI as a primary imaging technique; (3) studies primarily focused on other malignancies were excluded from the selection process. However, selected papers on multiple myeloma or prostate cancer were cited when relevant to describe WB-MRI acquisition techniques or technical aspects; (4) duplicate publications or studies with overlapping patient cohorts unless additional relevant data were provided.

A total of 317 records were initially identified through the database search. Of these, 92 records were excluded for various reasons, including duplicate entries, incomplete bibliographic information or lack of relevance to the review topic upon closer examination. Following this initial filtering, 225 records were screened based on their titles and abstracts. During this stage, 117 records were excluded for not meeting the inclusion criteria.

The eligibility assessment involved a detailed review of 110 full-text reports. At this stage, 67 studies were excluded because they included fewer than ten patients or were case series or case reports. Ultimately, 43 studies met the eligibility criteria and were included in the final review.

This study aims to review the existing literature to clarify the current role of WB-MRI in lymphoma management.

By examining its advantages and limitations, we hope to provide valuable insights into its practical applications in clinical settings.

The reporting of this study conforms to SANRA guidelines.[12]

Current Imaging for Lymphoma

Staging

Currently, the gold standard for staging disease in patients with HL and FDG-avid NHL lymphomas is 18F-FDG-PET/CT,

which guarantees morphological and functional information,[1,5,9] through the measurement of standardized uptake values (SUV) which is related to cellularity and aggressiveness of the tumor.

Contrast enhanced CT is recommended in case of variable or non-FDG-avid subtypes is also used in FDG-avid disease as complementary imaging to characterize parenchymal lesions, measure lymphadenopathies and to accurately evaluate vascular compression or thrombosis.[1]

Bone marrow biopsy has represented the gold standard technique for a long time but it has been replaced by 18F-FDG-PET/CT and is currently reserved for patients with DLBCL and negative PET to identify the possible presence of low-volume diffuse bone marrow involvement.[1,5]

Response to Therapy

According to the Lugano Classification, the gold standard for assessing the response to therapy, during and at the end of chemotherapy, is 18F-FDG-PET/CT in the FDG-avid subtype of lymphoma.[1,5] According to these recommendations, a five-point scale is used to assess the state of remission. A score of 1 or 2 is indicative of complete metabolic response and is characterized by the absence of FDG uptake at the end of chemotherapy,[5] even with residual masses and also if a residual FDG uptake higher than normal liver uptake has been noted ad interim. The interpretation of score 3 should be cautious and might be considered as inadequate response to avoid undertreatment, even if patients usually have a good response at the end of the standard treatment. A score of 4 or 5 is indicative of treatment failure.[1,5,7]

In the variable or non-FDG-avid subtypes the response to treatment is evaluated through contrast enhanced CT: a decrease in size of a mass is considered a partial response, in absence of histological confirmation.[1,5]

In the follow-up of patients with HL and NHL, FDG-PET has proven to be a valid tool although in some cases histological confirmation was fundamental in identifying the true recurrence.[13]

Moreover, the false positive rate is more than 20% resulting in an increase of unnecessary exams and a further increase in exposure to ionizing radiation, considering that, after the end of treatment, contrast enhanced CT is usually recommended every 3–6 months in the first two years.[1]

Current Role of Whole-Body MRI

Protocol

WB-MRI is a promising and revolutionizing next-generation imaging (NGI) technique in the staging of cancer patients.

Currently, there are no specific guidelines for the acquisition, interpretation and reporting of WB-MRI in lymphoma,[1] unlike multiple myeloma and prostate cancer, whose guidelines are represented by MY-RADS[14] and MET-RADS-P,[15] respectively. Therefore, in the absence of specific guidelines, the protocol used should not differ from that used in the staging of prostate cancer and multiple myeloma.

WB-MRI is a multiparametric technique acquired from the vertex to mid-thigh that does not require the administration of an intravenous contrast medium. Its protocol includes anatomical and functional sequences, with an acquisition time normally ranging from 30 to 60 min.[1,11] Figure 1.

Core anatomical sequences in whole-body MRI (WB-MRI) include both T1 and T2-weighted axial images. Generally gradient echo (GRE) sequences for T1-weighted imaging are preferred over fast spin echo sequences as they have shorter acquisition time and allow for the acquisition of 3D images. T1w GRE acquired using the Dixon method produce multiple sets of images within a single acquisition (ie in-phase, opposed-phase, fat-only, and water-only images).[1,11] To minimize motion artifacts, images of the chest and abdomen should be acquired during a breath-hold, while images of other regions may be taken during free breathing.[16] Fat-fraction (rF%) maps are calculated from fat-only and water-only images using the formula "$rF\% = (F / (F + W)) \times 100$" and provide a quantitative assessment of fat within tissues and lesions, used to characterize bone marrow infiltration.[1,11] A slice thickness of at least 5 mm is recommended for axial images, with contiguous spacing.[16]

T2-weighted imaging, typically acquired via single-shot or half-acquisition turbo spin echo (HASTE), is used to assess the morphology of parenchymal organs and to identify any potential complications such as extramedullary disease or spinal cord compression.

Whole spine sagittal sequences with STIR (short tau inversion recovery) or fat-suppressed T2-weighted images are crucial for detecting vertebral lesions, fractures, and spinal cord compression[1,11,16]; whole spine sagittal T1w TSE sequence may be acquired, but it is not considered necessary.[16]

The key functional sequence in WB-MRI is whole-body diffusion-weighted imaging (DWI) with background body signal suppression (DWIBS), which is essential for detecting highly cellular lesions. It is acquired using a single-shot diffusion-weighted echo-planar imaging sequence. Multiple averages of DWI data are acquired during free breathing to minimize motion artifacts and improve the signal-to-noise ratio and usually two b-values are sufficient to generate apparent diffusion coefficient (ADC) maps for lesion characterization and response assessment, with the lowest b-value typically ranging between 50 and 100 s/mm^2 and the highest between 800 and 1000 s/mm^2, which effectively detects hyper-cellular lesions. Axial acquisition is preferred because it closely aligns with the cross-sectional anatomy typical of other imaging modalities, such as CT.[1,11,17,18] Additionally, radial DWIBS maximum intensity projections from high b-value images are generated in 3D, on coronal and sagittal planes, for rapid disease assessment. These images are typically displayed in inverse grayscale to resemble a PET-like view.[1,11]

In DWIBS images, sites of highly cellular (active) disease will be characterized by markedly impeded diffusion, with high signal intensity on DWI and low ADC values. Low-cellular lesions

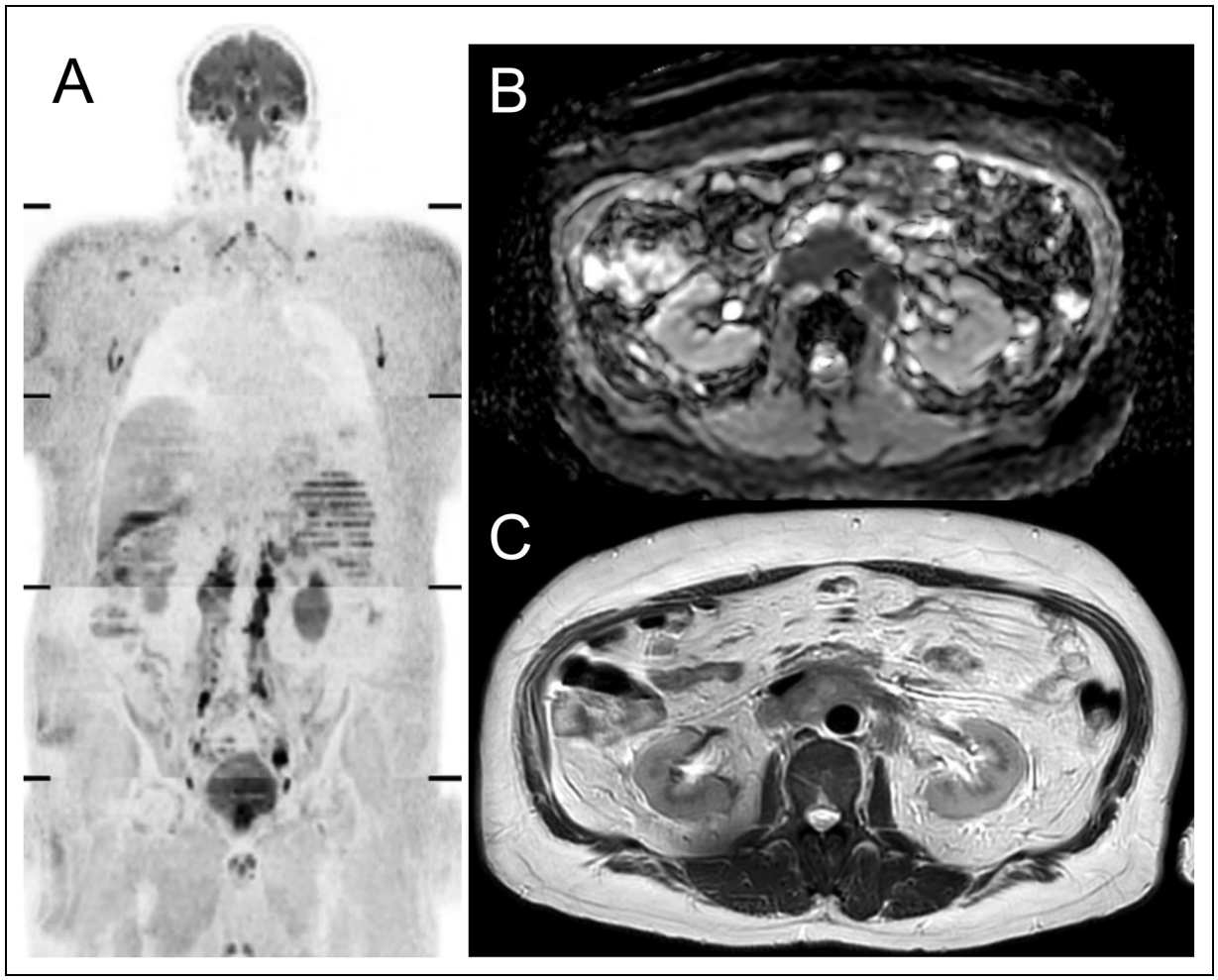

Figure 1. A 57-year-old Patient Presenting Multiple Coalescent Lymphadenopathies Within the Retroperitoneal Space, Showing Restricted Diffusion on the Coronal 3D MIP Inverted DWIBS Images (A) and in the Axial ADC Maps (B). Axial Morphological T2w Images (C) Confirm the Presence of Interaortocaval Adenopathy, Allowing for Measurements.

(including disease responding to treatment) normally present with low DWI signal intensity and / or high values.

WB-MRI can be performed on both 1.5 T and 3 T scanners. 1.5 T scanners are preferred for patients with non-removable metallic prostheses to minimize artifacts, while 3 T scanners offer a higher signal-to-noise ratio. Although 3 T units can enhance tumor detection, they are also more susceptible to image shearing, geometric distortion, chemical shifts, and ghosting artifacts.[1,11] Azzedine et al conducted a study comparing 1.5 T and 3 T whole-body MRI in 23 lymphoma patients, revealing similar diagnostic performance between the two systems, although significant artifacts were noted in 2 patients at 3 T.[19] Thus far, no studies have established the superiority of 3 T over 1.5 T in whole-body MRI.[1,11,18]

Whole-Body MRI Criteria in the Evaluation of Nodal and Extranodal Disease

Various whole-body MRI criteria have been proposed to identify lymph node involvement:

- The DWI signal is higher than that of the spinal cord;
- The DWI signal remains elevated at higher b-values, with diffusion restriction confirmed by low ADC values or central necrosis, regardless of nodal size;
- Lymph nodes coalesce into large nodal masses.[1,11,20,21]
- Longest diameter > 1.5 cm or < 1.5 cm but with the absence of fatty hilum with local grouping (although most studies used the cut off of 1,0 cm in the short axis).[22]

Despite ADC measurements in lymph nodes being reproducible, by manually placing a ROI on the visible lesion and avoiding necrotic areas, no standardized ADC cut-off values currently exist to distinguish normal nodes from lymphoma involvement.[9,21]

In general, characterizing small lymph nodes is challenging because both benign and malignant nodes exhibit signal restriction due to their high cellularity. In particular, ADC values, which are inversely proportional to cellularity, assist in tissue characterization through consistent measurements. Therefore, the ADC value has been proposed as a key distinguishing

parameter. Several studies indicate that ADC values are generally lower in pathological lymph nodes compared to benign ones; however, the significant overlap between these two populations limits a reliable differentiation.[1,11,23]

The literature on whole-body ADC values is limited, but a recent study has provided specific values for normal lymph nodes in healthy individuals. For example, the average ADC value of healthy lymph nodes is 1.12 ± 0.27. Pelvic lymph nodes have ADC values ranging from 0.98 to 1.18, while retroperitoneal lymph nodes exhibit higher average ADC values of 1.61[24] Furthermore, it remains unclear whether average or minimum ADC values should be used for this purpose.[9,21]

Horger et al demonstrated a significant increase in the apparent diffusion coefficient (ADC) of responding lesions in successfully treated Hodgkin lymphoma and non-Hodgkin lymphoma shortly after the initial chemotherapy course. In contrast, non-responding lesions exhibited stable ADC values, highlighting the potential of ADC measurements as an indicator of treatment response.[25]

In the evaluation of extranodal disease, an organ is considered involved if at least one of the following criteria is present:

- Splenomegaly (bipolar diameter > 13 cm);
- Focal or diffuse signal alteration on T2w sequences;
- Asymmetric enlargement of bilateral organs;
- Diffusion restriction on DWI sequences affecting the extranodal organs.[9,21]

Limitations and Perspectives of Whole-Body MRI

While whole-body MRI has shown excellent diagnostic performance in numerous studies, it has limitations in detecting small thoracic lesions, including hilar, mediastinal, and pulmonary abnormalities, as well as in tissues characterized by low anisotropic diffusion patterns, such as the spleen, nervous system, and renal parenchyma. The difficulties in detecting thoracic lesions are largely attributed to artifacts in diffusion-weighted imaging (DWI) sequences caused by cardiac pulsation and respiratory motion, which can interfere with apparent diffusion coefficient (ADC) calculations. Furthermore, identifying lymphoma in organs with inherently low ADC values poses additional challenges.[9,21]

In these scenarios, incorporating 3D T1-weighted imaging with gadolinium-based contrast agents may improve the detection of parenchymal lesions, however, some experts contend that unenhanced morphological evaluation using standard sequences, alongside DWI, is sufficiently effective for comprehensive lymphoma staging.[1,11]

As previously demonstrated by Gu et al, the inclusion of DWI alongside morphological sequences significantly enhances diagnostic sensitivity, both in terms of lesion number and size. The majority of these lesions (58%, n = 32) were located in pelvic or abdominal lymph nodes and bone marrow.[26]

Although FDG-PET/CT and contrast enhanced CT are the imaging techniques of choice for staging in FDG-avid and variably/low FDG-avid lymphomas, respectively,[1,5] WB-MRI has demonstrated superiority for detection of lymphoma with variable FDG avidity.[16] Specifically, WB-MRI demonstrates a sensitivity of 94%, outperforming both FDG-PET/CT (61%) and contrast-enhanced CT (71%) and should be the method of choice in young patients and pregnant women, to avoid or minimize exposure to radiation.[16]

Role of Whole-Body MRI in Staging

In the lymphoma staging, whole-body MRI has demonstrated good to excellent concordance with 18F-FDG-PET/CT for detecting both nodal and extranodal disease involvement, as reported in several studies.[1,11] Table 1.

Evidence suggests that, although WB-MRI is slightly less effective than 18F-FDG-PET/CT for staging FDG-avid lymphoma subtypes, WB-MRI may surpass both 18F-FDG-PET/CT and contrast-enhanced CT in detecting lymphomas with low or no FDG avidity.[27,28]

In terms of staging, the meta-analysis of Wang et al, which includes 8 studies and 338 patients, revealed that both WB-MRI and 18F-FDG PET/CT achieved high staging accuracies of 98% for Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (NHL). However, for indolent lymphoma, the accuracy of 18F-FDG PET/CT dropped to 87%, while WB-MRI maintained a higher accuracy of 96%.[6]

Multiple studies have confirmed the high accuracy of WB-MRI in staging Hodgkin's lymphoma (HL). In their prospective trial involving 140 lymphoma patients, Mayerhoefer and colleagues reported very high agreement between WB-MRI and 18F-FDG-PET/CT, with kappa values of 0.92 for high FDG-avid lymphomas and 0.89 for those with variable FDG avidity.[29]

Similarly, Maccioni and colleagues showed that WB-MRI achieves high agreement with 18F-FDG PET/CT for staging lymphoma and the concordance was strong in nodal assessment (Cohen's kappa of 0.95) and perfect for extra-nodal disease (kappa of 1.00), with the main discrepancies occurring in the pulmonary hilar region, likely due to motion artifacts of lungs and heart. Moreover, quantitatively, a strong negative correlation was found between ADCmean and SUVmean of nodal lesions in patients evaluated at baseline.[9]

The meta-analysis of Lambert et al, conducted on 15 studies encompassing 519 patients, highlighted that the sensitivity and specificity of the WB-MRI for identifying nodal involvement were 0.93 and 0.99, respectively. Similarly, sensitivity and specificity for detecting extranodal involvement were 0.89 and 0.99, respectively. Therefore, the overall agreement for staging of WB-MRI, in evaluating both nodal and extranodal lymphoma involvement, as measured by Cohen's kappa, was very high at 0.90, with nearly perfect agreement with the reference standard.[22]

Abdulqadhr et al demonstrated complete concordance in the staging of 18 patients with aggressive lymphoma subtypes such as DLBCL, primary mediastinal B-cell lymphoma, anaplastic large cell lymphoma, and T-cell lymphoma[30]; moreover, Lin et al reported 93% of agreement between WB-MRI and 18F-FDG-PET/CT in the staging of diffuse large B-cell lymphoma (DLBCL).[31]

Table 1. Summary of the Main Evidences Concerning the Role of Imaging in Staging Lymphoma.

Study	Study type	Population	MRI Protocol	Summary
Wang et al Onco Targets Ther, 2018	Metanalysis (8 studies analyzed)	338	DWI in all studies. Variability of T1w and/or T2w/STIR.	Diagnostic accuracies of WB-MRI and ^{18}F-FDG-PET/CT are compared during staging different subtypes of Lymphoma. • HL and aggressive NHL: comparable accuracies (98%) • Indolent lymphoma: drop in PET/CT accuracy (87%) versus WB-MRI (96%) • Low-FDG avidity indolent lymphoma: further increase in the discrepancy between the two techniques (PET/CT = 60%; WB-MRI = 98%). Conclusion: WB-MRI may serve as an alternative to PET/CT and is less histology-dependent.
Mayerhoefer et al Clin Cancer Res, 2014	Prospective study	140	DWI + T1w sequences	WB-MRI and FDG-PET/CT ± contrast-enhanced CT scan (CECT) are compared in baseline staging of patients with FDG-avid lymphoma (group A = 100) or lymphoma of variable FDG avidity (group B = 40). • Group A. WB-MRI sensitivity = 97%; agreement with reference standard (PET/CT) in 94/100 patients ($k = 0.94$) à WB-MRI is only slightly inferior compared to PET/CT. • Group B. Sensitivity WB-MRI = 94.4%; PET/CT = 60.9%; CECT = 70.7%. Agreement with reference standard (based on histology & imaging): WB-MRI = 37/40 ($k = 0.89$); PET/CT = 26/40 ($k = 0.52$); CECT = 24/401 ($k = 0.43$). Conclusion: DWI-MRI is slightly inferior to 18F-FDG-PET/CT in FDG-avid lymphoma but superior (both to PET and CECT) in variable FDG-avid subtypes.
Maccioni et al Radiol Med, 2023	Prospective study	61	DWI + T1w + T2w sequences	Agreement between WB-MRI & PET/CT in assessing nodal and extra-nodal disease in patients with lymphoma (both for baseline staging and interim evaluation) was calculated. • Nodal disease: agreement = 0.95 • Extra-nodal disease: agreement = 1.00 • Staging: agreement = 1.00
Lambert et al Quant Imaging Med Surg, 2022	Metanalysis (15 studies)	519	DWI (morphological sequences not specified)	WB-MRI pooled sensitivity and specificity in detecting nodal and extranodal disease are assessed. Agreement with reference standard (PET/CT or CECT) is also assessed. • Nodal disease: Pooled sensitivity = 0.93; Pooled specificity = 0.99; • Extranodal disease: Pooled sensitivity = 0.89; Pooled specificity = 0.99 • Pooled agreement with reference standard: $k = 0.90$ ➡ almost perfect
Abdulqadhr et al Acta Radiologica, 2011	Prospective study	31	DWIBS, T1w, T2-STIR	Prospective comparison of WB-MRI and FDG-PET/CT at baseline staging in patients with heterogeneous types of lymphomas (8/31 HL, 18 aggressive NHL, 5 indolent NHL). • Staging was the same on WB-MRI and PET/CT in 28/31 patients; • Staging was the same in all pts with HL and aggressive NHL;

(continued)

Table 1. Continued.

Study	Study type	Population	MRI Protocol	Summary
				• Three indolent lymphomas had higher stage on WB-MRI compared to PET/CT Conclusion: WB-MRI is a promising tool for staging both aggressive and indolent lymphoma.
Chieh Lin et al Eur Radiol, 2010	Prospective study	15	DWI only	Study compares the diagnostic performance of WB-MRI and FDG-PET/CT in detecting nodal and extranodal disease. • 296 nodal regions analysed. MRI mateched PET/CT in 94% of cases ($k = 0.85$). DWI sensibility 90%, specificity 94%. If ADC maps and nodal size were taken into account then the specificity grew to 100%, with 85% specificity. • For extranodal involvement agreement was 100%. • For Ann-Arbor staging, agreement was in 14 patients out of 15 (93%).
Kwee er al. J Magn Reson Imaging, 2014	Prospective multicenter study	108	DWI (104/108 pts) + T1w + T2w sequences	This prospective study compares the effectiveness of WB-MRI with CT in staging newly diagnosed lymphoma. The staging results of WB-MRI without DWI: • Matched CT results in 66.6% of cases; • Exceeded CT results in 24.1% of cases (15 were correct, 7 were incorrect, and 4 were unresolved); • Lower than CT results in 9.3% of cases (9 were incorrect, and 1 was unresolved). The staging results of WB-MRI with DWI showed: • Matched CT results in 65.4% of cases; • Exceeded CT results in 27.9% of cases (18 were correct, 6 were incorrect, and 5 were unresolved): • Lower than CT results in 6.7% of cases (6 were incorrect, and 1 was unresolved). Conclusion: The study indicates that whole-body MRI provides staging results comparable to CT for most patients with newly diagnosed lymphoma, with no clear benefit from adding DWI.
Balbo Mussetto et al Clinic Radiol, 2016	Prospective study	41	Axial DWI ($b = 0$ mm/s^{+} & $b = 1000$ mm/s^{2}) +Coronal T1 TSE, T2 TSE, T2 STIR	This study evaluates the diagnostic performance of whole-body magnetic resonance imaging with diffusion-weighted imaging (WB-MRI-DWI), 18F-FDG PET/CT, and contrast-enhanced CT (CECT) for baseline staging of lymphoma in a heterogeneous patient cohort. Nodal (1025 sites) and extranodal (458 sites) regions were assessed separately. A reference standard (RS) was established by combining PET/CT, CECT, and bone marrow histology findings. • Nodal Disease: RS identified disease in 217/1025 nodal sites. CE-CT showed 23 false negatives and 11 false positives, WB-MRI-DWI had 17 false negatives and 6 false positives, while PET-CT had no errors.

(continued)

Table 1. Continued.

Study	Study type	Population	MRI Protocol	Summary
				• Extranodal Disease: RS confirmed disease in 37/458 sites. PET-CT showed 4 false negatives and 2 false positives, CE-CT had 17 false negatives, and WB-MRI had only 1 false negative. WB-MRI demonstrated excellent accuracy in bone marrow assessment. • Final Staging Accuracy: PET/CT failed to correctly stage 4/41 patients, CECT failed in 12/41 cases, while WB-MRI-DWI achieved perfect staging accuracy. Conclusion: WB-MRI-DWI is highly sensitive and specific for lymphoma staging and can be a reliable alternative to CECT.
Stecco et al Gastroenterol Res Pract, 2015	Retrospective study	17	DWI + T1w + T2-STIRw sequences	This retrospective study compares the diagnostic performance of WB-MRI and FDG-PET/CT for staging in patients with gastrointestinal lymphoma. No statistically significant differences were found between WB-MRI and PET/CT ($p = .05$) for staging newly diagnosed lymphoma in terms of: • Sensitivity (100% WB-MRI vs 95.9% PET/CT); • Specificity (96.3% WB-MRI vs 100% PET/CT); • PPV/NPV (96.1%/100% WB-MRI vs 100%/96.4% PET/CT). Conclusion: WB-MRI is comparable to PET/CT for staging gastrointestinal lymphoma.

Ferrari et al Hell J Nucl Med, 2014	Prospective trial	27		This study compares the diagnostic performance of WB-MRI and FDG PET/CT for initial lymphoma staging and its impact on patient management. 27 newly diagnosed lymphoma patients (13 HL, 14 NHL) underwent both imaging modalities within 10 days of diagnosis and before treatment.
				• FDG PET/CT detected 85 lesions (74 nodal, 11 extranodal), while WB-MRI identified 91 sites (81 nodal, 13 extranodal). The overall agreement between the two modalities was very good ($\kappa = 0.815$).
				  • Histotypes: Agreement was slightly reduced in NHL, particularly for indolent forms, but remained very good for aggressive forms.
				  • Bone Marrow Involvement: WB-MRI achieved 100% sensitivity and specificity, outperforming PET/CT (50% sensitivity, 96% specificity) when compared to biopsy as the reference standard.
				  • Staging Accuracy: Concordance in staging was observed in 26/27 patients (96%), with WB-MRI resulting in one instance of overstaging.
				
				Conclusion: While PET/CT remains the gold standard for lymphoma staging, WB-MRI shows promise, particularly for histotypes that are not FDG-avid and for evaluating critical organs. The complementary nature of metabolic and functional imaging supports tailored therapeutic decisions.

WB-MRI has also shown promising results in comparison to contrast-enhanced CT; Kwee et al, in a study of 104 lymphoma patients, found that WB-MRI improved staging in 30% of cases by detecting hidden bone marrow involvement, although it missed pleural, lung, and lymph node involvement in about 7% of cases.[32]

Studies by Abdulqadhr et al and Balbo-Mussetto et al have demonstrated the superiority of WB-MRI over both contrast-enhanced CT and 18F-FDG-PET/CT in the staging of patients with indolent non-Hodgkin lymphomas (i-NHL).[30,33]

Moreover, Mayerhoefer et al highlighted WB-MRI's higher diagnostic performance in mucosa-associated lymphoid tissue (MALT) lymphomas, with 94.4% sensitivity compared to 60.9% of 18F-FDG-PET/CT and 70.7% of contrast-enhanced CT.[29] Similarly, Stecco et al demonstrated excellent concordance between WB-MRI and 18F-FDG-PET/CT in patients with gastrointestinal lymphomas, including 12 cases of i-NHL (kappa = 0.87).[34]

In the study conducted by Ferrari et al, the overall agreement between 18F-FDG-PET/CT and WB-MRI was excellent (k = 0.815). However, when considering histotypes, the agreement was slightly reduced in evaluating NHL for both nodal and extranodal involvement (nodal k = 0.763; extranodal k = 0.629). The agreement between the two imaging techniques was very good for aggressive lymphoma forms, but lower for indolent forms. In detecting bone marrow involvement, WB-MRI showed 100% sensitivity and specificity in detecting bone marrow involvement, compared to 50% and 96% for 18F-FDG-PET/CT.[35]

In fact, a strength of WB-MRI is the non-invasive evaluation of bone marrow involvement, especially when compared to contrast-enhanced CT, associated with its ability to detect both focal and diffuse bone marrow involvement that could be missed by blinded unilateral bone marrow biopsy of the iliac crest.[11,36]

Interestingly, patients with DLBCL and a negative bone marrow biopsy, but positive WB-MRI for marrow involvement, have shown a higher risk of disease progression and death compared to those with negative WB-MRI results.[37]

A comparative summary of sensitivity and specificity values for WB-MRI and 18F-FDG-PET/CT across selected studies is provided in Table 2.

Role of Whole-Body MRI in Response to Therapy and Follow-up

The standard imaging modality for post-treatment evaluation of Hodgkin lymphoma and aggressive lymphomas is 18F-FDG-PET/CT, while contrast-enhanced CT is often used for variable or non-FDG-avid subtypes. Both techniques are commonly employed for interim assessments during chemotherapy to predict early disease response.[1,5,37]

Young patients with lymphoma typically have a high overall survival rate of 90%–95% at 10 years[38] but, despite this positive outlook, 18F-FDG-PET/CT and contrast-enhanced CT remain recommended for post-treatment monitoring.[7] Despite the relative low dose of modern nuclear medicine and radiological imaging techniques compared to the past, concerns about radiation exposure in these younger patients with long life expectancy have led some experts to advocate for whole-body MRI for monitoring during watchful waiting or in cases of complete remission.[39] Notably, no studies have yet compared the clinical impact of imaging surveillance using whole-body MRI against 18F-FDG-PET/CT or contrast-enhanced CT in this patient population.

Albano et al showed that interim diffusion-weighted imaging (DWI) after a few cycles of chemotherapy can effectively identify Hodgkin lymphoma lesions responsive to treatment, reporting a significant increase of the ADC (apparent diffusion coefficient) in these lesions.[40] Similarly, Horger et al observed a notable rise in ADC values in responding lesions of both HL and NHL shortly after the start of chemotherapy courses; in contrast, non-responding lesions demonstrated

Table 2. Summary of Sensitivity and Specificity Values for WB-MRI and 18F-FDG-PET/CT Reported in key Comparative Studies Across Lymphoma Subtypes.

Study	Lymphoma subtype	WB-MRI Sensitivity (%)	WB-MRI Specificity (%)	PET/CT Sensitivity (%)	PET/CT Specificity (%)
Wang et al (2018)	HL, a-NHL, i-NHL	HL/NHL: 98 Indolent: 96	Not reported	HL/NHL: 98 Indolent: 87	Not reported
Mayerhoefer et al (2014)	FDG-avid and variable FDG-avid	FDG-avid: 97 Variable FDG: 94.4	Not reported	FDG-avid: ~100 Variable FDG: 60.9	Not reported
Lambert et al (2022)	Mixed	Nodal: 93 Extranodal: 89	Nodal: 99 Extranodal: 99	Nodal: ~93 Extranodal: ~90	Nodal: ~99 Extranodal: ~99
Maccioni et al (2023)	Mixed	Nodal: 95 Extranodal: 100	Nodal: 100 Extranodal: 100	Nodal: ~95 Extranodal: ~100	Nodal: 100 Extranodal: 100
Ferrari et al (2014)	HL and NHL	Bone marrow: 100	Bone marrow: 100	Bone marrow: 50	Bone marrow: 96
Balbo-Mussetto et al (2016)	Mixed	Nodal: ~92.2 Extranodal: ~97.3	Nodal: ~98.7 Extranodal: ~99.5	Nodal: 100 Extranodal: ~89.2	Nodal: 100 Extranodal: ~98.2

Where exact values were not available, estimations were derived from reported concordance data or staging performance. HL: Hodgkin lymphoma; a-NHL: aggressive non-Hodgkin lymphoma; i-NHL: indolent non-Hodgkin lymphoma; FN: false negative; FP: false positive.

stable ADC values, underscoring the potential of ADC measurements as reliable indicators of treatment response.[25]

In this context, De Paepe et al conducted a study with 14 patients diagnosed with aggressive lymphoma, utilizing whole-body MRI before treatment, after two cycles, and at the end of therapy. They identified significant differences in apparent diffusion coefficient (ADC) values between responding and non-responding lesions, with diffusion-weighted imaging (DWI) demonstrating a 100% negative predictive value and a correlation with progression-free survival ($p < .05$). In contrast, conventional morphological assessments of lymphomatous lesions were found to be insufficient for evaluating early treatment responses.[41]

Maccioni et al, in their subgroup of Hodgkin lymphoma patients, demonstrated that effective chemotherapy responses were characterized by increased ADC values and decreased SUVmax. This pattern aligns with existing research, where rising ADC values signal reduced cellular density within the tumor as treatment progresses, and declining SUVmax indicates a drop in metabolic activity, although previous studies yielded mixed findings about the relationship between ADC and SUV values in lymphoma, perhaps due to the distinct nature of these measurement, as SUVmax captures the highest FDG uptake within a single voxel, reflecting peak metabolic activity, while ADCmean measures cellularity across the entire lesion.[9]

Despite the biological differences captured by WB-MRI and 18FDG-PET/CT, they found a meaningful relationship between changes in SUVmax and ADC values post-treatment, suggesting that these parameters can serve as complementary indicators for monitoring therapeutic response.[9]

Latifoltojar and colleagues notably highlighted that WB-MRI may underestimate the treatment response in extra-nodal disease sites following therapy.[42] In patients with diffuse large B-cell lymphoma (DLBCL), an increase of ADC values in enlarged masses post-treatment has also been observed, underscoring the limitations of solely evaluating lesion size for assessing lymphoma response.[31,41] Moreover, Mayerhoefer et al recently demonstrated that whole-body MRI is comparable to 18F-FDG-PET/CT for evaluating treatment response during and after chemotherapy in a cohort of 64 lymphoma patients.[43]

Additionally, whole-body MRI is highly effective in detecting osteonecrotic lesions that may develop after chemotherapy, especially following high corticosteroid doses. This imaging technique offers a thorough assessment of the skeletal system and excels at the early identification of multifocal osteonecrosis, distinguishing these lesions from lymphoma sites. An observed association between steroid dosage, the number of chemotherapy cycles, and the risk of osteonecrosis further emphasizes the value of whole-body MRI in patients' surveillance.[44]

Discussion

This review highlights the evolving role of WB-MRI in the management of lymphomas, presenting it as a valuable alternative to conventional imaging techniques. Given the significant radiation exposure associated with 18F-FDG-PET/CT and contrast-enhanced CT, particularly for young patients with high survival rates, the non-ionizing nature of WB-MRI presents a compelling advantage. The findings suggest that WB-MRI can effectively assess disease involvement, with studies reporting a sensitivity of 94%, outperforming 18F-FDG-PET/CT in low or variable FDG-avid lymphomas. Furthermore, WB-MRI demonstrates excellent diagnostic performance in monitoring treatment responses through diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements, which correlate with progression-free survival. Nonetheless, WB-MRI still shows some limitations; notably, its reduced sensitivity in assessing small thoracic lesions—especially in the hilar, mediastinal, and pulmonary regions—remains a significant concern. This is primarily due to respiratory and cardiac motion artifacts affecting diffusion-weighted imaging sequences, which may compromise lesion detection and ADC accuracy in the thoracic area.

Future research should focus on establishing standardized protocols and guidelines for WB-MRI in lymphoma staging and response assessment, ensuring its integration into routine clinical practice.

When assessing lymphoma, the choice of imaging modality is crucial, as each has its strengths and weaknesses. In this context, WB-MRI could be progressively integrated into clinical practice for selected patient populations in which the avoidance of ionizing radiation is particularly desirable. These include children, adolescents, pregnant women, and patients requiring long-term surveillance, such as those with indolent lymphoma. Moreover, its value may be especially relevant in cases of low or variable FDG-avidity, where standard PET/CT may have reduced diagnostic accuracy. In these settings, WB-MRI offers a safer, reliable alternative for staging, treatment monitoring, and follow-up.

The following discussion explores the advantages and limitations of three prominent imaging techniques: whole-body MRI, contrast-enhanced CT, and 18F-FDG-PET/CT.

Whole-Body MRI

Whole-body MRI is particularly strong in visualizing soft tissues and bone marrow, providing exceptional contrast resolution. Additionally, the use of diffusion-weighted imaging (DWI) enables cellularity assessment, which can help identify more aggressive forms of the disease. One of the standout features of whole-body MRI is that it does not expose patients to ionizing radiation, making it a safer choice for vulnerable populations, including pregnant patients. Moreover, it does not require administration of contrast medium, avoiding the risk of allergic reactions.

On the other hand, WB-MRI presents with some limitations, primarily linked to MRI's own contraindications (such as in patients with pace-maker or suffering from severe claustrophobia) and to its limited availability. Furthermore, WB-MRI performance can be suboptimal in the assessment of the thorax (in particular lung parenchyma and mediastinal and hilar nodes), due to potential motion artifacts.

Contrast-Enhanced CT

Contrast-enhanced CT is widely available and employs standard acquisition protocols, making it a common choice in many medical facilities. Its high spatial resolution provides detailed anatomical images that are crucial for accurately staging lymphoma. Additionally, the short acquisition time makes it an efficient option for rapid evaluations, which is crucial in clinical practice.

Despite these advantages, contrast-enhanced CT has notable weaknesses. It lacks the ability to provide functional or metabolic insights into lesions, which can be a critical aspect of lymphoma assessment. The necessity for contrast media introduces risks, including potential allergic reactions and renal damage, especially in patients with pre-existing conditions. Moreover, the exposure to ionizing radiation, although relatively low with modern scanners, has been representing an additional concern, particularly for younger patients or those requiring multiple scans over time.

18F-FDG-PET/CT

18F-FDG-PET/CT offers a unique advantage in metabolic evaluation, allowing for the assessment of metabolic activity through standardized uptake values (SUVmax). This is particularly beneficial for evaluating treatment responses in lymphoma patients. The Deauville Score provides a standardized framework for interpreting results, enhancing the reliability of assessments. Additionally, like contrast-enhanced CT, 18F-FDG-PET/CT is widely accessible in clinical practice.

However, this modality has its own drawbacks. Its effectiveness can vary significantly depending on the lymphoma subtype, as some may not exhibit substantial FDG uptake, complicating the assessment. The high radiation burden associated with 18F-FDG-PET/CT raises the risk of secondary cancers over time. Lastly, the scanning process is relatively lengthy, which can be inconvenient for both patients and healthcare providers.

In conclusion, the choice of imaging modality in lymphoma should be guided by a clear understanding of each technique's advantages and limitations. WB-MRI stands out for its safety and excellent soft tissue contrast, making it particularly useful in patients with low or variable FDG-avidity. Contrast-enhanced CT offers rapid anatomical detail, while 18F-FDG-PET/CT provides essential metabolic information, albeit at the cost of higher radiation exposure—even though modern protocols have reduced this burden. A patient-centered, context-specific strategy remains key to optimizing care.

Future research should aim to standardize WB-MRI protocols for lymphoma, including acquisition parameters and reporting criteria. Prospective multicentric trials comparing WB-MRI with PET/CT and contrast-enhanced CT across various subtypes and clinical settings are needed to confirm its clinical value. Functional imaging biomarkers such as ADC values, and the integration of artificial intelligence, may further enhance the diagnostic and prognostic potential of WB-MRI.

Conclusion

Whole-body MRI emerges as a promising imaging modality for evaluating patients with lymphoma, offering significant benefits in terms of safety and diagnostic accuracy. Its ability to provide comprehensive insights into disease staging and treatment response makes it a valuable addition to lymphoma management, particularly in young patients, pregnant women, and those with lymphomas of low or variable FDG avidity.

WB-MRI demonstrates high concordance with 18F-FDG-PET/CT and may outperform it in certain subtypes, while avoiding exposure to ionizing radiation and the need for intravenous contrast agents. Moreover, diffusion-weighted imaging and ADC measurements have shown great potential for early assessment of treatment response and for guiding follow-up strategies.

However, WB-MRI still presents limitations, notably a reduced sensitivity in detecting small thoracic lesions—particularly in the hilar, mediastinal, and pulmonary regions—due to motion artifacts affecting diffusion-weighted sequences.

While current findings are encouraging, further validation through larger, multicentric trials is essential to standardize WB-MRI protocols and enhance its clinical applicability. As the field evolves, integrating WB-MRI into routine practice could significantly improve patient care and outcomes in lymphoma management.

ORCID iDs

Benedetta Renzetti https://orcid.org/0009-0009-6578-775X
Arrigo Cattabriga https://orcid.org/0000-0002-9574-586X
Stefano Brocchi https://orcid.org/0000-0002-7563-8936
Caterina Gaudiano https://orcid.org/0000-0002-3849-8428
Marta Assenza https://orcid.org/0009-0009-8222-1512
Cristina Nanni https://orcid.org/0000-0003-2000-1599
Alessandro Broccoli https://orcid.org/0000-0001-5633-7313
PierLuigi Zinzani https://orcid.org/0000-0002-2112-2651
Stefano Fanti https://orcid.org/0000-0002-7563-8936
Cristina Mosconi https://orcid.org/0000-0001-6822-9053

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