

## Evaluation of Diffusion-Weighted MRI for Pretherapeutic Assessment and Staging of Lymphoma: Results of a Prospective Study in 140 Patients

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### Abstract

**Purpose:** To determine the value of diffusion-weighted MRI (DWI-MRI) for pretherapeutic imaging of fluorodeoxyglucose (FDG)-avid lymphoma and lymphoma with variable FDG avidity.

**Experimental Design:** Treatment-naïve patients with lymphoma who were referred for whole-body staging were included in this prospective study. Group A included patients with FDG-avid lymphoma (e.g., Hodgkin, diffuse large B-cell, and follicular lymphoma), whereas Group B included patients with lymphoma of variable FDG avidity [e.g., extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)]. All patients underwent DWI-MRI and 18F-FDG-positron emission tomography/computed tomography (PET/CT). Region-based sensitivity and agreement with Ann Arbor staging, relative to the reference standard, were calculated for DWI-MRI, and, in Group B, also 18F-FDG-PET/CT and contrast-enhanced (CE-) CT.

**Results:** In Group A (100 patients), DWI-MRI had a region-based sensitivity of 97%, and with regard to staging, agreed with the reference standard in 94 of 100 patients ( $\kappa$ , 0.92). In Group B (40 patients; 38 MALT lymphomas and 2 small lymphocytic lymphomas/chronic lymphocytic leukemias), DWI-MRI, 18F-FDG-PET/CT, and CE-CT had region-based sensitivities of 94.4%, 60.9%, and 70.7%, respectively. With regard to staging in Group B, DWI-MRI, 18F-FDG-PET/CT, and CE-CT agreed with the reference standard in 37 of 40, 26 of 40, and 24 of 40 patients, with  $\kappa$  values of 0.89, 0.52, and 0.43, respectively.

**Conclusions:** In patients with FDG-avid lymphoma, DWI-MRI seems to be only slightly inferior to 18F-FDG-PET/CT with regard to pretherapeutic regional assessment and staging. In patients with lymphoma subtypes that show a variable FDG avidity (e.g., MALT lymphoma), DWI-MRI seems to be superior to both 18F-FDG-PET/CT and CE-CT. *Clin Cancer Res*; 20(11); 2984–93. ©2014 AACR.

### Introduction

Positron emission tomography/computed tomography (PET/CT) after application of the radiotracer 18F-fluorodeoxyglucose (FDG) is the current functional imaging method of choice for the most common lymphoma subtypes, because it visualizes the elevated glucose metabolism in these lesions (1–6). Although the benefits of this

imaging technique clearly outweigh the detriments, 18F-FDG-PET/CT is associated with a nonnegligible radiation dose, which is of particular concern for younger patients, because of the risk of radiation-induced secondary malignancies. Although of lesser relevance, 18F-FDG-PET/CT is also cost intensive, and because most PET/CT devices are installed at metropolitan tertiary care centers, country-wide access is limited. Furthermore, certain lymphoma subtypes, such as extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT), are frequently not FDG-avid (1, 7–10), and thus, 18F-FDG-PET/CT is generally not recommended in these cases (11). In the latter lymphoma subtypes, contrast-enhanced (CE) CT, which relies exclusively on morphology, is therefore the standard imaging test, because no functional technique has been established so far.

Recently, it has been proposed that diffusion-weighted imaging (DWI), a functional MRI technique that relies on the restriction of water movement in hypercellular tumors due to extracellular space narrowing, may represent a

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### Translational Relevance

Diffusion-weighted imaging (DWI) is a functional MRI technique that enables an indirect assessment of cell density. Our results suggest that in patients with FDG-avid lymphoma [e.g., Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma], DWI-MRI may be an alternative to 18F-FDG-PET/CT, which is the current imaging reference standard, for pretherapeutic staging. In patients with lymphoma subtypes with a variable FDG avidity, and in particular, MALT lymphoma, DWI-MRI seems to be clearly superior not only to 18F-FDG-PET/CT, but also to contrast-enhanced CT, which is the currently recommended imaging test in this group of lymphomas. These findings are of particular relevance for younger patients with lymphoma, because, contrary to 18F-FDG-PET/CT or CE-CT, DWI-MRI is not associated with potentially harmful radiation, and may thus be better suited for life-long follow-up.

possible, radiation-free alternative to 18F-FDG-PET/CT for lymphoma staging (12). Notably, several recent, smaller-sized studies suggest that DWI-MRI may—similar to 18F-FDG-PET/CT, and unlike standard morphologic MRI or CE-CT—possibly be able to distinguish between vital tumor tissue and residual changes (e.g., fibrosis) after therapy (13–17). The data that support the notion that DWI-MRI is comparable with 18F-FDG-PET/CT for lymphoma staging are, however, mainly based on patients with diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma, and/or a limited sample size (18–21). Very little data are available with regard to the comparative performances of DWI-MRI and 18F-FDG-PET/CT in patients with indolent Non-Hodgkin lymphomas.

It was thus the aim of the present, prospective study to determine, in a larger patient cohort, whether (1) DWI-MRI can indeed serve as a radiation-free alternative to 18F-FDG-PET/CT in lymphoma subtypes for which PET/CT is the current imaging reference standard; and (2) whether DWI-MRI might be superior to 18F-FDG-PET/CT, and also to CE-CT, in terms of sensitivity, specificity, and for pretherapeutic staging, in the (mostly indolent) lymphoma subtypes for which a variable FDG avidity has been reported, and for which no established functional imaging technique exists at present.

### Patients and Methods

#### Patients and design

Our prospective, Institutional Review Board–approved study included treatment-naïve patients with lymphoma that were referred to the Department of Radiology and Nuclear Medicine of the local tertiary care center for pretherapeutic whole-body staging between August 2011 and August 2013. Lymphoma subtypes were diagnosed on the basis of tissue samples obtained by biopsy or surgery,

according to the criteria outlined in the current World Health Organization (WHO) classification of hematologic and lymphoid malignancies, by a reference pathologist. Patients who gave written informed consent were referred for DWI-MRI and 18F-FDG-PET/CT, with a maximum of 7 days between the examinations. Pregnancy, general contraindications to MRI, and therapeutic interventions between DWI-MRI and 18F-FDG-PET/CT were used as exclusion criteria.

#### Imaging

MRI was performed on a 3 Tesla system (TrioTim; Siemens). A single-shot, echo-planar imaging-based, spectral adiabatic inversion recovery DWI sequence was obtained with *b* values of 50 and 1,000, a repetition time (TR)/echo time (TE) of 5,100/73 ms, 5 averages, 86 phase encoding steps, a 192 × 115 matrix, and a 5-mm slice thickness with no gap. Images were obtained during free breathing, with a scan duration of 4 minutes and 5 seconds per body region; only for the lower neck and the chest, respiratory triggering was used, which increased the scan duration per region to 5 minutes and 2 seconds. Apparent diffusion coefficient (ADC) maps were calculated. In addition, a T1-weighted turbo spin-echo (scan duration, 1 minutes and 5 seconds per body region) or, in case of breathing difficulties, a fast gradient-echo (FLASH, fast low angle short) sequence (scan duration, 43 seconds per body region) was obtained for better anatomic/morphologic correlation, and to generate fused color-coded DWI-MRI images. Altogether, four to five image stacks (i.e., body regions), depending on the height of the patient, were necessary to cover the anatomy (vertex to upper thigh).

18F-FDG-PET/CT was performed using a 64-row multi-detector PET/CT system (Biograph TruePoint64; Siemens). Patients fasted for 5 hours before imaging; the glucose cutoff level was 150 mg/dL. PET was performed 50 to 60 minutes after the intravenous administration of 300 MBq of 18F-FDG, with 3-minutes/bed position. PET images were reconstructed using the TrueX algorithm, with four iterations per 21 subsets, a 5-mm slice thickness, and a 168 × 168 matrix. According to our standard clinical PET/CT protocol, venous-phase CE-CT was obtained, in all patients, after the intravenous injection of 100 mL of a tri-iodinated, nonionic contrast medium (Iomeron 300; Bracco) at a rate of 2 mL/s, followed by a 50 mL saline flush; a tube voltage of 120 mA, a tube current of 230 kV, a collimation of 64 × 0.6 mm, a slice thickness of 3 mm with 2 mm increment, and a 512 × 512 matrix, were used. The duration of the PET/CT scan (i.e., time spent in the scanner) was approximately 20 minutes.

#### Image interpretation

The 14 nodal regions defined at the Rye symposium (22), and the following 12 extranodal regions were evaluated: Waldeyer ring, lungs, liver, spleen, stomach, small intestine, large intestine, right kidney, left kidney, bones, soft tissues (skin/fat/muscle), and other organs/tissues (e.g., salivary glands). On the basis of the above, staging according to the modified Ann Arbor system (stages I to IV) was performed.

In addition, stage 0 was reported when, following surgery, no further lesions were observed. All raters were blinded to the clinical information, including the histologic subtypes.

DWI-MRI was evaluated independently by two board-certified radiologists who were blinded to the corresponding 18-F-FDG-PET/CT and CE-CT. Regions were rated as positive for lymphoma when at least one lymph node or lesion showed a restricted diffusion on DWI, defined as a high signal on the b50 images (relative to the surrounding tissues), and a persistence or increase of the signal on the b1000 images (relative to the b50 images, and the surrounding tissues), or a high signal on the b50 images and low signal on the ADC map (relative to the surrounding tissues; ref. 23). Because the normal spleen frequently shows a higher signal on DWI than other abdominal or retroperitoneal organs (24, 25), signal inhomogeneity or well-circumscribed lesions with restricted diffusion were rated as positive in this organ. The bone marrow was rated as positive when, in addition to diffusion restriction, there was a low signal on the T1-weighted images. Following the raters' independent regional assessment and staging, a consensus reading was performed.

18F-FDG-PET/CT was evaluated independently by two board-certified nuclear medicine physicians who were blinded to the corresponding DWI-MRI. Nodal and extranodal regions were rated as positive for lymphoma when there was at least one focal (or, for bone marrow, diffuse) area of increased tracer accumulation on PET, relative to the surrounding tissue or mediastinal blood pool activity. The spleen was rated as positive if the tracer uptake was higher than that in the liver (2), or if well-circumscribed FDG-avid lesions were present. For the PET/CT evaluation, CE-CT was used primarily for anatomic correlation and morphologic lesion confirmation. Similar to DWI-MRI, a consensus rating was performed following the raters' independent regional assessment and staging.

CE-CT as a "stand-alone" technique was only evaluated in patients from Group B, in which it is the current standard imaging test, according to the guidelines. CE-CT evaluation was performed independently by two board-certified radiologists who were not identical to those who evaluated DWI-MRI, and who were blinded to the corresponding 18F-FDG-PET and PET/CT, as well as to DWI-MRI. Lymph nodes were rated as positive if they had a long-axis diameter >1.5 cm, or a long axis and short-axis diameter of each >1 cm, according to the Cheson criteria (3). For extranodal regions, no size criteria were applied, but instead, all noncystic, non-fatty lesions (i.e., those with Hounsfield units >20) were rated as positive for lymphoma, unless they showed well-established benign features (e.g., nodular peripheral enhancement in hemangiomas of the liver or calcified fibroids of the uterus). Again, a consensus reading was performed, following the raters' independent regional assessment and staging.

#### Reference standard and statistical analysis

On the basis of our histologic subtype assessment and the rates of FDG avidity for the different lymphoma subtypes as

established by Weiler-Sagie in a cohort of 766 patients (1), patients were divided into two groups:

- Group A included patients with lymphomas for which a high FDG avidity (90%–100%) had been reported; and
- Group B included patients with lymphomas for which a variable FDG avidity (<90%) had been reported.

In Group A, a sample size calculation ( $\alpha$ , 0.05) based on 95% confidence intervals (CI) for relative frequencies revealed that, for an expected region-based sensitivity of 85% for DWI-MRI, 196 lymphoma-positive regions would be required. On the basis of the assumption that approximately two regions per patient would be positive for lymphoma, at least 98 patients would be required. Patient-based, as well as region-based sensitivities of DWI-MRI (consensus rating), calculated separately for nodal, extranodal, and all regions combined, were used as the main outcome measure; specificities were also calculated. 18F-FDG-PET/CT formed the basis of the reference standard; only for regions that were biopsied was histology used rather than the PET/CT result, and any disagreement between 18F-FDG-PET/CT and histology was recorded.

In Group B, a sample size calculation ( $\alpha$ , 0.05; power, 0.8) based on  $\chi^2$  testing of equal proportions revealed that to detect an estimated patient-based sensitivity difference of 25% between 18F-FDG-PET/CT (expected sensitivity, 70%) and DWI-MRI (expected sensitivity, 95%), a sample size of at least 36 patients would be required. The expected sensitivity of 70% for 18F-FDG-PET/CT was based on the arithmetic mean of the patient-based sensitivities of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) and MALT lymphoma, the two most common types of Non-Hodgkin lymphoma with variable FDG avidity (1). Patient- and region-based (nodal, extranodal, and combined) sensitivities of DWI-MRI, 18F-FDG-PET/CT, and CE-CT were used as main outcome measures; specificities were also calculated. In addition, sensitivities and specificities were also assessed for the combination of 18F-FDG-PET/CT and CE-CT; here, patients and regions were rated as positive if either 18F-FDG-PET/CT, or CE-CT, or both, were positive. In this group, histology formed the basis of the reference standard; in particular, all extranodal manifestations had to be biopsied. For nodal sites not biopsied (e.g., when multiple nodal regions were involved), agreement between the three imaging techniques was considered as sufficient proof, provided that involvement of at least one nodal region was confirmed histologically. If there was no agreement between the three imaging techniques, the lymph node had to be biopsied (provided that the information was relevant for staging and treatment decisions), or there had to be a size progression or regression of at least a single node per region, according to the Cheson criteria (3), on 3-month follow-up imaging after therapy.

General estimation equations (GEE) were used for sensitivity and specificity comparisons (to take multiple regions per patient into account), and Bonferroni correction was applied, as appropriate. Kappa coefficients were used to

compare DWI-MRI-based, 18F-FDG-PET/CT-based, and in Group B, also CE-CT-based sensitivities and specificities, and also to assess interobserver agreement. In addition, combined CE-CT and 18F-PET/CT-based staging was evaluated, where, in case of a discrepancy between CE-CT and PET/CT, the higher stage was used for comparison with the reference standard. The 95% CIs were based on GEE estimations (according to Wald). In both patient groups (A+B), the reference standard for staging was the assessment by a senior oncologist who evaluated all histologic and imaging results. In addition, it was stipulated that for lymphoma subtypes with >20 patients, a separate calculation of region-based sensitivity and agreement of staging with the reference standard would be performed. The specified level of significance was  $P \leq 0.05$  for all tests.

## Results

### Patient characteristics

There were 151 patients who matched our criteria for inclusion in the study. Six of these patients were excluded because of claustrophobia, and 5 were excluded because of MR-incompatible implantable medical devices. Of the remaining 140 patients (70 females and 70 males; mean age,  $57.6 \pm 15.6$  years; age range, 19–88 years), 38 were diagnosed with MALT lymphoma, 31 with DLBCL, 28 with follicular lymphoma, 22 with Hodgkin lymphoma, 10 with nodal marginal zone lymphoma (nMZL), 6 with mantle cell lymphoma (MCL), two with SLL/CLL, 2 with peripheral T-cell lymphoma, and 1 patient with anaplastic large cell lymphoma (ALCL). Ann Arbor stage 0 was observed in 19 patients, stage I in 46 patients, stage II in 18 patients, stage III in 23 patients, and stage IV in 34 patients according to our reference standard. Nodal and extranodal involve-

ments were observed in 89 of 140 and 73 of 140 patients, respectively.

### DWI-MRI in FDG-avid lymphoma (Group A)

Group A included 100 patients with DLBCL, follicular lymphoma, Hodgkin lymphoma, nMZL, MCL, peripheral T-cell lymphoma, and ALCL. The patient-based sensitivity of DWI-MRI in this group was 97.8% (95% CI, 92.3% to 99.4%), and specificity was 100% (95% CI, 70.1% to 100.0%). Region-based sensitivities and specificities are provided in Table 1. With regard to staging, DWI-MRI agreed with the reference standard in 94 of 100 patients (94%), with  $\kappa = 0.92$  ( $P < 0.0001$ ; Table 2). Results for the individual nodal and extranodal regions are provided in Supplementary Table S1.

With more than 20 patients each, DLBCL, follicular lymphoma, and Hodgkin lymphoma were also evaluated separately. Overall region-based sensitivities for DLBCL, follicular, and Hodgkin lymphoma were 88.7% (95% CI, 70.1% to 96.3%), 97.1% (95% CI, 92.3% to 98.9%), and 89.2% (95% CI, 75.2% to 95.8%), respectively; nodal and extranodal sensitivities are provided in Fig. 1 and Supplementary Table S2. DWI-MRI sensitivities between DLBCL, follicular, and Hodgkin lymphoma did not differ significantly ( $P = 0.096$ ). 18F-FDG-PET/CT differed from histology in 1 patient with follicular lymphoma (single bone lesion missed), in 1 patient with nMZL (infradiaphragmatic nodal involvement missed), and in 2 patients with MCL (diffuse bone marrow and orbital involvement missed in 1 patient; and infradiaphragmatic nodal involvement missed in the other); 2 of these patients (one nMZL, and one MCL) would have been understaged by one stage (stage III instead of IV, and stage II instead of III). DWI-MRI provided the

**Table 1.** Region-based sensitivities and specificities (and 95% CIs) for DWI-MRI in Group A (DLBCL, follicular lymphoma, Hodgkin lymphoma, nMZL, MCL, peripheral T-cell lymphoma, and ALCL), and DWI-MRI, 18F-FDG-PET/CT<sup>a</sup>, CE-CT, and the combination of 18F-FDG-PET/CT and CE-CT<sup>b</sup> in Group B (MALT lymphoma, SLL/CLL)

	Overall (%)	Nodal (%)	Extranodal (%)
<b>Group A</b>			
DWI-MRI sensitivity	97 (93.8–100)	93.8 (90.0–97.5)	98.6 (95.8–100)
DWI-MRI specificity	99.8 (99.6–100)	99.8 (99.6–100)	99.8 (99.6–100)
<b>Group B</b>			
DWI-MRI sensitivity	94.4 (89.2–99.7)	94.9 (88.3–100)	93.9 (85.7–100)
PET/CT sensitivity <sup>a</sup>	60.9 (38.6–83.2)	64.1 (27.4–100)	57.6 (38.8–76.3)
CE-CT sensitivity	70.7 (59.7–81.8)	76.9 (63.3–90.5)	63.6 (46.5–80.8)
PET/CT+CE-CT sensitivity <sup>b</sup>	81.9 (71.5–89.1)	94.9 (83.1–98.6)	66.7 (49.6–80.2)
DWI-MRI specificity	100 (100–100)	100 (100–100)	100 (100–100)
PET/CT specificity <sup>a</sup>	99.8 (99.4–100)	99.8 (99.4–100)	99.8 (99.3–100)
CE-CT specificity	99.1 (98.5–99.7)	99 (98.3–99.8)	99.1 (98.3–99.9)
PET/CT+CE-CT specificity <sup>b</sup>	98.9 (89.0–99.4)	98.9 (97.4–99.5)	98.8 (97.5–99.5)

<sup>a</sup>CT used only for anatomic and morphologic correlation.

<sup>b</sup>Regions rated as positive if either 18F-FDG-PET/CT or CE-CT was positive.

**Table 2.** Staging of 140 patients with lymphoma: results of DWI-MRI in Group A (DLBCL, follicular lymphoma, Hodgkin lymphoma, nMZL, MCL, peripheral T-cell lymphoma, and ALCL), and DWI-MRI, 18F-FDG-PET/CT<sup>a</sup>, CE-CT, and the combination of 18F-FDG-PET/CT and CE-CT<sup>b</sup> in Group B (MALT lymphoma, SLL/CLL)

		Reference standard					
		Stage 0	Stage I	Stage II	Stage III	Stage IV	Total
Group A							
Stage 0	DWI-MRI	10	2	0	0	0	12
Stage I	DWI-MRI	0	25	1	1	0	27
Stage II	DWI-MRI	0	1	15	0	0	16
Stage III	DWI-MRI	0	0	0	19	0	19
Stage IV	DWI-MRI	0	0	0	1	25	26
Total		10	28	16	21	25	100
Group B							
Stage 0	DWI-MRI	9	2	0	0	0	11
	PET/CT <sup>a</sup>	9	9	0	0	2	20
	CE-CT	4	8	0	0	1	13
	CE-CT+PET/CT <sup>b</sup>	4	5	0	0	0	9
Stage I	DWI-MRI	0	16	0	0	0	16
	PET/CT <sup>a</sup>	0	8	1	1	0	10
	CE-CT	5	10	0	0	2	17
	CE-CT+PET/CT <sup>b</sup>	6	11	1	0	0	18
Stage II	DWI-MRI	0	0	1	0	0	1
	PET/CT <sup>a</sup>	0	1	1	0	0	2
	CE-CT	0	0	2	0	0	2
	CE-CT+PET/CT <sup>b</sup>	0	0	2	0	0	2
Stage III	DWI-MRI	0	0	0	2	0	2
	PET/CT <sup>a</sup>	0	0	0	1	0	1
	CE-CT	0	0	0	2	0	2
	CE-CT+PET/CT <sup>b</sup>	0	0	0	2	0	2
Stage IV	DWI-MRI	0	0	1	0	9	10
	PET/CT <sup>a</sup>	0	0	0	0	7	7
	CE-CT	0	0	0	0	6	6
	CE-CT+PET/CT <sup>b</sup>	1	1	0	0	7	9
Total		9	18	2	2	9	40

<sup>a</sup>CT used only for anatomic and morphologic correlation.

<sup>b</sup>In case of a disagreement between PET/CT and CE-CT, the higher stage was used.

correct result in all of these cases. With regard to staging, DWI-MRI agreed with the reference standard in 29 of 31 patients (93.5%) for DLBCL, in 26 of 28 patients (92.9%) for follicular lymphoma (Fig. 2), and in 20 of 22 patients (90.9%) for Hodgkin lymphoma, with  $\kappa$  values of 0.91 ( $P < 0.0001$ ), 0.9 ( $P < 0.0001$ ), and 0.87 ( $P < 0.0001$ ), respectively. Interobserver  $\kappa$  values for DWI-MRI and 18F-FDG-PET/CT were 0.93 ( $P < 0.0001$ ) and 0.96 ( $P < 0.0001$ ).

#### DWI-MRI versus 18F-FDG-PET/CT versus CE-CT in lymphoma with variable FDG avidity (Group B)

Group B included 40 patients, 38 with MALT lymphoma and 2 with SLL/CLL. The patient-based sensitivities of DWI-MRI, 18F-FDG-PET/CT, and CE-CT were 93.5% (95% CI, 79.3% to 98.2%), 64.5% (95% CI, 46.9% to 78.1%), and

71% (95% CI, 53.4% to 83.9%), and specificities were 100% (95% CI, 70.1% to 100%), 100% (95% CI, 70.1% to 100%), and 44.4% (95% CI, 18.9% to 73.3%), respectively. Patient-based sensitivities differed significantly between DWI-MRI and 18F-FDG-PET/CT ( $P < 0.0001$ ), DWI-MRI and CE-CT ( $P = 0.003$ ), but not between 18F-FDG-PET/CT and CE-CT ( $P = 0.41$ ). Patient-based specificities differed significantly between DWI-MRI and CE-CT ( $P = 0.001$ ), and between 18F-FDG-PET/CT and CE-CT ( $P = 0.001$ ), but not between DWI-MRI and 18F-FDG-PET/CT ( $P = 1.0$ ). The combination of 18F-FDG-PET/CT and CE-CT (i.e., patients rated as positive if at least one imaging test gave a positive result) yielded a patient-based sensitivity of 77.4% (95% CI, 60.2% to 88.6%), and a specificity of 44.4% (95% CI, 18.9% to 73.3%), which differed

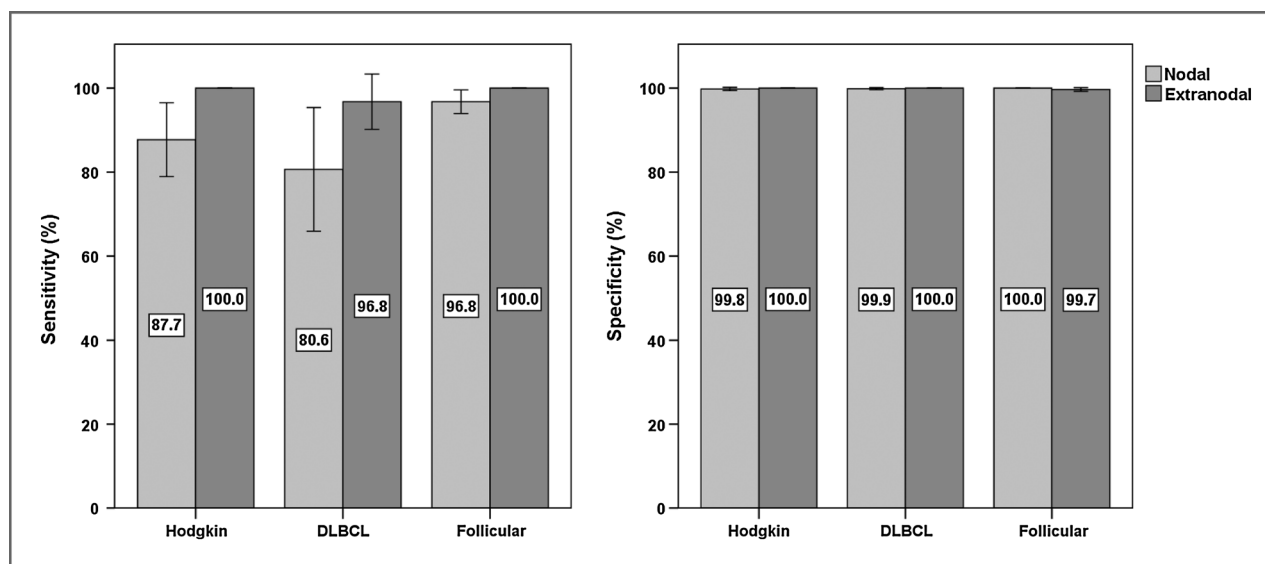


Figure 1. Bar charts depicting the region-based sensitivities and specificities of DWI-MRI for detection of nodal and extranodal involvement in patients with DLBCL, follicular lymphoma, and Hodgkin lymphoma.

significantly from DWI-MRI sensitivity ( $P = 0.015$ ) and specificity ( $P = 0.001$ ). Region-based sensitivities and specificities are provided in Table 1. Region-based sensitivities differed significantly between DWI-MRI and 18F-FDG-PET/CT ( $P = 0.007$ ), and DWI-MRI and CE-CT ( $P < 0.0001$ ), but not between 18F-FDG-PET/CT and CE-CT ( $P = 0.46$ ); whereas region-based specificities differed significantly between DWI-MRI and CE-CT ( $P = 0.003$ ), but not between DWI-MRI and 18F-FDG-PET/CT ( $P = 0.31$ ), or 18F-FDG-PET/CT and CE-CT ( $P = 0.059$ ). The combination of 18F-FDG-PET/CT and CE-CT (i.e., regions rated as positive if at least one imaging test gave a positive result) differed significantly from DWI-MRI in terms of region-based sensitivity ( $P = 0.031$ ) and specificity ( $P = 0.001$ ). With regard to staging, DWI-MRI agreed with the reference standard in 37 of 40 patients (92.5%), with  $\kappa = 0.89$  ( $P < 0.0001$ ). 18F-FDG-PET/CT agreed with the reference standard in 26 of 40 patients (65%), with  $\kappa = 0.52$  ( $P < 0.0001$ ), whereas CE-CT

agreed with the reference standard in 24 of 40 patients (60%), with  $\kappa = 0.43$  ( $P < 0.0001$ ; Table 2). Finally, the combination of PET/CT and CE-CT agreed with the reference standard in 26 of 40 patients (65%), with  $\kappa = 0.50$  ( $P < 0.0001$ ). Results for the individual nodal and extranodal regions are provided in Supplementary Table S1. Interobserver  $\kappa$  values for DWI-MRI, 18F-FDG-PET/CT, and CE-CT were 0.98 ( $P < 0.0001$ ), 0.97 ( $P < 0.0001$ ), and 0.79 ( $P < 0.0001$ ), respectively.

With more than 20 patients, MALT lymphoma was evaluated separately. Here, overall region-based sensitivities were 93.3% (95% CI, 84.2% to 97.3%), 71.7% (95% CI, 52.3% to 85.4%), and 66.7% (95% CI, 54.1% to 77.3%), respectively. Results for nodal and extranodal involvement are provided in Fig. 3. With regard to staging, DWI-MRI, 18F-FDG-PET/CT, and CE-CT agreed with the reference standard in 35 of 38 (92.1%), 26 of 38 patients (68.4%), and 22 of 38 patients (57.9%) with kappa values of 0.89 ( $P <$

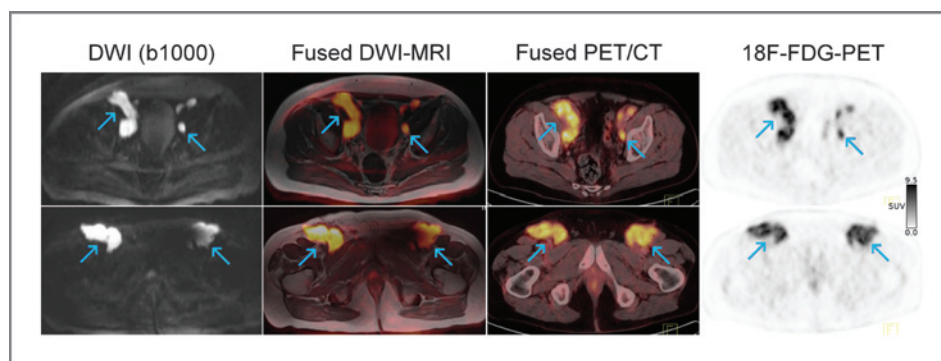


Figure 2. A 68-year-old male patient with histologically verified follicular lymphoma in the parailiac and inguinal lymph nodes on both sides (light blue arrows). There is a perfect match between DWI (and the fused color-coded DWI-MRI) and 18F-FDG-PET (and the fused color-coded PET/CT) with regard to the number of involved regions and the Ann Arbor stage, even though the images are based on different properties of the lymphoma (18F-FDG-PET, glycolytic activity; DWI-MRI, high cell density).

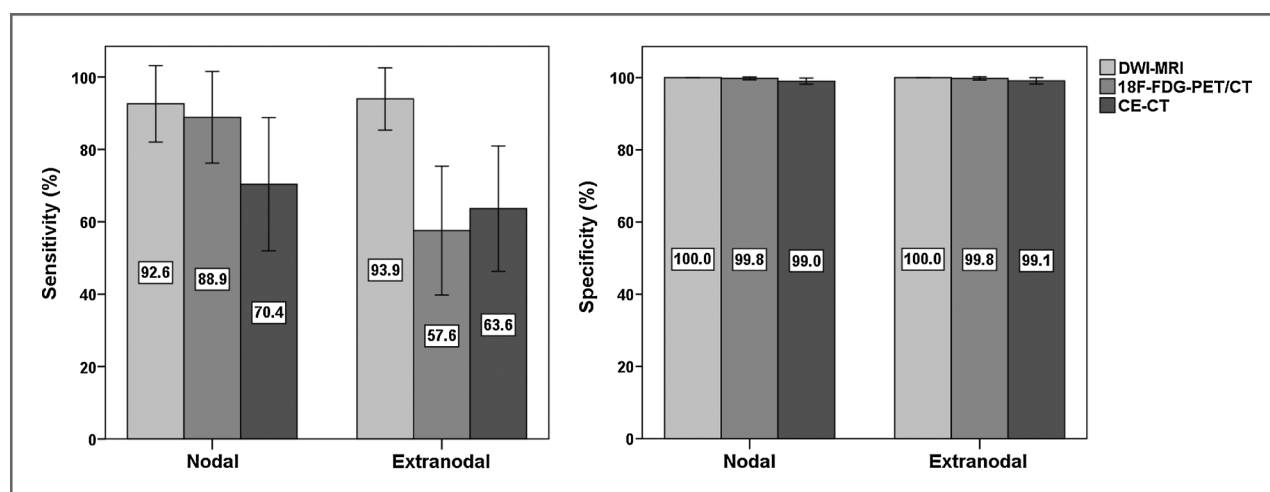


Figure 3. Bar charts depicting the region-based sensitivities and specificities of DWI-MRI, PET/CT, and CE-CT for detection of nodal and extranodal involvement in patients with MALT lymphoma.

0.0001), 0.57 ( $P < 0.0001$ ), and 0.39 ( $P < 0.0001$ ), respectively (Table 2 and Fig. 4).

## Discussion

Our study results clearly show that DWI-MRI is a very useful technique for pretherapeutic imaging and staging of lymphoma. This includes the most common lymphoma subtypes, i.e., DLBCL, follicular lymphoma, and Hodgkin lymphoma, for which 18F-FDG-PET/CT is currently the recommended imaging test (3–6), and also less FDG-avid subtypes such as MALT lymphoma. These findings indicate that DWI-MRI is a less histology-dependent functional imaging technique than 18F-FDG-PET/CT, probably because the high cellular density assessed by DWI is a more general lymphoma feature than the elevated glucose metabolism visualized by 18F-FDG-PET. False-negative results of

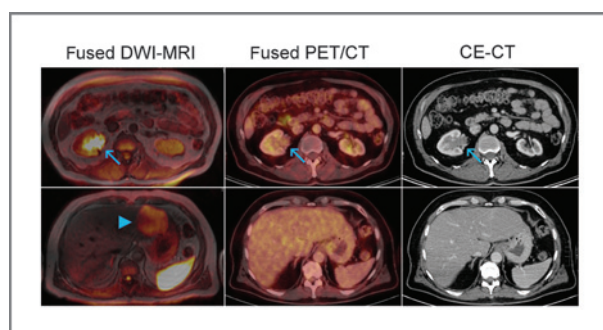


Figure 4. A 62-year-old male patient with histologically verified MALT lymphoma of the right renal pelvis (light blue arrows) and the left liver lobe (light blue arrowhead). Both lesions are clearly visible with a high signal (i.e., diffusion restriction) on the fused color-coded DWI-MRI images due to a high cellular density. On the other hand, the lesions do not show an abnormal tracer uptake on the fused color-coded PET/CT images, indicating a lack of glycolytic activity. Despite its size, the liver lesion is not visible on CE-CT and was thus missed, whereas the lesion in the renal pelvis was detected because of its higher density (>20 Hounsfield units) on CE-CT.

DWI-MRI were most frequently observed in those nodal regions that are, according to the literature (20), prone to image degradation by breathing motion artifacts (Supplementary Table S1). Although image quality was not formally evaluated in the present study, an analysis of these 12 false-negative regions (6 infraclavicular, 4 mediastinal, and 2 hilar) on DWI-MRI revealed that, despite the use of respiratory triggering, motion artifacts were indeed present in 8 of 12 regions. Thus, DWI-MRI seems to be generally inferior to 18F-FDG-PET/CT in these regions.

Accordingly, in DLBCL and Hodgkin lymphoma, the region-based sensitivity for nodal involvement was slightly less than 90%, which shows that DWI-MRI is almost, but not quite, as good as 18F-FDG-PET/CT, which served as the *de facto* reference standard for these lymphoma subtypes, as it did not show any disagreement with histology. For detection of extranodal involvement, DWI-MRI showed an almost perfect sensitivity, *en par* with 18F-FDG-PET/CT. Furthermore, in terms of staging, there was a strong agreement between DWI-MRI and 18F-FDG-PET/CT, in accordance with the previous smaller-sized studies in DLBCL and Hodgkin lymphoma (18–21). DWI-MRI disagreed with the reference standard in 6 of 100 patients in Group A (Table 2), and in only a single case, understaging by DWI-MRI would have had a relevant effect on treatment (stage I instead of stage III). Thus, DWI-MRI may, in terms of staging, be considered as an alternative for patients with DLBCL or Hodgkin lymphoma from areas where no 18F-FDG-PET/CT is available, or for younger patients for whom the risk of radiation-induced secondary malignancy needs to be reduced, at the cost of a lower sensitivity for nodal involvement. Nevertheless, 18F-FDG-PET/CT remains the reference standard for imaging of DLBCL and Hodgkin lymphoma. For follicular lymphoma, only limited comparative DWI-MRI and 18F-FDG-PET/CT data have been published to date—all previous studies combined included 12 patients (19, 20, 26), less than half as many as in our own study ( $n = 28$ )—and no separate data evaluation in this

lymphoma subtype has been performed. Our data show that DWI-MRI was practically equal to 18F-FDG-PET/CT, in terms of region-based sensitivity (Table 1, Figs. 1 and 2), and there was even one case in which MRI-DWI detected regional involvement that was missed on 18F-FDG-PET/CT. In terms of staging, DWI-MRI again showed a high level of agreement (>90%) with the reference standard, and may thus possibly be a true alternative to 18F-FDG-PET/CT for this indolent lymphoma subtype, which, according to the literature, is FDG-avid in 95% of the patients (1), but shows a lower relative 18F-FDG uptake than aggressive lymphomas (27).

Notably, DWI-MRI detected a higher number of involved regions than 18F-FDG-PET/CT in 2 patients with MCL and 1 patient with nMZL, which seems to contradict the previously reported FDG avidity of 100% for these lymphoma subtypes (1). It is important to note, however, that this FDG avidity of 100% was based on patients, rather than on regions, and indeed, on a per-patient basis, there were no false-negative MCL or nMZL cases on 18F-FDG-PET/CT in our study. Nevertheless, larger sample sizes are necessary to determine the comparative performances of the two imaging techniques for MCL and nMZL, because it is possible that a higher region-based sensitivity may affect staging, and thus, clinical decision making in these patients.

In patients with MALT lymphoma, which is the third most common subtype of Non-Hodgkin lymphoma, the region-based sensitivity of DWI-MRI was considerably greater than that of 18F-FDG-PET/CT, and also greater than that of CE-CT, which is the currently recommended imaging test. A more in-depth analysis revealed that these sensitivity differences of more than 20% (18F-FDG-PET/CT), and more than 25% (CE-CT), were mainly caused by the low sensitivities of 18F-FDG-PET/CT and CE-CT for extranodal disease (Table 1, Fig. 3), which was, in the present study, verified histologically in all cases. For both imaging tests, the most common sites of missed lymphoma involvement were the stomach, where CE-CT is known to detect abnormalities only in less than 70% of the patients (28), and 18F-FDG-PET/CT may be slightly limited because of the frequently observed, physiologic, mild-to-moderate uptake in the gastrointestinal (GI) tract, and other tissues such as the lacrimal and salivary glands (Supplementary Table S1 and Supplementary Fig. S1). DWI-MRI was also clearly more useful for staging (Table 2). Notably, 18F-FDG-PET/CT understaged 10 patients with MALT lymphoma; among them, 8 were with stage I and 2 with stage IV disease that was rated as stage 0 on 18F-FDG-PET/CT (Fig. 4); in the latter two cases, this would have had an impact on treatment. Similarly, CE-CT understaged 11 patients, among them, 8 were with stage I and 1 with stage IV disease that was rated as stage 0, and 2 with stage IV disease that was rated as stage I on CE-CT. In contrast, DWI-MRI understaged only 2 patients (stage 0 rather than stage I). It has been previously reported that the FDG avidity of MALT lymphoma is only moderate, i.e., between 54% and 82% (1, 7-10). Our own results, which demonstrate a patient-based FDG avidity of 65.5% (19 of 29 patients) are in good accordance with these data. Diffusion

restriction in MALT lymphoma, on the other hand, which we observed in 93.1% (27 of 29) of the patients, has thus far been poorly documented. The largest study available included 7 patients with MALT lymphoma, and focused on a comparison with CE-CT (29). Only a single study that compared the staging performances of DWI-MRI and 18F-FDG-PET/CT included a total of 2 patients with MALT lymphoma (19). On the basis of our own, larger MALT subgroup of 38 patients—indeed, it was the largest subgroup in our study, which is atypical and may be attributed to the fact that one referring oncologist was a specialist for this distinct lymphoma subtype—DWI-MRI seems to be the imaging test of choice.

No such direct conclusions can be drawn for SLL/CLL, because our patient population included only 2 such patients. However, it is striking that our findings, i.e., the good performance of DWI-MRI and the poor performance of 18F-FDG-PET/CT in these patients (Supplementary Fig. S2), resemble the results of two previous studies with a total of 6 patients (19, 20), even though an FDG avidity of 83% has been previously reported in this lymphoma subtype (1).

It has recently been argued that bone marrow biopsy might be unnecessary in patients with Hodgkin lymphoma who have undergone 18F-FDG-PET/CT (30). In our own study, 2 of 17 patients (11.7%; 1 with MCL and 1 with MALT lymphoma) were false-negative for bone (marrow) involvement on 18F-FDG-PET/CT. While 18F-FDG-PET/CT was, thus, quite useful, indeed, for the detection of bone (marrow) involvement, MRI-DWI was positive in all 17 patients, and might therefore be superior in this regard. A superiority of MRI (with and without DWI) for detection of bone marrow involvement, compared with CE-CT, has already been demonstrated in a recent study (29).

There is presently no international consensus with regard to the diagnostic use of CT, and the use of contrast media, in the context of 18F-FDG-PET/CT. Several centers (such as our own) routinely use CE-CT in an attempt to improve sensitivity and specificity, whereas many other centers perform diagnostic or low-dose, unenhanced (or rarely, contrast-enhanced) CT just for attenuation correction and anatomic/morphologic correlation. For this reason, we used both approaches in the group of lymphomas with variable FDG avidity. Here, the combination of 18F-FDG-PET/CT and CE-CT moderately improved patient- and region-based sensitivities, compared with "stand-alone" 18F-FDG-PET/CT (where CT was just used for anatomic and morphologic correlation), although they were still significantly lower than DWI-MRI sensitivities. Furthermore, patient-based specificity was decreased by the combination of 18F-FDG-PET/CT and CE-CT, and the staging performance of 18F-FDG-PET/CT was practically unaffected by the additional CE-CT information. Thus, with regard to lymphoma staging, the value of CE-CT information for 18F-FDG-PET/CT remains questionable.

Although our study is, with 140 patients, the largest on this topic, the sample size was still too low for lymphoma subtypes such as MCL, nMZL, and SLL/CLL to allow a meaningful comparison between DWI-MRI, 18F-FDG-



PET/CT, and CE-CT. Another limitation refers to our reference standard: in Group B (lymphomas with variable FDG avidity), we used histology for nodal involvement wherever clinically justifiable, but because not all lymph nodes in patients with multiple involved regions can be biopsied, a consensus between the three imaging techniques, or comparison with follow-up imaging, were regarded as sufficient proof for the remaining cases. Finally, our study did not address the dependence of DWI sensitivity and specificity on the sequence protocol (including the choice of *b* values), acquisition technique (breath-hold, respiratory-triggered, or free-breathing DWI), and MRI scanner model/vendor, even though this topic is important for future multicentric DWI studies in patients with lymphoma.

In conclusion, our study confirms that DWI-MRI is a feasible alternative to 18F-FDG-PET/CT for pretherapeutic staging in FDG-avid lymphoma. Although 18F-FDG-PET/CT is moderately superior to DWI-MRI in DLBCL and Hodgkin lymphoma, and thus remains the imaging test of choice for these subtypes, DWI-MRI is practically equal to 18F-FDG-PET/CT in follicular lymphoma. In lymphoma with variable FDG avidity, in particular, MALT lymphoma, DWI-MRI seems to be superior not only to 18F-FDG-PET/CT, but also to CE-CT, the current standard imaging test in these lymphoma subtypes. This finding is of particular relevance for younger patients with MALT lymphoma, because, contrary to 18F-FDG-PET/CT or CE-CT, DWI-MRI is not associated with potentially harmful radiation, and may thus be better suited for the life-long follow-up that is warranted in these patients due to the substantial rate of relapses over time (31, 32). Because our results are only based on data from a single center, and due to the fact that several different approaches to DWI acquisition (e.g., breath-hold, respiratory-triggered, and free-breathing DWI)

are presently in use, a multicentric study, involving MRI systems from different vendors, but using a predefined DWI acquisition technique and pulse sequence protocol, is required to further confirm that DWI-MRI can indeed be considered as a true alternative to 18F-FDG-PET/CT in routine clinical practice.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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