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Clinical Cancer Research

Evaluation of Diffusion-Weighted Magnetic Resonance Imaging for Follow-up and Treatment Response Assessment of Lymphoma: Results of an 18F-FDG-PET/CT–Controlled Prospective Study in 64 Patients

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Abstract

Purpose: To determine the value of diffusion-weighted MRI (DWI-MRI) for treatment response assessment in 2-[18F]fluoro-2-deoxy-D-glucose (FDG)–avid lymphoma.

Experimental Design: Patients with FDG-avid Hodgkin (HL) or non-Hodgkin lymphoma (NHL) at pretherapeutic 18F-FDG-PET/CT, who had also undergone pretherapeutic whole-body DWI-MRI, were included in this prospective study. Depending on the histologic lymphoma subtype, patients received different systemic treatment regimens, and follow-up DWI-MRI and 18F-FDG-PET/CT were performed at one or more time points, depending on the clinical course. For each follow-up DWI-MRI, region-based rates of agreement, and rates of agreement in terms of treatment response (complete remission, partial remission, stable disease, or progressive disease), relative to the corresponding 18F-FDG-PET/CT, were calculated.

Results: Sixty-four patients were included: 10 with HL, 22 with aggressive NHL, and 32 with indolent NHL. The overall region-based agreement of DWI-MRI with 18F-FDG-PET/CT was 99.4%. For the 51 interim examinations (performed after 1–3 therapy cycles), region-based agreement of DWI-MRI with 18F-FDG-PET/CT was 99.2%, and for the 48 end-of-treatment examinations, agreement was 99.8%. No significant differences, in terms of region-based agreement between DWI-MRI and 18F-FDG-PET/CT, were observed between the three lymphoma groups (HL, aggressive NHL, indolent NHL; $P = 0.25$), or between interim and end-of-treatment examinations ($P = 0.21$). With regard to treatment response assessment, DWI-MRI agreed with 18F-FDG-PET/CT in 99 of 102 follow-up examinations (97.1%), with a κ value of 0.94 ($P < 0.0001$).

Conclusions: In patients with FDG-avid lymphoma, DWI-MRI may be a feasible alternative to 18F-FDG-PET/CT for follow-up and treatment response assessment. *Clin Cancer Res; 1–8. ©2015 AACR.*

Introduction

PET after application of the radiotracer 2-[18F]fluoro-2-deoxy-D-glucose (FDG) is the current imaging technique of choice for treatment response assessment in the majority of lymphomas (1–5). The use of 18F-FDG-PET or, today, mostly 18F-FDG-PET/CT, is justified for follow-up in patients that show FDG-avid lymphoma manifestations on pretherapeutic 18F-FDG-PET/CT (5). This is because 18F-FDG-PET/CT shows a higher sensitivity for therapy response in general, and complete remission in particular, than contrast-enhanced (CE-)CT (6). However, 18F-FDG-PET/CT is cost-intensive, country-wide access is limited, and due to the associated substantial dose of ionizing radiation, there is some concern for younger patients that may require life-long follow-up, because of the risk of radiation-induced secondary malignancies.

Diffusion-weighted imaging (DWI), a functional MRI technique that relies on the restriction of water movement in hypercellular tumors due to extracellular space narrowing, is presently discussed as a radiation-free alternative to 18F-FDG-PET/CT for treatment response assessment in lymphoma (7). This is because several studies in different cancers suggest that DWI may, contrary to standard morphologic MRI, be potentially able to distinguish between residual tumor tissue and non-neoplastic residual changes (e.g., fibrosis) after therapy (8–12).

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Translational Relevance

In patients with 2-[18F]fluoro-2-deoxy-D-glucose (FDG)–avid lymphoma, diffusion-weighted imaging (DWI), a functional MRI technique that enables an indirect assessment of cellular density, provides results that are almost equal to those of 18F-FDG-PET/CT, in terms of restaging and treatment response evaluation. This performance of DWI-MRI appears to be independent of the lymphoma subtype (i.e., Hodgkin, aggressive or indolent Non-Hodgkin lymphoma), and also independent of the duration of treatment (i.e., the number of therapy cycles). Our findings thus provide further evidence that DWI-MRI–although, unlike 18F-FDG-PET, it cannot directly assess treatment-induced functional and metabolic changes at a cellular level–may be a useful alternative to 18F-FDG-PET/CT for both interim- and end-of-treatment response assessment. In addition, DWI is also attractive from an economic point of view, and in terms of general availability, in particular in comparison with PET/CT.

In lymphoma, treatment response assessment by DWI has so far only been investigated in a small number of studies that were either limited by a small sample size (between 8 and 27 patients, with a mean of 15 patients/study; refs. 13–19), or a retrospective design (20). In addition, these studies included almost exclusively patients with diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma—there are practically no data for indolent non-Hodgkin lymphomas (NHL). Finally, almost all previous studies focused on treatment-induced changes of apparent diffusion coefficients (ADC) in target lesions (14–19); only a single study in 15 DLBCL patients directly compared DWI with 18F-FDG-PET/CT in terms of detection of residual lymphoma after therapy (13), albeit without further subcategorization of the response status (i.e., complete or partial remission, stable disease, or progression).

It was therefore the aim of our prospective study to determine, in a larger cohort of patients with FDG-avid lymphoma, whether DWI-MRI—even though it cannot (unlike 18F-FDG-PET) assess cellular metabolism, but is only a marker of cell density—can indeed serve as a radiation-free alternative to 18F-FDG-PET/CT, in terms of follow-up and treatment response assessment, according to the International Harmonization Project (IHP) criteria of the International Working Group (IWG; ref. 1). It was also of interest to determine whether DWI-MRI performs equally well for interim and end-of-treatment response assessment.

Patients and Methods

Patients and design

The present study was part of a prospective, Institutional Review Board-approved trial that included lymphoma patients who were referred to the Department of Radiology and Nuclear Medicine of the local tertiary care center for staging and follow-up by means of DWI-MRI and 18F-FDG-PET/CT between August 2011 and January 2014. Lymphoma subtypes were diagnosed based on tissue samples obtained by biopsy or surgery, according to the criteria of the current WHO classification of hematologic and lymphoid malignancies, by a reference pathologist. Patients who gave written informed consent underwent baseline 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 corresponding DWI-MRI and 18F-FDG-PET/CT examinations were used as exclusion criteria.

For the present follow-up/treatment response assessment study, additional inclusion criteria were availability of one or more follow-up DWI-MRI and 18F-FDG-PET/CT examinations, again with a maximum of 7 days between the corresponding examinations; and a time interval of at least 2 weeks between the last day of a chemotherapy cycle and the imaging tests. A lack of FDG avidity of the lymphoma on pretherapeutic 18F-FDG-PET/CT, according to the original reports from routine clinical practice, was used as the single additional exclusion criterion.

Imaging

MRI was performed, from the vertex to the upper thigh, on a 3-Tesla system (TrioTIM; Siemens), equipped with a phased-array body coil. 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, a 192 × 115 matrix, and a 5-mm slice thickness with no gap. Images were obtained during free breathing; only for the neck and chest, respiratory triggering was used. ADC maps were calculated, and a T1-weighted turbo spin-echo or, in case of breathing difficulties, a fast gradient-echo sequence was obtained for better anatomical/morphologic correlation, and to generate fused color-coded DWI-MRI images.

18F-FDG-PET/CT was performed, from the vertex to the upper thigh, using a 64-row multidetector PET/CT system (Biograph TruePoint 64; Siemens), with a transaxial field-of-view (FOV) of 605 mm (axial FOV, 216 mm), a PET sensitivity of 7.6 cps/kBq, and a transaxial PET resolution of 4 to 5 mm (full width at half maximum). Patients fasted for 5 hours before imaging; the glucose cut-off level was 150 mg/dL. PET was performed 50 to 60 minutes after a weight-dependent, intravenous administration of 18F-FDG (target dose, 300 MBq; individual dose, 270–340 MBq), with 3 minutes/bed position, four iterations per 21 subsets, a 5-mm slice thickness, and a 168 × 168 matrix, using the TrueX reconstruction algorithm. Venous-phase CE-CT was obtained after the intravenous injection of 100 mL of a tri-iodinated, nonionic contrast medium at a rate of 2 mL/second; a tube voltage of 120 kV, a tube current of 230 mA, a collimation of 64 × 0.6 mm, a 3-mm slice thickness with 2 mm increment, and a 512 × 512 matrix, were used. PET attenuation correction was based on CE-CT because previous studies have shown that the use of CE-CT instead of unenhanced CT does not negatively influence clinical diagnostic PET image interpretation (21–23).

Image interpretation

The 14 nodal regions defined at the Rye symposium (24), and the following twelve extranodal regions were evaluated on pre- and posttherapeutic images: 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).

DWI-MRI was evaluated independently by two board-certified radiologists that were blinded to the corresponding 18F-FDG-PET/CT. On pre- and posttherapeutic images, 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

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to the b50 images); or a high signal on the b50 images and low signal on the ADC map (relative to the surrounding tissues; ref. 25). Because the normal spleen frequently shows a higher signal on DWI than other abdominal/retroperitoneal organs (26, 27), 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, it showed a lower signal than the adjacent skeletal muscle on the T1-weighted images. Other regions or structures with known high signal on DWI, such as ovaries, testes of younger patients, and bowel contents (28, 29), were not regarded as pathologic. Where appropriate, lesion diameters were measured on the T1-weighted images. Following the raters' independent regional assessment and (re-)staging, a consensus reading (i.e., a reevaluation according to the above defined criteria for MRI-DWI positivity) was performed for all examinations where discrepancies between the two readers were noted in the findings. For the evaluation of posttherapeutic DWI-MRI, raters had access to all previous DWI-MRI images.

18F-FDG-PET/CT was evaluated independently by two board-certified nuclear medicine physicians that were blinded to the corresponding DWI-MRI. Nodal and extranodal regions were rated as positive for viable lymphoma when there was at least one focal (or, for bone marrow, diffuse) area of increased tracer accumulation, relative to the surrounding tissue or mediastinal blood pool activity (30). As previously recommended, the spleen was rated as positive when the tracer uptake was higher than in the liver (5). In addition, for interim restaging of patients with Hodgkin lymphoma and DLBCL, all nodal and extranodal lesions were also only rated as positive on PET if their uptake exceeded that in the liver, as previously reported (31, 32)—this is in accordance with the consensus of the "Second International Workshop on Interim Positron Emission Tomography in Lymphoma", where a Deauville score $\geq$4 was recommended for this purpose (33). The CE-CT component of 18F-FDG-PET/CT was used primarily for anatomical correlation and lesion confirmation, and, where appropriate, to measure lesion diameters. Similar to DWI-MRI, a consensus rating was performed for all examinations where discrepancies between the two readers were noted, following the raters' independent regional assessment and (re-) staging. For the evaluation of posttherapeutic 18F-FDG-PET/CT, raters had access to all previous 18F-FDG-PET/CT images.

Assessment of treatment response status

Pretherapeutic staging has been previously performed and reported by our group in a larger population that also included patients eligible for the present study (34). In the present study, the performance of DWI-MRI for treatment response evaluation was determined, based on the pre- and posttherapeutic regional assessments, according to the IHP criteria of the IWG for 18F-FDG-PET/CT (30), and their application to DWI-MRI (Table 1).

Table 1. Summary of the IHP criteria for treatment response assessment on 18F-FDG-PET/CT, and their application to DWI-MRI

Complete remission (CR)	Resolution of all lesions with elevated FDG uptake on PET, or diffusion restriction on DWI, respectively. Residual masses are permitted as long as they are PET-negative, or DWI-negative, respectively.
Partial remission (PR)	A $\geq$50% decrease in the sum of the product of the diameters of the up to six largest lesions, provided that at least one of them is still PET-positive, or DWI-positive, respectively, and provided that there is no increase in size of other lymph nodes or the spleen, and no new lesion.
Stable disease (SD)	Persistent, increased FDG uptake on PET, or diffusion restriction on DWI, in previously involved sites that do not meet the size criteria for PR or PD, provided that there are no new lesions.
Progressive disease (PD)/relapse	Appearance of new PET-positive, or DWI-positive, nodal or extranodal lesions, respectively; or a $\geq$50% increase in the sum of the product of the diameters of any previous lesions.

Statistical analysis

Region-based rates of agreement between DWI-MRI and 18F-FDG-PET/CT (consensus ratings) were calculated, separately for nodal, extranodal, and all regions combined. These calculations were also performed independently for interim (i.e., after 1–3 therapy cycles) and end-of-treatment examinations, as well as the three larger lymphoma subgroups (Hodgkin lymphoma, aggressive, and indolent NHL). General estimation equations were used for group comparisons (interim vs. end-of-treatment restaging; nodal vs. extranodal involvement; Hodgkin lymphoma vs. aggressive NHL vs. indolent NHL), and Bonferroni correction was applied, as appropriate. κ coefficients were used to determine the agreement of DWI-MRI with 18F-FDG-PET/CT, based on regions and IHP response status, first for all examinations combined, and then independently for interim DWI-MRI (i.e., after 1–3 therapy cycles) and end-of-treatment DWI-MRI. κ coefficients were also used to assess interobserver agreement. The specified level of significance was $P \leq 0.05$ for all tests. The software package SPSS 21.0 (SPSS Inc.) was used for all statistical calculations.

Results

Patient characteristics

Of 140 lymphoma patients that received pretherapeutic staging by means of 18F-FDG-PET/CT and DWI-MRI (34), 73 patients matched the inclusion criteria for participation in our prospective follow-up/response assessment study. Of these, 9 patients [8 with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) lymphoma, and one with small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL)] were excluded due to a lack of FDG avidity of the lymphoma. None of the remaining 64 patients showed elevated glucose levels (i.e., >150 mg/dL).

Of the 64 patients (35 females and 29 males; mean age, 56.0 $\pm$ 16.7 years; age range, 19–84 years), 17 were diagnosed with MALT lymphoma, 15 with DLBCL, 13 with follicular lymphoma, 10 with Hodgkin lymphoma, 5 with mantle cell lymphoma, and one patient each with nodal marginal zone lymphoma, anaplastic large cell lymphoma, peripheral T-cell lymphoma, and SLL/CLL. Thus, the patient population comprised 10 patients with Hodgkin lymphoma, 22 patients with aggressive NHL, and 32 patients with indolent NHL. Eighteen patients received immunotherapy (including 2 patients who received brentuximab-vedotin); 34 patients received chemo- and immunotherapy; and 11 patients received chemotherapy (Supplementary Table S1). One patient received no treatment at all, but instead, a "wait-and-see" strategy was used.

Thirty patients underwent one, 30 underwent two, and 4 patients underwent three DWI-MRI and 18F-FDG-PET/CT

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Table 2. True-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) regions, and percentages of agreement for DWI-MRI, relative to 18F-FDG-PET/CT

	TP	FN	FP	TN	Agreement
Nodal					
Overall[a]	45	1	12	1,370	99.1%
Interim	19	1	7	687	98.9%
EOT	16	0	3	653	99.6%
Extranodal					
Overall[a]	37	1	1	1,185	99.8%
Interim	20	1	1	590	99.7%
EOT	17	0	0	559	100%

Abbreviation: EOT, end-of-treatment (>3 therapy cycles).
[a]Including three examinations after a "wait-and-see" interval.

follow-ups. Thus, a total of 102 follow-up scans (i.e., 1,428 nodal and 1,224 extranodal regions) were evaluated, of which 51 were categorized as "interim" (i.e., performed after 1–3 therapy cycles), and 48 as "end-of-treatment"; the remaining three examinations were performed after a "wait-and-see" interval.

Follow-up: sensitivities and specificities

At baseline, nodal and extranodal involvements were observed in 184 of 896 and 53 of 768 regions of the 64 patients, respectively, according to the reference standard (Supplementary Table S2). At follow-up (i.e., for all 102 examinations combined), nodal and extranodal (residual or newly developed) involvements were observed in 46 of 1,428 and 38 of 1,224 regions (Supplementary Table S2), according to 18F-FDG-PET/CT. The overall region-based agreement of DWI-MRI with 18F-FDG-PET/CT for detection of lymphoma at follow-up was 99.4% (Table 2). Individual results for the three lymphoma subgroups (i.e., Hodgkin lymphoma, aggressive NHL, and indolent NHL) are provided in Table 3. No significant differences, in terms of region-based agreement between DWI-MRI and 18F-FDG-PET/CT, were observed between the three lymphoma groups ($P = 0.25$).

Of the12 nodal regions that were false positive on follow-up DWI-MRI, nine were cervical regions, two were inguinal regions, and one was a pelvic region; one cervical region was false negative (Supplementary Table S2). With regard to extranodal regions, the spleen was rated false positive in one patient, and the liver false negative in another patient, on follow-up DWI-MRI. There was a significant difference, in terms of agreement between DWI-MRI and 18F-FDG-PET/CT, between nodal and extranodal regions ($P = 0.017$).

For the 51 interim follow-up examinations (after 1–3 therapy cycles), region-based agreement of DWI-MRI with 18F-FDG-PET/CT was 99.2%. For the 48 end-of-treatment examinations, region-based agreement of DWI-MRI with 18F-FDG-PET/CT was 99.8% (Tables 2 and 3). With regard to the agreement between DWI-MRI and 18F-FDG-PET/CT, no significant difference between interim and end-of-treatment examinations was observed ($P = 0.21$).

Region-based interobserver agreement, calculated for all 102 follow-up examinations combined, was high for both DWI-MRI and 18F-FDG-PET/CT, with κ values of 0.89 ($P < 0.0001$) and 0.97 ($P < 0.0001$), respectively. κ values for Hodgkin lymphoma, aggressive NHL, and indolent NHL were 0.87, 0.81, and 0.94 for DWI-MRI, and 1.0, 0.96, and 0.97 for 18F-FDG-PET/CT, respectively.

Table 3. Region-based agreement between DWI-MRI and 18F-FDG-PET/CT, and numbers of examinations, by lymphoma group (Hodgkin lymphoma, aggressive NHL, and indolent NHL)

		Overall	Interim	EOT
Hodgkin	Examinations	15	10	5
	Agreement (regions)	98.7%	98.8%	98.5%
Aggressive NHL	Examinations	31	15	16
	Agreement (regions)	99.8%	99.5%	100%
Indolent NHL	Examinations	56[a]	26	27
	Agreement (regions)	99.5%	99.3%	99.9%

Abbreviation: EOT, end-of-treatment (>3 therapy cycles).
[a]Including three examinations after a "wait-and-see" interval.

Restaging and response status

At baseline, Ann Arbor stage was 0 in 6 patients; stage I in 19 patients; stage II in 11 patients; stage III in 8 patients; and stage IV in 20 patients; according to our reference standard. With regard to the IHP response status, DWI-MRI agreed with 18F-FDG-PET/CT in 99 of 102 follow-up examinations (97.1%), with a κ value of 0.94 ($P < 0.0001$; see Table 4, and Figs. 1 and 2). Of the three cases of disagreement between DWI-MRI and 18F-FDG-PET/CT, one occurred at interim restaging of a patient with follicular lymphoma, and two occurred at both interim and end-of-treatment restaging in a single patient with Hodgkin lymphoma. All three cases were rated as complete remission on 18F-FDG-PET/CT, and as partial remission, due to a false-positive result in a single nodal region, on DWI-MRI.

Discussion

The results of our study suggest that DWI-MRI is almost equal to 18F-FDG PET/CT for follow-up and therapy response assessment in patients with lymphoma, in accordance with the results of previous smaller-sized studies (13–20). This is of interest, because only the image pattern, but not the underlying information (i.e., tumor property) assessed is similar between the two techniques: DWI visualizes intercellular space narrowing, and thus, cell density (35); whereas 18F-FDG-PET visualizes glucose metabolism, which in turn has been shown to correlate with cell proliferation (36, 37). We hypothesize that the reason for our findings is that, at least in the FDG-avid lymphomas included in the present study, there is more glucose consumption in areas of higher cell density, such a correlation between cell density and glucose metabolism has already been reported for malignant lung nodules and pancreatic adenocarcinoma (38, 39). In other, very slowly growing lymphomas (e.g., in a certain percentage of MALT lymphomas and SLL/CLL), there may, however, be no such association between cellularity and glucose metabolism.

Notably, our study is the first to apply the IHP criteria for response classification of lymphoma to DWI-MRI. This was done because we felt that, although they rely on different physiological properties, DWI-MRI is a functional imaging technique just like 18F-FDG-PET/CT, and should therefore be used in the same way. For instance, the criterion for complete remission on DWI-MRI was the resolution of lesions with restricted diffusion at follow-up, regardless of whether or not a residual mass was still visible—this resembles the criterion for complete remission on 18F-FDG-PET/CT, where residual masses are permitted as long as there is no increased tracer uptake. Using this strategy, overstaging by DWI-MRI at follow-up occurred in only three of 102 examinations (partial instead of complete remission), and understaging did not occur at all (Table 3). Accordingly, region-based overstaging was also observed more frequently than understaging (Table 2), with the cervical lymph node regions being the most common sites for

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Table 4. Restaging of 64 lymphoma patients, according the IHP criteria, and their application to DWI-MRI: absolute numbers of patients with complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD)

		18F-FDG-PET/CT				
		CR	PR	SD	PD	Total
DWI-MRI	CR	65	0	0	0	65
DWI-MRI	PR	3	17	0	0	20
DWI-MRI	SD	0	0	10	0	10
DWI-MRI	PD	0	0	0	7	7
DWI-MRI	Total	68	17	10	7	102

false-positive results (Supplementary Table S2). Our results are thus in good accordance with a previous study, which reported that DWI-MRI has a tendency to overestimate, rather than underestimate, the extent of disease, compared with 18F-FDG-PET/CT (40).

With 64 patients, our study is presently the largest on this topic – the largest previous, prospective study included 27 patients (17), and the largest retrospective study included 39 patients (20). Unlike these previous studies, we also included a considerable number of indolent lymphomas – actually, half of our patients were diagnosed with an indolent NHL, and MALT lymphoma was, with 17 patients, even the most common subtype

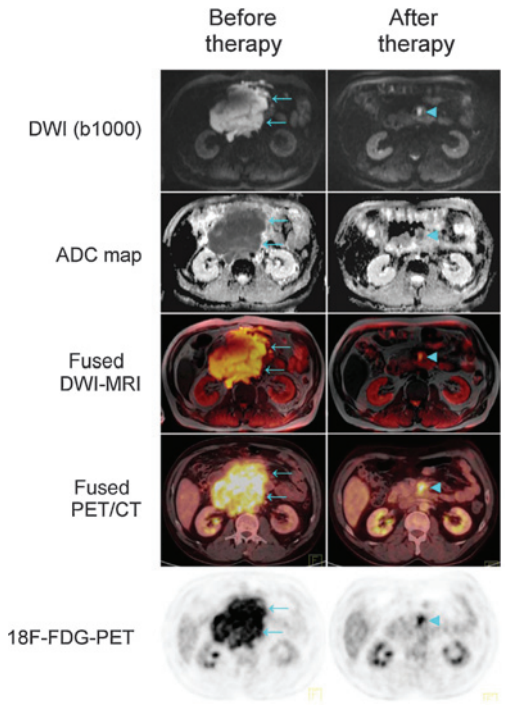

Figure 1.
A 57-year-old male patient with histologically verified follicular lymphoma. The large lymphoma manifestation of the periaortic/mesenteric lymph nodes (light-blue arrows) shows a high signal on the axial DWI and the fused color-coded DWI-MRI images (with a visible dielectric artifact in the right anterior portion that leads to signal inhomogeneity), and a low signal on the ADC map, indicative of diffusion restriction, before therapy; the ADC map closely resembles the increased tracer uptake on the respective axial 18F-FDG-PET and the fused color-coded PET/CT images. After six cycles of chemo- and immunotherapy, there is still a small area of persistent diffusion restriction on DWI(-MRI) within the residual tissue (light-blue arrowheads), which also still shows an increased tracer uptake on 18F-FDG-PET(/CT). Thus, the patient was diagnosed with "partial remission" on both imaging tests.

in our study. This atypical distribution is probably due to the fact that one of the referring oncologists is a specialist for the management of MALT lymphoma. Although 18F-FDG-PET/CT is generally not recommended in MALT lymphoma and SLL/CLL (3), it is well known that 50% to 60% of patients with MALT lymphoma, and about 80% of patients with SLL/CLL, may show an increased FDG uptake (41). Because we only included such FDG-avid cases of MALT lymphoma and SLL/CLL, we considered it justifiable to also use 18F-FDG-PET/CT as reference standard for these. Although the low number of patients misclassified by DWI-MRI, in terms of restaging ($n = 2$), prevented us from performing a dedicated statistical analysis, we did not observe any trend toward a better, or poorer, performance of DWI-MRI in indolent NHL, compared with Hodgkin lymphoma or aggressive NHL.

The concept of interim restaging in lymphoma, which is typically performed after one to three therapy cycles, has received considerable attention over the last couple of years, and is still controversial. Even for Hodgkin lymphoma and DLBCL, there is, at present, still no official recommendation for interim restaging outside of clinical trials, even though some 18F-FDG-PET/CT studies have suggested that this imaging technique potentially enables an early outcome prediction, particularly when the FDG uptake in the liver is used as a reference (31). Therefore, a Deauville score of ≥ 4 was used as the criterion for residual disease in Hodgkin lymphoma and DLBCL on interim 18F-FDG-PET/CT, as previously recommended (33), whereas for all other lymphoma subtypes, the unmodified IHP criteria for PET were used, because the Deauville criteria have not yet been evaluated here. We not only found that DWI-MRI was equally suitable for interim restaging, compared with 18F-FDG-PET/CT, but we also found that there was no statistically significant difference, in terms of region-based sensitivity/specificity, between DWI-MRI-based interim restaging and end-of-treatment restaging. These results suggest that the value of DWI-MRI for follow-up imaging in lymphoma does not depend on the treatment duration. It is important to note, however, that our results are based on imaging after extended time periods posttreatment, during which cell death, which DWI can capture due to a reduction of cell density, may have occurred. Although there are presently no comparative data available with regard to this topic, it seems unlikely that DWI would be able to capture very early treatment response—for instance, only hours after treatment initiation—because, unlike PET, it cannot directly assess treatment-induced functional and metabolic changes at a cellular level. In a previous study, it was shown that 18-FDG-PET can capture treatment-induced changes as early as 2 hours after treatment (42).

Apart from its diagnostic value, DWI is also attractive from an economic point of view, and in terms of general availability. Originally introduced into clinical practice for neurologic applications (e.g., stroke), DWI is now considered a standard pulse sequence that is suitable for whole-body imaging, and is provided for all modern 1.5- or 3-Tesla MR scanners. A German study demonstrated that, with regard to oncologic staging of the five most frequent tumors, the overall cost for whole-body MRI is lower by a factor of 1.8 to 2 (43), compared with 18F-FDG-PET/CT. Thus, whole-body MRI techniques, including DWI, may be an interesting alternative to 18F-FDG-PET/CT in an era of limited financial resources and increasing healthcare costs. A drawback of the use of DWI, however, is the sensitivity of this technique to artifacts (see Fig. 1), in particular insufficient fast suppression artifacts due to magnetic field inhomogeneity, motion artifacts (in

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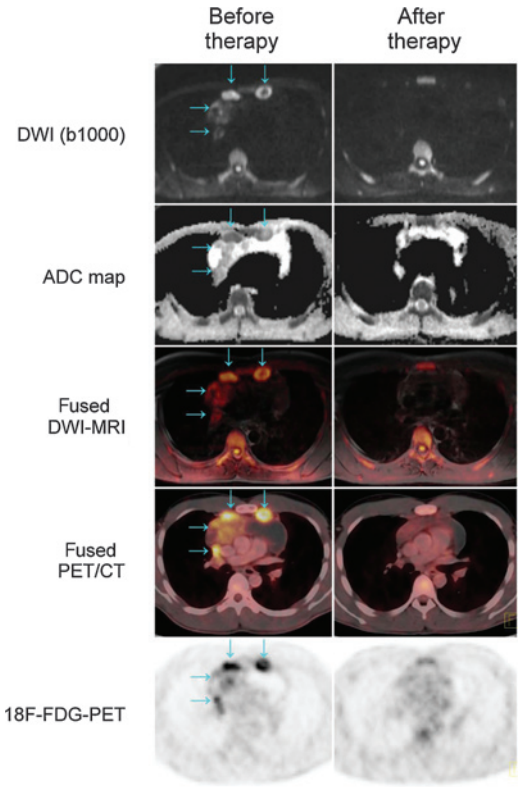

Figure 2.
A 23-year-old male patient with histologically verified, partly cystic Hodgkin lymphoma, limited to the anterior mediastinum. The solid components of these nodal lymphoma manifestations (light-blue arrows) show a high signal on the axial DWI and the fused color-coded DWI-MRI images, and a low signal on the ADC map, indicative of diffusion restriction, before therapy; this closely resembles the increased tracer uptake on the respective axial 18F-FDG-PET and the fused color-coded PET/CT images. After two cycles of chemotherapy, there are no signs of diffusion restriction on DWI(-MRI) within the residual tissue, and there is also no increased tracer uptake on 18F-FDG-PET(/CT) anymore; thus, the patient was diagnosed with "complete remission" on both imaging tests.

particular in the neck and chest regions), as well as susceptibility artifacts. Techniques to reduce these artifacts include multiple signal averaging, sampling bandwidth maximization, and the use of breath-holding or respiratory triggering for image acquisition. Nevertheless, despite the use of such MRI artifact reduction techniques, artifacts were a major source for both false-negative (e.g., one liver manifestation) and false-positive findings (e.g., cervical lymph nodes) in the present study. Another limitation of DWI is the fact that lymph nodes <1cm are often equivocal – here, a combination of the DWI signal with established size criteria (i.e., the Cheson criteria) for lymphoma involvement might be helpful to reduce false-positive results.

Our study is limited by the fact that we only included patients with lymphomas that were FDG-avid on pretherapeutic 18F-FDG-PET/CT, and thus, we cannot comment on the performance of DWI-MRI in the entire lymphoma population, in terms of restaging. However, this strategy was chosen because not all regions with suspected residual or progressive disease on follow-up DWI-MRI can be verified histologically, and 18F-FDG-PET/CT is the established imaging reference standard for follow-up of patients with FDG-avid lymphoma at baseline (5). Because of the inclusion of different lymphoma subtypes, our patient population was heterogeneous with regard to the treatment regimens used. However, prediction of outcome and survival after different types of therapy were not within the scope of our study—instead, we focused on a comparison between DWI-MRI and 18F-FDG-PET/CT. Finally, no quantitative data from PET (e.g., standardized uptake values) or DWI (i.e., ADCs) were collected as markers for treatment response, because, for 18F-FDG-PET, the current IHP guidelines recommend a purely visual assessment, and hence, we saw no justification for using a different approach for DWI. Should future treatment response criteria rely on quantitative, rather than on qualitative imaging parameters, the possible role of DWI must be reevaluated, because of the known shortcomings of this technique, such as a sensitivity of ADC values to the choice of scanner model and vendor, field strength, gradient system and coils, pulse-sequence design, acquisition parameters (including b values), and artifacts related to susceptibility effects or eddy currents (44).

In conclusion, our results provide further evidence that DWI-MRI may be a feasible alternative to 18F-FDG-PET/CT for the follow-up of lymphoma patients, as previously suggested by smaller-sized studies. This includes treatment response assessment, according to the IHP response criteria; DWI-MRI in this regard appears to be suitable for both interim and end-of-treatment restaging. Despite these encouraging results, an additional follow-up, noninferiority study that uses progression-free survival as the reference standard, as well as larger multicentric studies, involving MRI systems from different vendors, but using a predefined MRI protocol, are required to further evaluate the role of DWI-MRI for treatment response assessment in lymphoma in day-to-day practice. Because DWI-MRI demonstrated a tendency toward overstaging, definition of reference tissues for response evaluation, similar to the Deauville criteria for 18F-FDG-PET, should be considered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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