



## REVIEW

# Whole-body magnetic resonance imaging (WB-MRI) in lymphoma: State of the art

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## Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1002/hon.2676/>.

## Abstract

The improvements in magnetic resonance imaging (MRI) technology and the concern related to the increased cancer risk in patients with lymphoma, also due to radiation exposure associated with imaging examinations, have led to the introduction of whole-body MRI (WB-MRI) as a radiation-free alternative to standard imaging procedures. WB-MRI seems a less histology-dependent functional imaging test than <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/CT (<sup>18</sup>F-FDG-PET/CT). In patients with FDG-avid lymphomas, such as diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HL), <sup>18</sup>F-FDG-PET/CT remains the imaging reference standard for staging, with WB-MRI potentially being a complementary modality that could replace CT, especially in young patients. On the other hand, WB-MRI is a valuable imaging procedure for lymphoma surveillance and in lymphomas with variable/low FDG avidity and nonfollicular indolent lymphomas. The aim of this paper is to discuss the current state of the art of WB-MRI in lymphoma by evaluating its diagnostic performance in different lymphoma subtypes: Hodgkin, aggressive, and indolent lymphomas.

## KEYWORDS

lymphoma, magnetic resonance imaging, positron emission tomography, whole-body imaging

## 1 | INTRODUCTION

Lymphoma accounts for about 5% to 6% of all malignancies.<sup>1</sup> Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are the third most common cancers in children, with HL being the fourth most common cancer in pregnancy.<sup>2,3</sup> To date, contrast-enhanced CT (CECT) and <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/CT (<sup>18</sup>F-FDG-PET/CT) are both recommended for lymphoma staging, with the latter being more accurate, mainly due to its higher sensitivity in displaying extranodal locations.<sup>4</sup> <sup>18</sup>F-FDG-PET/CT represents the reference standard for staging and response assessment in FDG-avid lymphomas; CECT is recommended to image variably/low FDG-avid lymphomas.<sup>5</sup> CECT is routinely included in lymphoma staging due to its robustness in nodal size measurement, evaluation of compression or

thrombosis of central vessels, and discrimination between a single mass and an aggregate of single nodes.<sup>5</sup> For surveillance of patients with stage I/II, the National Comprehensive Cancer Network (NCCN) guidelines recommend clinical examination and blood test every 3 to 6 months for 5 years and imaging only if signs of disease relapse occur, whereas CECT every 6 months for 2 years in stage III/IV patients.<sup>6</sup>

Concerns have been raised on radiation exposure due to imaging examinations and its association with increased risk of secondary cancer in patients with lymphoma.<sup>7,8</sup> This has favored an emerging interest for the use of whole-body magnetic resonance imaging (WB-MRI) as a radiation-free alternative to standard imaging procedures.<sup>9,10</sup> The improvements in MRI technology have further sustained the inclusion of WB-MRI among the diagnostic tools for patients with lymphoma.

The actual role of WB-MRI in the diagnostic workup in lymphoma is examined in the present review. The current state of the art of WB-MRI and its diagnostic performance in different lymphoma subtypes, namely, HL, aggressive lymphomas, and indolent lymphomas, is discussed.

## 2 | WB-MRI: MAIN ASPECTS OF ITS USE IN LYMPHOMA

WB-MRI provides images of the body from head to toe including patient arms, although it generally covers from the vertex to midthigh. There is no consensus on the best protocol for WB-MRI in lymphoma. Different approaches have been proposed in previous studies including unenhanced T1- and T2-weighted, short tau inversion recovery and diffusion-weighted imaging (DWI) sequences.<sup>10,11</sup> The “functional” evaluation is based on DWI through the visualization and quantification of the random Brownian motion of water molecules in the biologic tissues, assessed by apparent diffusion coefficient (ADC).<sup>12</sup> However, there is no agreement on DWI parameters (*b* values) to be used. Lymphoma is characterized by high cellularity and elevated nuclear-to-cytoplasm ratio leading to restricted diffusion of water molecules than in normal tissues, thus producing high signal intensity on DWI and low ADC values, which help to easily identify the sites of disease.<sup>13</sup> Gradient-echo Dixon sequence has been more and more used. This allows a homogeneous water/fat suppression with great advantages for bone marrow imaging.<sup>14</sup>

Different WB-MRI criteria have been proposed for the evaluation of lymph nodal involvement, in addition to standard dimensional criteria (longest diameter > 1.5 cm).<sup>9</sup> Lymph nodes can be considered involved when DWI signal (a) has greater intensity than that of spinal cord or muscles; (b) maintains high signal intensity at higher *b* values, with restriction confirmed by low ADC or in the presence of central necrosis, disregarding the dimension; and (c) coalesced into large nodal mass.<sup>15</sup> Nevertheless, no clear cutoff of ADC values has been established to differentiate normal lymph nodes from lymphoma in clinical practice. Further, although lymph nodal ADC measurements have shown to be reproducible, it has not been defined whether mean or minimum ADC values should be employed.

In literature, excellent agreement ( $k = 0.82\text{--}1.00$ ) between WB-MRI and <sup>18</sup>F-FDG-PET/CT has been reported for the detection of both nodal and extranodal locations.<sup>16</sup> WB-MRI at 1.5 and 3T scanner have shown similar diagnostic performance for lymphoma staging.<sup>17</sup> WB-MRI seems to be slightly inferior to <sup>18</sup>F-FDG-PET/CT for staging FDG-avid subtypes, while it seems superior to both <sup>18</sup>F-FDG-PET/CT and CECT in lymphomas with variable FDG avidity.<sup>18,19</sup> The reported results have led several authors to propose WB-MRI as the optimal imaging tool for monitoring indolent lymphomas (i-NHLs) and aggressive lymphomas in complete remission, as well.<sup>20</sup>

Despite its good diagnostic performance, WB-MRI has shown weaknesses to evaluate small mediastinal and pulmonary hilar lymph

nodes due to artifacts on DWI by cardiac pulsation and breathing, with miscalculation of ADC values.<sup>21</sup> In addition, the characterization of focal splenic lesions by WB-MRI can be challenging due to the anisotropic physiologically restricted pattern of diffusion of normal splenic parenchyma on DWI.<sup>22</sup> Thus, a conjunction of DWI with standard morphologic WB-MRI images is needed to identify focal splenic involvement.<sup>4</sup>

The administration of gadolinium-based contrast agents during WB-MRI in lymphoma may improve the accuracy to identify parenchymal lesions. It seems particularly helpful in cases with high risk of extranodal localizations.<sup>23,24</sup> Conversely, some authors believe that unenhanced morphologic evaluation with DWI is sufficiently effective. This is corroborated by the increasing awareness of gadolinium accumulation in human tissues, whose clinical implication is still unclear.<sup>25,26</sup>

WB-MRI acquisition timing is related to the MRI unit and imaging protocol, ranging from 30 minutes to more than 1 hour, approximately. Overall, the whole procedure takes shorter time than <sup>18</sup>F-FDG-PET/CT—including the time between radiopharmaceutical injection and images acquisition.<sup>27,28</sup> Further, Plathow et al highlighted the potential economic impact of WB-MRI, since the total cost of WB-MRI results lower than that of <sup>18</sup>F-FDG-PET/CT,<sup>27</sup> although the costs might vary according to the different health care systems and countries.

Regarding patient compliance, WB-MRI, <sup>18</sup>F-FDG-PET/CT, and CT are all well tolerated with high degree of patient acceptance.<sup>28,29</sup> The sources of discomfort and/or anxiety of undergoing <sup>18</sup>F-FDG-PET/CT and CT are pain and fear for injection of radioactive substances or contrast media, fasting period, radiation exposure, and the need to limit contact with people after <sup>18</sup>F-FDG-PET/CT.<sup>28,29</sup> On the other hand, a major concern for patients undergoing WB-MRI is claustrophobia due to the anxiety of being for a long time in the closed space of MRI machine, partly relieved by taking oral sedatives.<sup>28</sup> Advantages and disadvantages in the use of the main imaging modalities in patients with lymphoma are reported in Table 1.

## 3 | HODGKIN LYMPHOMAS

HL is subdivided into two main subgroups: classical HL representing over 90% of HL, with high FDG uptake, and nodular lymphocyte-predominant HL, which typically shows indolent behavior and low if any FDG uptake.<sup>30</sup> <sup>18</sup>F-FDG-PET/CT has been included as standard imaging modality for staging and posttreatment assessment in classical HL.<sup>5</sup> Moreover, PET scan has been extensively employed as interim evaluation during chemotherapy for the early assessment of disease response.<sup>31,32</sup> Several studies have reported high accuracy of WB-MRI for HL staging showing better agreement between WB-MRI and <sup>18</sup>F-FDG-PET/CT in patients with HL than in those with NHL.<sup>22,33,34</sup> In a prospective study on 140 lymphoma patients, Mayerhoefer et al reported a strong agreement between WB-MRI and <sup>18</sup>F-FDG-PET/CT for staging HL, suggesting that WB-MRI could be a valuable alternative tool for lymphoma staging, especially in younger patients or in

**TABLE 1** Advantages and disadvantages in the use of the main imaging modalities in patients with lymphoma

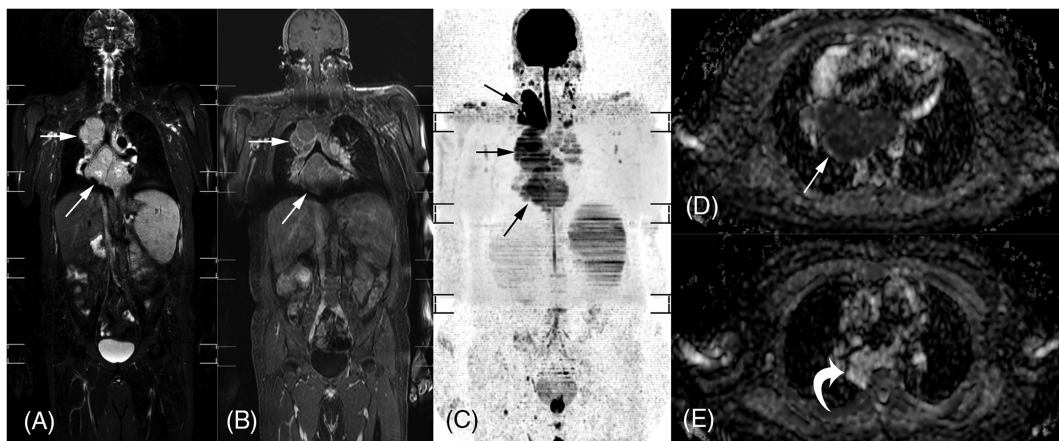
Technique	Advantages	Disadvantages
<sup>18</sup> F-FDG-PET/CT	<ul style="list-style-type: none"> <li>- Wide availability</li> <li>- Functional evaluation with FDG uptake</li> <li>- Clear SUV<sub>max</sub> cutoff</li> <li>- Reproducibility</li> <li>- Standard imaging protocol</li> </ul>	<ul style="list-style-type: none"> <li>- Radiation exposure</li> <li>- No FDG uptake of some lymphomas</li> <li>- Long examination time</li> </ul>
CT	<ul style="list-style-type: none"> <li>- Wide availability</li> <li>- Short acquisition time</li> <li>- High spatial resolution</li> <li>- Reproducibility</li> <li>- Standard imaging protocol</li> </ul>	<ul style="list-style-type: none"> <li>- Radiation exposure</li> <li>- Contrast injection</li> <li>- Only morphologic evaluation</li> </ul>
WB-MRI	<ul style="list-style-type: none"> <li>- No radiation exposure</li> <li>- Not necessary contrast injection</li> <li>- High contrast resolution</li> <li>- Bone marrow evaluation</li> <li>- Functional evaluation with DWI</li> <li>- Less histology dependent</li> <li>- Feasible in pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>- No clear ADC cutoff values</li> <li>- Lower availability</li> <li>- Limited accuracy for lung evaluation</li> <li>- Patient anxiety due to claustrophobia</li> <li>- Long examination time</li> </ul>

Abbreviations: <sup>18</sup>F-FDG-PET/CT, <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/CT; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; WB-MRI, whole-body magnetic resonance imaging.

areas where <sup>18</sup>F-FDG-PET/CT is not available.<sup>22</sup> Albano et al compared WB-MRI and <sup>18</sup>F-FDG-PET/CT in staging 68 patients with FDG-avid lymphomas, including 37 HLs.<sup>34</sup> The agreement between

the two procedures was excellent ( $k = 0.92$ ) in HL (concurrency in 35/37, 95%). WB-MRI overstaged one patient with HL considering involved a peri-aortic lymph node without FDG uptake and understaged a patient with a lung lesion wrongly interpreted as a peribronchial lymph node.<sup>34</sup> In another study, the same authors have recently reported that DWI could be helpful to differentiate responder from nonresponder HL lesions on interim-WB-MRI during ABVD treatment (Figure 1).<sup>35</sup> Interestingly, Horger et al have demonstrated a significant increase of ADC of responding lesions in successfully treated HL and NHL since early after the first chemotherapy course whereas nonresponding lesions showed unchanged ADC values. Size changes were also recorded although at a less marked extent between responding and nonresponding lesions.<sup>36</sup> Latifoltojar et al recently confirmed the value of WB-MRI for the assessment of both nodal and extranodal involvement in pediatric HL patients.<sup>37</sup> However, they stressed that disease response might have been underestimated by WB-MRI in extranodal sites, making questionable the use of this modality in place of standard examinations, namely, <sup>18</sup>F-FDG-PET/CT. Regarding standard MRI features, both T2 signal intensity and contrast enhancement of lymphomatous lesions have a tendency to decrease after treatment.<sup>38</sup> However, these findings cannot be used to differentiate responding from nonresponding lesions. The reduction of T2 signal may be related to fibrotic stroma and collagen; nevertheless, immature fibrotic tissue, necrosis, or edema can produce an increase T2 signal limiting its utility in this setting.<sup>38</sup>

WB-MRI has also shown effectiveness to detect certain and recently described complications, namely, the osteonecrosis, that may occur in HL patients treated with chemotherapeutic regimens including high doses of corticosteroids. Indeed, a proven association between dose of steroids, courses of chemotherapy, and risk of osteonecrosis has been reported.<sup>39,40</sup> In this setting, WB-MRI is the optimal imaging modality taking advantage of the well-established excellent accuracy of MRI to early identify osteonecrosis and the



**FIGURE 1** A 31-year-old man with Hodgkin lymphoma (HL). Pre-treatment coronal short tau inversion recovery (STIR) (A), postcontrast coronal 3D-GRE T1-weighted (B), coronal maximum intensity projection (MIP) grey-scale inverted diffusion-weighted imaging (DWI) (C), and axial apparent diffusion coefficient (ADC) map (D) show multiple nodal locations in mediastinal and supraclavicular regions (A,B,C; arrows), with very low ADC values (D, arrow); ADC map after two courses of ABVD treatment (E) shows the substantial size reduction of mediastinal lymph nodes that also present high ADC values (arrowhead)

possibility to investigate all skeletal segments with a single test (Figure 2).<sup>41,42</sup>

In HL patients, WB-MRI can be considered a complementary imaging modality that could take the place of CECT in diagnostic workup and lymphoma surveillance, especially in young patients, but, to date, WB-MRI will hardly replace <sup>18</sup>F-FDG-PET/CT for staging and response assessment of HL.

#### 4 | AGGRESSIVE LYMPHOMAS

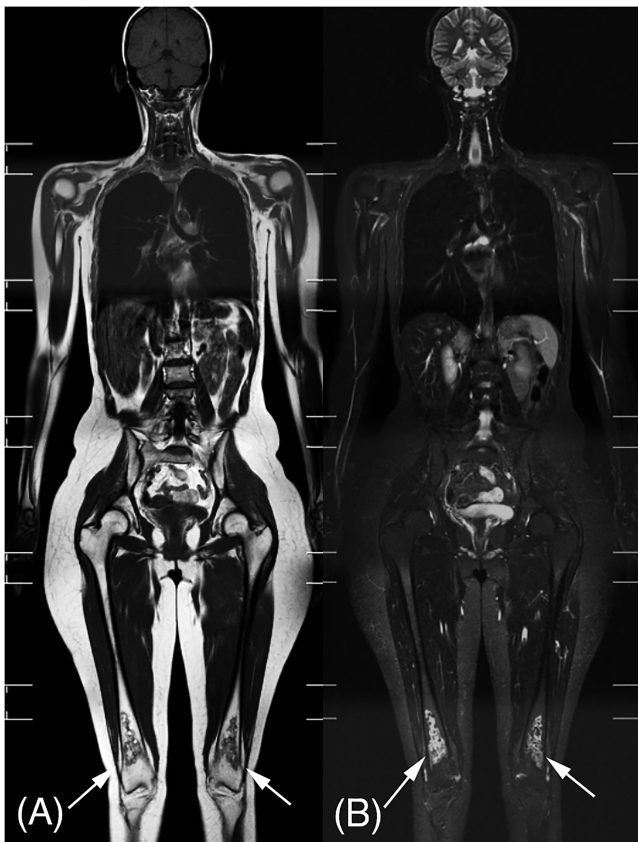
The aggressive lymphoma subgroup includes several subtypes characterized by rapid tumor growth and the usual need of immediate treatment. Diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Burkitt lymphoma, and peripheral T-cell lymphomas represent the main aggressive subtypes. DLBCL is the most common accounting for approximately 30% of all NHLs.<sup>43,44</sup> DLBCL, like most aggressive lymphomas, displays high FDG uptake.<sup>45</sup> Distinct features are shown by MCL, which accounts for approximately 2% of all NHLs, and, as opposed to DLBCL, has variable behavior on <sup>18</sup>F-FDG-PET/CT.<sup>46,47</sup>

Several studies have investigated the diagnostic performance of WB-MRI in aggressive lymphomas in comparison with <sup>18</sup>F-FDG-PET/CT and/or CECT. Most of these works included different lymphoma

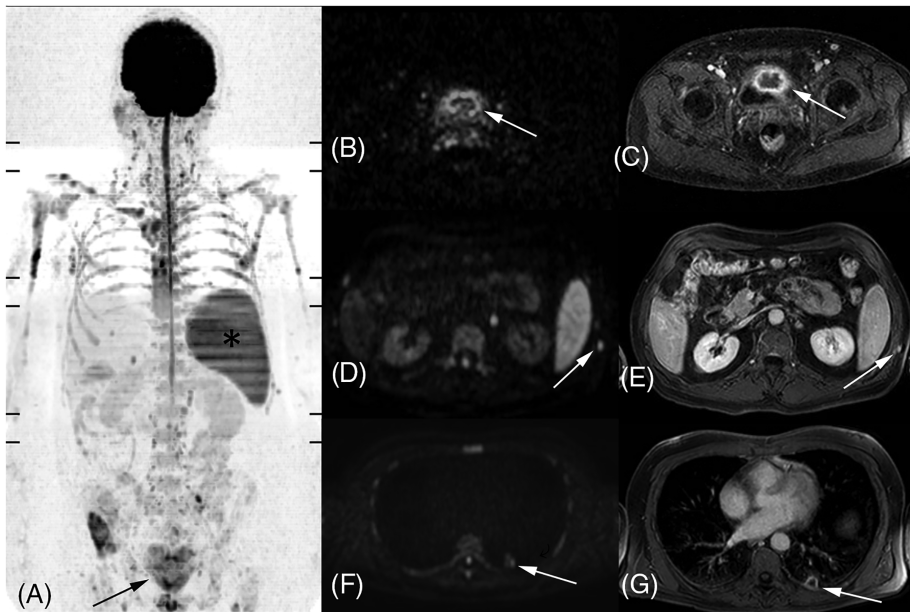
subtypes.<sup>18,48-51</sup> Lin et al have demonstrated the value of WB-MRI in diagnostic workup of DLBCL, showing whole agreement between WB-MRI and <sup>18</sup>F-FDG-PET/CT in staging 93% of patients.<sup>51</sup> Abdulqadhr et al compared WB-MRI with <sup>18</sup>F-FDG-PET/CT for staging of 31 patients, including 18 aggressive subtypes (13 DLBCLs, three primary mediastinal B-cell lymphomas, one anaplastic large cell lymphoma, and one T-cell lymphoma). Patients were uniformly staged by both modalities with perfect agreement (18/18, 100%) in stage definition (Figures 3 and 4).<sup>52</sup> Similarly, Mayerhoefer et al demonstrated a quite good agreement (93%) between WB-MRI and <sup>18</sup>F-FDG-PET/CT in a series of 28 DLBCLs.<sup>22</sup> MCL is often staged with CECT, due to the variable FDG uptake in MCL. However, CECT provides just morphological information, and it has lower sensitivity for the assessment of bone marrow involvement (BMI) than WB-MRI.<sup>22,47</sup> A few studies have compared WB-MRI and CECT stressing the higher accuracy of WB-MRI compared with CECT. This is associated with the well-known advantages of WB-MRI, namely, its radiation-free imaging modality with no need of contrast injection.<sup>49,50,53</sup> In particular, Kwee et al compared WB-MRI and CECT in 104 patients, including 34 DLBCLs and eight MCLs, showing an agreement in staging definition for approximately two-thirds of patients. WB-MRI allowed a correct upstaging in almost 30% of patients due to a better evaluation of BMI, although it led to an incorrect downstaging in 6.7%, due to omitted detection of some pleural/lung and lymph nodal involvements.<sup>49</sup>

The evaluation of BMI is a crucial step in lymphoma staging, and it is usually performed through bone marrow biopsy (BMB), at least in NHLs.<sup>5</sup> WB-MRI is well established to investigate diffuse and focal BMI, and several reports have investigated WB-MRI performance to detect lymphomatous BMI.<sup>19,53</sup> In aggressive lymphomas, WB-MRI has shown to be accurate especially to identify focal BMI, which can be occasionally missed by BMB.<sup>54</sup> Notably, Adams et al have shown an increased risk of disease progression and death in DLBCL patients with WB-MRI positive for lymphomatous BMI in comparison with WB-MRI negative patients, suggesting a potential prognostic role of WB-MRI in DLBCL patients with negative BMB.<sup>55</sup> However, the accuracy of DWI and ADC values to detect BMI and to assess treatment response is still an issue of controversy, with some authors reporting no significant differences between lymphomatous BMI and normal bone marrow while others support the possible role of ADC values to assess short-term response to treatment.<sup>19,56</sup>

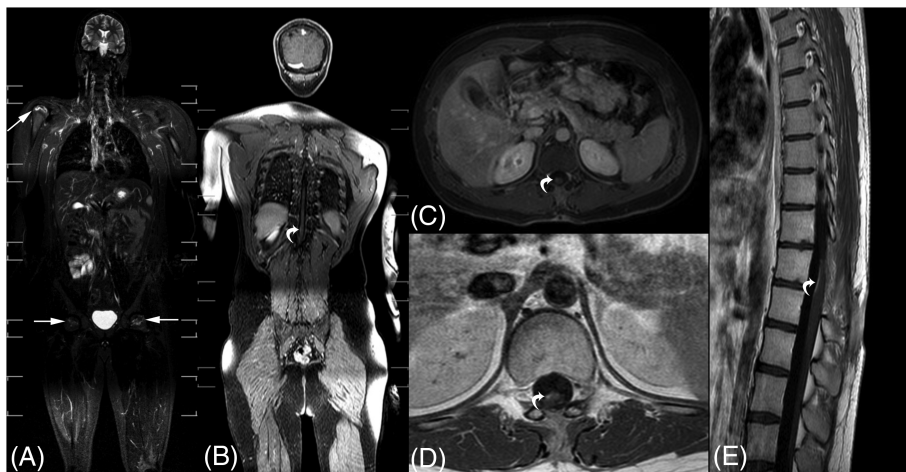
The potential role of WB-MRI to assess treatment response in DLBCL has been addressed in several studies. Early in 2011, Lin et al reported a significant increase of ADC in enlarged masses persisting after therapy.<sup>57</sup> Similar results were obtained by De Paepe et al in 14 aggressive lymphoma patients (12 DLBCLs and two T-cell lymphomas) undergoing WB-MRI at 3T MRI before therapy, after two courses and at therapy completion.<sup>58</sup> ADC measurements allowed to differentiate responder from nonresponder nodal/extranodal lesions with 100% negative predictive value and 86% positive predictive value, also with significant correlation between ADC changes and progression free survival ( $P < .05$ ).<sup>58</sup> Conversely, size changes of the lesions did not enable to correctly assess early treatment response. The reported



**FIGURE 2** A 28-year-old woman with Hodgkin lymphoma (HL) treated by BEACOPP. Coronal T1-weighted (A) and short tau inversion recovery (STIR) images (B) after treatment show osteonecrotic lesions of both femurs (arrows)



**FIGURE 3** A 62-year-old man with peripheral T-cell lymphoma. Coronal maximum intensity projection (MIP) grey-scale inverted diffusion-weighted imaging (DWI) (A), axial DWI (B,D,F), and axial postcontrast 3D-GRE T1-weighted images (C,E,G) show multiple extranodal locations (arrows): prevescical (A,B,C), subcutaneous (D,E), and pulmonary (F,G). Also note the enlargement of the spleen (A; asterisk)



**FIGURE 4** A 23-year-old man with relapsed mantle cell lymphoma (MCL) after chemotherapy and transplant. Coronal short tau inversion recovery (STIR) (A), coronal postcontrast 3D-GRE T1-weighted (B), axial postcontrast 3D-GRE T1-weighted (C), axial postcontrast T1-weighted (D), and sagittal postcontrast T1-weighted images (E) show meningeal recurrence in thoracic medullary cord (curved arrows). Also note the osteonecrotic lesions in the right humeral head and in both femoral heads (A; arrows) due to the high doses of corticosteroids received by the patient after transplant

results support the value of DWI-MRI with ADC measurement for the short-term response evaluation in lymphoma.<sup>58</sup> Mayerhoefer et al in a recent study on 64 patients (22 aggressive lymphomas) proved that WB-MRI is almost equal to <sup>18</sup>F-FDG-PET/CT for both response assessment after few (one to three therapy cycles) chemotherapy courses and at end-of-treatment evaluation.<sup>48</sup> The authors propose a possible correlation between cell density (higher diffusion restriction on DWI and lower ADC values) and glucose consumption (FDG uptake).<sup>59</sup> Indeed, the possible correlation between DWI/ADC and lymphoma proliferation remains a controversial issue. Previous studies have shown no correlation between ADC values and SUV<sub>max</sub> of lymphoma sites in both NHL and HL.<sup>35,60</sup> Conversely, a recent study has shown an inverse correlation between ADC and KI-67 index.<sup>61</sup> Future radiomic studies may clarify the degree of correlation among MRI, <sup>18</sup>F-FDG-PET/CT, CECT and histology, cell proliferation, and even molecular features of various aggressive lymphoma subtypes.

The prognostic impact of BMI in DLBCL patients has been discussed for years, and no univocal conclusions have been reached yet. In the future, the widespread use of WB-MRI in patients with lymphoma could be helpful to clarify this controversial point.

## 5 | INDOLENT LYMPHOMAS

The indolent lymphoma (i-NHL) subgroup includes slow-growing malignancies characterized by prolonged natural history and generally few if any clinical symptoms.<sup>62</sup> Follicular lymphoma (FL) is the most common i-NHL and represents more than 20% of all NHLs. Generally, immediate treatment is not needed for i-NHLs, with watchful waiting (WW) being considered a reasonable strategy in most cases. Treatment is delayed as much as possible, and monitoring these patients with imaging follow-up, laboratory tests, and clinical examinations is the main recommendation.<sup>63,64</sup> Imaging during WW is performed

through  $^{18}\text{F}$ -FDG-PET/CT and/or CECT for FDG-avid lymphomas like FL, whereas CECT is recommended for non-FDG-avid subtypes.<sup>65,66</sup>

Previous studies have demonstrated that WB-MRI is a useful diagnostic approach for i-NHL (Figure 5), with reports documenting that WB-MRI has equal or even greater accuracy than CECT in staging workup.<sup>49,67</sup> Balbo-Mussetto et al included 16 i-NHLs (13 FLs and three MCLs) in their series of 41 patients, who underwent WB-MRI, CECT, and  $^{18}\text{F}$ -FDG-PET/CT.<sup>67</sup> In their study, WB-MRI was superior to CECT, especially to detect extranodal locations, with some false negatives nodes in mediastinum, which is the intrinsic weakness of WB-MRI.<sup>21</sup> Kwee et al compared WB-MRI without DWI, WB-DWI-MRI, and CECT in 108 patients; almost half of them were i-NHLs.<sup>49</sup> WB-MRI allowed to obtain the same stage as with CECT, without any reported advantage by adding DWI. WB-MRI showed to be more accurate to detect BMI but missed some involved lymph nodes and some lung/pleural and liver lesions. Regarding focal hepatic lesions, the main problem of WB-MRI was the wrong interpretation of hemangiomas. In this setting, contrast media injection could be helpful, as demonstrated for the detection of splenic HL involvement.<sup>24</sup> About the utility of DWI, several authors have proven its key role in WB-MRI staging of lymphomas. Littooi et al confirmed the strength of WB-DWI-MRI in the detection of residual disease after therapy. This is especially true if the procedure includes the quantitative assessment of diffusion restriction with ADC that gives information regarding tissue viability.<sup>68</sup> In their series of 31 patients with lymphoma, Abdulqadhr et al found disagreements between WB-MRI and  $^{18}\text{F}$ -FDG-PET/CT in three i-NHL patients, with WB-MRI allowing a correct upstaging of disease.<sup>52</sup> Stecco et al found an excellent agreement between WB-MRI and  $^{18}\text{F}$ -FDG-PET/CT in staging gastrointestinal lymphomas in a series of 17 patients including 12 i-NHLs.<sup>69</sup> In a series of FL patients, Mayerhoefer et al reported a strong agreement (26/28, 93%) between WB-MRI and  $^{18}\text{F}$ -FDG-PET/CT.<sup>22</sup> The same authors demonstrated that the sensitivity of WB-MRI (94.4%) is much higher than that of  $^{18}\text{F}$ -FDG-PET/CT (60.9%) and CECT (70.7%) in lymphoma

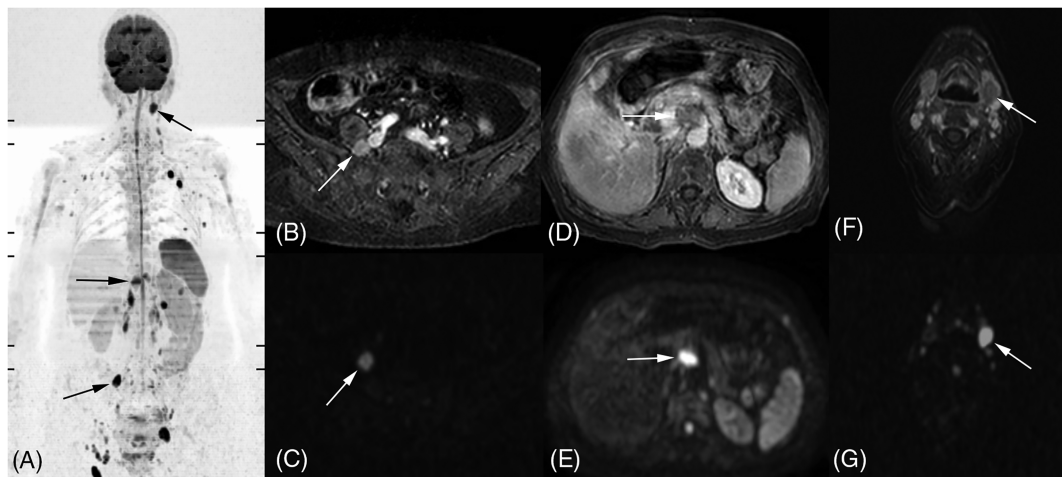
subtypes with variable FDG avidity, in particular mucosa-associated lymphoid tissue (MALT) lymphomas.<sup>22</sup> Furthermore, in a small series of patients with MALT lymphoma treated with rituximab, both quantitative evaluation obtained on  $^{18}\text{F}$ -FDG-PET/CT ( $\text{SUV}_{\text{max}}$  and  $\text{SUV}_{\text{mean}}$ ) and WB-DWI-MRI ( $\text{ADC}_{\text{min}}$  and  $\text{ADC}_{\text{mean}}$ ) seemed to be able to predict complete remission after therapy.<sup>70</sup> Of note, Mosavi et al evaluated 50 patients with lymphoma (12 HLs, 29 aggressive lymphomas, and nine i-NHLs) by WB-MRI and reported significantly lower ADC values in i-NHLs than in other lymphomas. This suggests the potential application of WB-MRI to detect the transformation of i-NHLs in aggressive NHL.<sup>71</sup> As previously mentioned, both  $^{18}\text{F}$ -FDG-PET/CT and WB-MRI have shown to be valid tools to detect BMI in aggressive lymphomas. However, this does not hold true in i-NHLs, where both  $^{18}\text{F}$ -FDG-PET/CT and WB-MRI are considered complementary imaging modalities to BMB.<sup>19,72</sup>

It should be stressed that  $^{18}\text{F}$ -FDG-PET/CT is pivotal in FL management.  $^{18}\text{F}$ -FDG-PET/CT is the most accurate modality for FL staging<sup>73</sup> and allows to identify FL transformation presenting with significantly increased FDG uptake in transformed areas.<sup>74</sup> This is especially crucial in FL that shows the highest risk of secondary transformation among all i-NHLs.<sup>75</sup>

WB-MRI should be considered as a valid imaging tool in disorders with long life expectancy like nonfollicular i-NHLs, potentially replacing diagnostic examinations that expose to ionizing radiations. This could be helpful in the effort to reduce toxicity and cancer risk related to treatments.

## 6 | FUTURE PERSPECTIVES

The introduction of  $^{18}\text{F}$ -FDG-PET/MRI is of great interest for its potential application in lymphoma, although its role has not been fully established. This modality enables to reduce radiation exposure compared with  $^{18}\text{F}$ -FDG-PET/CT, and it represents a valuable option especially in pediatric patients suffering from lymphoma. Besides the



**FIGURE 5** A 62-year-old man with follicular lymphoma (FL). Coronal maximum intensity projection (MIP) grey-scale inverted diffusion-weighted imaging (DWI) (A), axial postcontrast 3D-GRE T1-weighted (B,D,F), and axial DWI (C,E,G) show multiple nodal locations (arrows) in right common iliac level (A,B,C), celiac trunk (A,D,E), and left laterocervical region (A,F,G)

advantage of the high contrast resolution, MRI with the use of both DWI and PET findings allows to obtain a combined “functional” evaluation of cell density and metabolic activity.<sup>76,77</sup> Indeed, the addition of DWI to PET/MRI is still debatable in lymphoma. A recent study in 34 lymphoma patients demonstrated that <sup>18</sup>F-FDG-PET/MRI without DWI and <sup>18</sup>F-FDG-PET/CT have similar accuracy in HL and aggressive NHL.<sup>78</sup> However, the inclusion of DWI in <sup>18</sup>F-FDG-PET/MRI protocol allowed to achieve higher diagnostic performance than <sup>18</sup>F-FDG-PET/CT, especially in MALT lymphomas.<sup>78</sup> Conversely, Afaq et al did not report any improvement of diagnostic performance of <sup>18</sup>F-FDG-PET/MRI by adding DWI.<sup>79</sup> Hermann et al evaluated 61 patients reporting similar diagnostic performance of <sup>18</sup>F-FDG-PET/MRI and <sup>18</sup>F-FDG-PET/CT.<sup>80</sup> This led the authors to postulate that WB-MRI may have a role in specific settings such as imaging surveillance and i-NHLs.<sup>80</sup>

New interesting perspectives include also the application of texture analysis on WB-MRI performed in lymphoma patients, although few studies have focused on this tool. Radiomics extracts a large number of image features, which can be “seen” only by computers, being beyond human perception.<sup>81</sup> Texture analysis can quantify the spatial pattern and arrangement of pixel intensities in medical images allowing to provide crucial information regarding tumor phenotype, thereby highlighting intratumor heterogeneity. Several works have demonstrated that this heterogeneity could have remarkable implications on tumor prognosis being a typical pattern of malignancies associated with aggressive behavior and poor response to therapies.<sup>82,83</sup> In a recent study on 28 patients with NHL, De Paepe et al have demonstrated that first-order ADC texture analysis on WB-DWI-MRI at 3T can increase the accuracy of lymph node characterization in comparison with ADC<sub>mean</sub>.<sup>84</sup> Wu et al have explored the applicability of texture analysis on postcontrast T1-weighted MRI images to differentiate FL and DLBCL reporting high diagnostic accuracy to distinguish these subtypes.<sup>85</sup> Thus, this tool could be potentially helpful to early identify a transformed lymphoma during imaging follow-up of FL. However, there is still poor knowledge on this topic, and more studies are needed to clarify the practical use of radiomics applied to the different imaging techniques.

## 7 | CONCLUSIONS

WB-MRI is an important novel diagnostic tool in lymphoma. However, its precise role in diagnostic workup has not been clearly defined. WB-MRI seems a less histology-dependent functional imaging test than <sup>18</sup>F-FDG-PET/CT. Moreover, it does not require radiation exposure. In patients with FDG-avid lymphomas, such as DLBCL and HL, <sup>18</sup>F-FDG-PET/CT remains the imaging reference standard for staging, with WB-MRI potentially being a complementary modality that could replace CECT, especially in young patients. On the other hand, WB-MRI is a valuable imaging procedure for lymphoma surveillance, in lymphomas with variable/low FDG avidity and nonfollicular indolent lymphomas.<sup>86</sup> According to the directive 2013/59 by the European Union,<sup>86</sup> whether a radiation-free imaging modality guarantees the same diagnostic results, it should always be preferred. Based on this

recommendation, the use WB-MRI should be further explored and viewed with particular interest by the scientific community to define the ideal place of WB-MRI in diagnostic imaging pathway for patients with lymphoma.

## FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional Review Board approval was not required for the present study as patients are not involved.

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**How to cite this article:** Albano D, Bruno A, Patti C, et al. Whole-body magnetic resonance imaging (WB-MRI) in lymphoma: State of the art. *Hematological Oncology*. 2020;38:12-21. <https://doi.org/10.1002/hon.2676>