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Comparison of diffusion-weighted MRI and [^{18}F]FDG PET/MRI for treatment monitoring in pediatric Hodgkin and non-Hodgkin lymphoma

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Abstract

Objective To compare tumor therapy response assessments with whole-body diffusion-weighted imaging (WB-DWI) and 18F-fluorodeoxyglucose ([^{18}F]FDG) PET/MRI in pediatric patients with Hodgkin lymphoma and non-Hodgkin lymphoma.

Materials and methods In a retrospective, non-randomized single-center study, we reviewed serial simultaneous WB-DWI and [^{18}F]FDG PET/MRI scans of 45 children and young adults (27 males; mean age, 13 years ± 5 [standard deviation]; age range, 1–21 years) with Hodgkin lymphoma ($n = 20$) and non-Hodgkin lymphoma ($n = 25$) between February 2018 and October 2022. We measured minimum tumor apparent diffusion coefficient (ADCmin) and maximum standardized uptake value (SUVmax) of up to six target lesions and assessed therapy response according to Lugano criteria and modified criteria for WB-DWI. We evaluated the agreement between WB-DWI- and [^{18}F]FDG PET/MRI–based response classifications with Gwet's agreement coefficient (AC).

Results After induction chemotherapy, 95% (19 of 20) of patients with Hodgkin lymphoma and 72% (18 of 25) of patients with non-Hodgkin lymphoma showed concordant response in tumor metabolism and proton diffusion. We found a high agreement between treatment response assessments on WB-DWI and [^{18}F]FDG PET/MRI (Gwet's AC = 0.94; 95% confidence interval [CI]: 0.82, 1.00) in patients with Hodgkin lymphoma, and a lower agreement for patients with non-Hodgkin lymphoma (Gwet's AC = 0.66; 95% CI: 0.43, 0.90). After completion of therapy, there was an excellent agreement between WB-DWI and [^{18}F]FDG PET/MRI response assessments (Gwet's AC = 0.97; 95% CI: 0.91, 1).

Conclusion Therapy response of Hodgkin lymphoma can be evaluated with either [^{18}F]FDG PET or WB-DWI, whereas patients with non-Hodgkin lymphoma may benefit from a combined approach.

Clinical relevance statement Hodgkin lymphoma and non-Hodgkin lymphoma exhibit different patterns of tumor response to induction chemotherapy on diffusion-weighted MRI and PET/MRI.

Key Points

- *Diffusion-weighted imaging has been proposed as an alternative imaging to assess tumor response without ionizing radiation.*
- *After induction therapy, whole-body diffusion-weighted imaging and PET/MRI revealed a higher agreement in patients with Hodgkin lymphoma than in those with non-Hodgkin lymphoma.*
- *At the end of therapy, whole-body diffusion-weighted imaging and PET/MRI revealed an excellent agreement for overall tumor therapy responses for all lymphoma types.*

Keywords Lymphoma · Hodgkin disease · Positron emission tomography · Diffusion magnetic resonance imaging

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Abbreviations

AC	Agreement coefficient
ADC	Apparent diffusion coefficient
CR	Complete response
[^{18}F]FDG	Fluorine-18 fluorodeoxyglucose
HL	Hodgkin lymphoma
NHL	Non-Hodgkin lymphoma
PD	Progressive disease

PR	Partial response
SD	Stable disease
SUV	Standardized uptake value
WB-DWI	Whole-body diffusion-weighted imaging

Introduction

Fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) PET is the imaging modality of choice for monitoring treatment response in pediatric patients with lymphoma [1, 2]. [^{18}F]FDG PET measures the glucose metabolism of tumor cells, which can be quantified using standardized uptake values (SUVs) to provide an estimate of tumor metabolic activity [3]. Chemotherapy damages tumor cells, resulting in reducing the cellular [^{18}F]FDG uptake and lowering the SUV of lymphoma on [^{18}F]FDG PET scans [4]. [^{18}F]FDG PET/MRI is a reliable alternative to [^{18}F]FDG PET/CT for pediatric patients with lymphoma. Because both technologies rely on [^{18}F]FDG PET imaging, they provide a similar diagnostic accuracy [5]. Replacing CT with MRI for anatomical colocalization of [^{18}F]FDG PET data significantly reduces ionizing radiation exposure in children with cancer [6–8].

However, the availability of [^{18}F]FDG PET/MRI is limited to large tertiary medical centers in world-leading countries, in contrast to the worldwide availability of conventional MRI. Whole-body (WB) MRI is another feasible alternative method that provides both anatomical information and diffusion-weighted imaging (DWI) for functional information without ionizing radiation [9]. DWI measures the mobility of water molecules in the tumor microenvironment and can be quantified as the apparent diffusion coefficient (ADC) to provide an indirect estimate of tumor cell density [10]. At the time of diagnosis, most lymphomas have low ADC values due to high cell density and high nuclear-to-cytoplasmic ratios [11]. Chemotherapy induces cell death and necrosis. The breakdown of cellular barriers in necrotic tissue leads to increased diffusion of water molecules and increased ADC values of lymphoma on DWI scans [12].

Nevertheless, it is unclear whether DWI is comparable to [^{18}F]FDG PET for treatment monitoring in lymphoma patients. The results in the literature to date are inconsistent regarding the information provided by [^{18}F]FDG PET and DWI [13–16]. SUVs and ADCs are considered independent biomarkers for lymphomas [14]. Some authors reported concordant therapy response of lymphomas on [^{18}F]FDG PET or DWI [17–19], while others reported discordant therapy response [20–22]. Therapy-induced changes in pediatric lymphomas on DWI and [^{18}F]FDG PET may depend on underlying tumor histology. Few studies have assessed how different types of lymphoma respond to chemotherapy in terms of changes in tumor metabolism and diffusion using [^{18}F]FDG PET and DWI, respectively [18, 23]. Mayerhoefer et al reported different patterns of metabolic activity and ADC changes in specific lymphoma subtypes after treatment initiation in adult patients [23]. However, WB-DWI and [^{18}F]FDG PET response assessments have not been compared according to tumor type in the pediatric population.

Therefore, the purpose of our study was to compare tumor therapy response assessments using WB-DWI and [^{18}F]FDG PET/MRI in pediatric patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

Materials and methods

Study participants

Our study was approved by the institutional review board (IRB) of our institution. We collected de-identified imaging studies and relevant clinical information (patient age, sex, tumor type, serum lactate dehydrogenase, stage, bone marrow, and central nervous system involvement) in a centralized image registry. Parents provided written informed consent and pediatric patients provided assent to donate their medical images and related clinical data to the registry for research analyses. All patients younger than 25 years with histologically confirmed lymphoma who underwent combined [^{18}F]FDG PET/MRI and WB-DWI in the same examinations between February 2018 and October 2022 were included. The exclusion criteria were incomplete imaging data and the absence of measurable lesions.

Imaging

All patients with blood glucose levels < 140 mg/dL were injected with [^{18}F]FDG (3–5 megabecquerel per kg body weight) and scanned 60 min later, on a 3-T Signa PET/MRI scanner (GE Healthcare), using appropriate surface coils. The imaging protocol consisted of axial DWI (b values = 50 and 600 or 800 s/mm^2), Dixon sequences, and breath-hold fat-saturated T1-weighted gradient-echo sequences after gadolinium-chelate administration. PET data were reconstructed using scanner-specific algorithms. ADC maps were generated from DWI data using the OsiriX MD software (version 13.0.0; Pixmeo).

Assessments

One radiologist (W.M.) and one nuclear medicine physician (L.B.) evaluated the original and fused [^{18}F]FDG PET/MRI and WB-DWI side by side to identify and select the target lesions for quantitative analysis in consensus. Fourteen nodal regions according to anatomical regions for the staging of lymphoma and other organs as extranodal

Table 1 Lugano criteria for response assessment after induction therapy for [18]F]FDG PET/MRI and modified criteria for whole-body DWI

	[18]F]FDG PET/MRI	Whole-body DWI
Complete response (CR)	Complete metabolic response with D5PS of 1, 2, or 3 with or without residual mass	ADCmin values of all lesions are higher than that of the muscle or surrounding tissue with or without residual mass
Partial response (PR)	Partial metabolic response with D5PS of 4 or 5 with reduced uptake compared to baseline	Increase of ADCmin values from baseline but still restricted diffusion
Stable disease (SD)	No metabolic response with D5PS of 4 or 5 with no significant change in FDG from baseline	No significant change of ADCmin values from baseline
Progressive disease (PD)	Progressive metabolic response with D5PS of 4 or 5 with increase in FDG from baseline and/or new FDG-avid lesion consistent with lymphoma	Decrease of ADCmin values from baseline and/or new diffusion restriction consistent with lymphoma

[18]F]FDG, fluorine-18 fluorodeoxyglucose; *D5PS*, Deauville 5-point score; *DWI*, diffusion-weighted imaging; *ADCmin*, minimum apparent diffusion coefficient; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

regions were evaluated [24]. According to the Lugano criteria, we identified up to six largest measurable target lesions in different body regions per patient. Tumor lesions were considered measurable if they were larger than 15 mm in the longest diameter for nodal lesions and 10 mm in the longest diameter for extranodal lesions [25]. The lesion also must be visible on both [18]F]FDG PET images and DWI. Imaging characteristics on T2-weighted and post-contrast T1-weighted images, including enhancement pattern, tumoral necrosis, effusion, ascites, region of disease involvement, and number of extranodal involvement, were recorded. The investigators were blinded to tumor histopathology, clinical data, and treatment outcome.

The nuclear medicine physician (L.B.) measured the maximum standardized [18]F]FDG uptake values (SUVmax) of the target lesions on [18]F]FDG PET/MR scans using the MIM software (version 7.2.8; MIM Software Inc.) based on isocontour volumes of interest (VOIs) constructed using a 41% SUVmax threshold. The radiologist (W.M.) assessed target lesions on WB-DWI and measured the minimum apparent diffusion coefficient (ADCmin) on ADC maps based on manually defined regions of interest (ROIs).

To determine reproducibility, a radiologist (W.M.) measured the SUV and a nuclear medicine physician (L.B.) measured the ADC of random 20 tumors (10 HL and 10

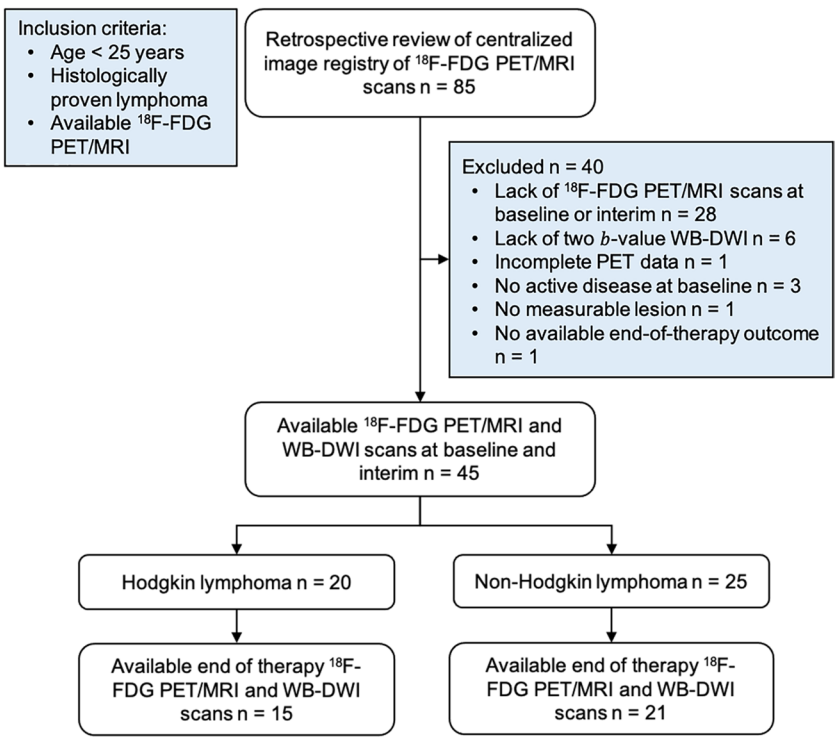

Fig. 1 The retrospective study with inclusion and exclusion criteria. Baseline, before initiation of chemotherapy; [18]F]FDG, fluorine-18 fluorodeoxyglucose; interim, after induction chemotherapy; WB-DWI, whole-body diffusion-weighted imaging

NHL) at least 2 weeks apart. The concordance correlation between the first and second measurements was calculated.

Interim [^{18}F]FDG PET/MRI scans were performed after 1–3 cycles of chemotherapy. End-of-therapy [^{18}F]FDG PET/MRI scans were defined as the first scan after completion of chemotherapy. The Lugano classification was used to evaluate the tumor therapeutic response for [^{18}F]FDG PET/MRI [25]. The modified tumor response assessment for WB-DWI was adapted from prior studies (Table 1) [18, 19]. Lesions with restricted diffusion were defined as lesions that demonstrated high signal on high *b* value DWI and low signal on ADC map as compared to the muscle for nodal lesions or compared to surrounding tissue for extranodal lesions [18, 26]. Baseline scans were available to compare with interim and end-of-therapy scans to ensure that the same target lesions were measured. The treatment response was evaluated and assigned to four categories based on SUV and ADC measurements: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The least response target lesion represented disease response of each patient on each modality.

All clinical data at the end of therapy, including histology and imaging, served as the reference standard for tumor therapy response. Based on their response to therapy, we divided patients into two groups, responders (CR and PR) and non-responders (SD and PD).

The amount of ionizing radiation that patients received during the [^{18}F]FDG PET/MRI scan was calculated using the RADAR Medical Procedure Radiation Dose Calculator [27].

Statistical analysis

An expert statistician (T.L.) performed all analyses. The agreement between WB-DWI- and [^{18}F]FDG PET/MRI–based therapy response assessments (CR, PR, SD, PD) after chemotherapy induction and at the end of therapy was determined using Gwet's agreement coefficient (AC) based on per-patient basis. In addition, a correlation of SUVmax and ADCmin values of the lesions was tested using the Spearman rank correlation. The agreement between

Table 2 Patient demographics

Characteristic	Hodgkin lymphoma ($n=20$)	Non-Hodgkin lymphoma ($n=25$)	All patients ($n=45$)
Age (years)			
Mean ± standard deviation	15 ± 3	13 ± 6	13 ± 5
Range	7–18	1–21	1–21
Sex			
Male	9 (45)	18 (72)	27 (60)
Female	11 (55)	7 (28)	18 (40)
Serum lactate dehydrogenase (U/l)			
Mean ± SD	242 ± 76	657 ± 469	473 ± 408
Range	168–407	185–1800	168–1800
Stage			
I	1 (5)	0	1 (2)
II	11 (55)	1 (4)	12 (27)
III	1 (5)	14 (56)	15 (33)
IV	7 (35)	10 (40)	17 (38)
Bone marrow involvement			
Yes	3 (15)	9 (36)	12 (27)
No	17 (85)	16 (64)	33 (73)
Central nervous system involvement			
Yes	0	4 (16)	4 (9)
No	20 (100)	21 (84)	41 (91)
Time interval between baseline and interim scan (weeks)			
Median	9	6	8
Range	7–14	3–12	3–14
Time interval between baseline and end-of-therapy scan (weeks)			
Median	22	16	19
Range	12–36	7–97	7–97

Unless otherwise indicated, data are numbers of patients with percentages in parentheses

WB-DWI- and [^{18}F]FDG PET/MRI–based therapy response assessments after chemotherapy induction and clinical response assessments at the end of therapy was determined using Gwet's AC. The Kaplan–Meier survival analysis was performed to assess the progression-free survival (PFS). The log-rank test was used to test equality of survival functions between responders and non-responders based on interim [^{18}F]FDG PET/MRI and WB-DWI. Statistical analyses were performed with the STATA software (version 17.0; StataCorp), assuming significant differences for $p < 0.05$.

Results

Patient demographics

The participant flowchart is shown in Fig. 1. Based on our registry, we retrospectively identified 85 pediatric patients with lymphoma. Forty patients were excluded because of incomplete imaging data ($n = 36$) and no measurable lesions ($n = 4$). We analyzed imaging data of 45 patients with HL ($n = 20$) and NHL ($n = 25$), including 27 males and 18 females with a mean age of 13 years ± 5 (range 1–21 years). The demographic and clinical information of the patients is shown in Table 2. The histological subtypes are provided in Table S1.

Mean and median ionizing radiation exposure from [^{18}F]FDG PET were 2.81 mSv ± 1.02, and 2.94 mSv (interquartile range 2.10–3.53), respectively.

Evaluation of the baseline scans

Qualitative imaging characteristics were not significantly different between patients with HL and NHL. A total of 65% of HL and 60% of NHL cases demonstrated homogeneous contrast enhancement on gadolinium-chelate-enhanced T1-weighted MRI scans. NHL demonstrated a tendency towards a higher incidence of tumoral necrosis (36% vs. 15%), extranodal involvement (68% vs. 40%), and presence of pleural effusion or ascites (36% vs. 15%) compared to HL (Table 3). Among seven patients with diffuse large B cell lymphoma (DLBCL), three patients with Epstein-Barr virus (EBV)–positive DLBCL showed a large central necrosis with a thin rim of contrast enhancement (Fig. 2). The remaining four patients with DLBCL, which were not otherwise specified, presented as predominantly solid masses.

At baseline, all HL showed a strong metabolic activity on [^{18}F]FDG PET (mean SUVmax 10.98 ± 5.78 g/mL) and restricted diffusion on WB-DWI (mean ADCmin $0.72 \pm 0.31 \times 10^{-3}$ mm^2/s). Similarly, all NHL showed a strong and inhomogeneous metabolic activity on [^{18}F]FDG PET (mean SUVmax 11.90 ± 7.51 g/ml) and restricted diffusion on WB-DWI (mean ADCmin $0.73 \pm 0.33 \times 10^{-3}$ mm^2/s). NHL that subsequently responded to chemotherapy (CR and PR) showed a mean baseline SUVmax of 10.68 ± 6.14 g/ml and a mean baseline ADCmin of $0.71 \pm 0.33 \times 10^{-3}$ mm^2/s. NHL that did not respond to therapy (SD and PD) showed a mean baseline SUVmax of 21.21 ± 10.45 g/ml and a mean ADCmin of $0.86 \pm 0.28 \times 10^{-3}$ mm^2/s.

To assess reproducibility, the SUVmax and ADCmin of 10 HL and 10 NHL tumor foci were measured by two different readers. Concordance correlation was calculated, and no significant difference between the measurements of the two readers was observed. Bland–Altman plots are available in supplementary materials (Fig. S1).

Therapy response assessment on interim scans

Hodgkin lymphoma After induction chemotherapy, 19 of 20 patients with HL (95%) showed a decreased tumor metabolic activity on [^{18}F]FDG PET and increased ADC values on WB-DWI, consistent with a concordant complete ($n = 18$) (Fig. 3) or partial response to therapy ($n = 1$). One patient (5%) showed a complete response on [^{18}F]FDG PET/MRI but only a partial response on WB-DWI. HL responders demonstrated a relative change in SUVmax between baseline and interim scans of − 79.52% ± 14.22 and a relative change in ADCmin of 161.14% ± 126.78. Interim therapy response assessments with WB-DWI and [^{18}F]FDG PET/

Table 3 Imaging characteristics on T2- and post-contrast T1-weighted MRI

Characteristic	Hodgkin lymphoma ($n = 20$)	Non-Hodgkin lymphoma ($n = 25$)
Pattern of enhancement		
Homogeneous	13 (65)	15 (60)
Heterogeneous	7 (35)	7 (28)
Rim enhancement	0	3 (12)
Tumoral necrosis		
Yes	3 (15)	9 (36)
No	17 (85)	16 (64)
Region of nodal involvement		
Neck	16 (80)	15 (60)
Chest	16 (80)	17 (68)
Abdomen and pelvis	6 (30)	14 (56)
Number of extranodal involvement		
0	12 (60)	8 (32)
1	6 (30)	1 (4)
≥ 2	2 (10)	16 (64)
Pleural effusion or ascites		
Yes	3 (15)	9 (36)
No	17 (85)	16 (64)

Data are numbers of patients with percentages in parentheses

MRI demonstrated a very good agreement in patients with HL (Gwet's AC = 0.94; Table 4). Compared to the clinical end of therapy as the reference standard, both interim [^{18}F]FDG PET/MRI and WB-DWI showed 100% agreement with the end-of-therapy response (Gwet's AC = 1; Table S2).

Non-Hodgkin lymphoma After induction chemotherapy, 15 of the 25 patients with NHL (60%) showed concordant complete (n = 14) or partial response (n = 1) on [^{18}F]FDG PET/MRI and WB-DWI. Two patients (8%) showed an increased tumor SUV and decreased ADC values, consistent with progressive disease. One patient (4%) showed no significant changes in SUV and ADC values, consistent with stable disease.

Seven patients (28%) showed discordant therapy response. Three patients (one with extranodal NK/T cell lymphoma, one with ALK-positive anaplastic large cell lymphoma, and one with primary mediastinal large B cell lymphoma) showed a complete response on [^{18}F]FDG PET/MRI and a partial response on WB-DWI. One patient with EBV-positive DLBCL showed a partial response on [^{18}F]FDG PET/MRI and stable disease on WB-DWI. Two patients (one with Burkitt lymphoma and one with primary mediastinal large B cell lymphoma) showed a partial response on [^{18}F]FDG PET/MRI and a complete response on WB-DWI (Fig. 4). One patient with T-lymphoblastic lymphoma had stable disease on ^{18}F]FDG PET/MRI, but a complete response on WB-DWI (Table 5). WB-DWI and [^{18}F]FDG PET/MRI interim assessments of therapy response for NHL patients showed a moderate agreement (Gwet's AC = 0.66; Table 4).

From baseline to interim scans, NHL responders (CR and PR) showed a mean relative change in SUVmax of − 73.36% ± 16.73 and a mean relative change in ADCmin of 183.63% ± 197.72. In contrast, NHL non-responders (SD and PD) showed a mean relative change in SUVmax and a mean relative change in ADCmin of 21.22% ± 59.63 and − 7.71% ± 66.56, respectively.

Eighty percent of interim [^{18}F]FDG PET/MRI (20 of 25) and 88% of interim WB-DWI (22 of 25) agreed with the clinical response at the end of therapy in NHL patients (Gwet's

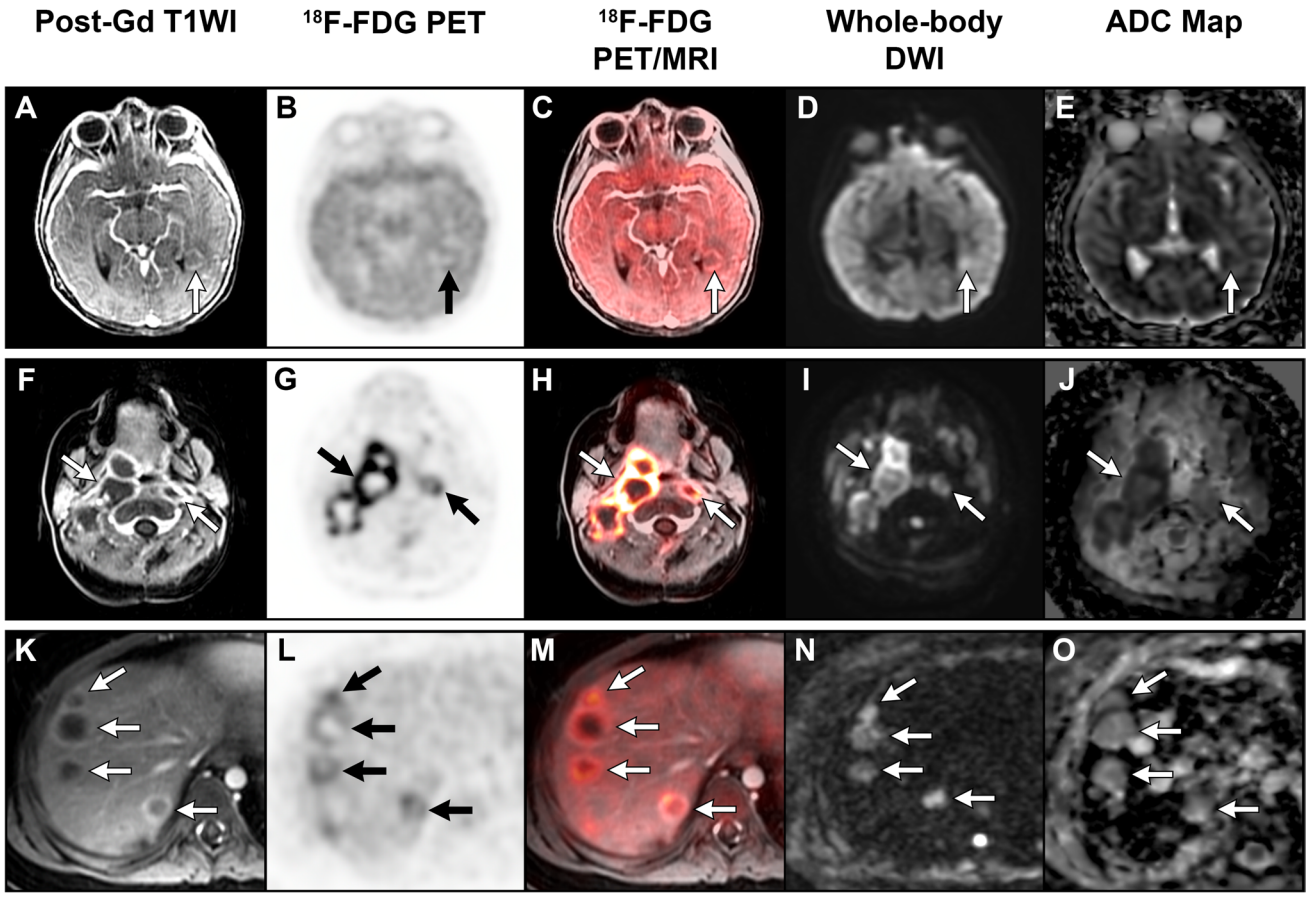

Fig. 2 A 7-year-old male with Epstein-Barr virus (EBV)–positive diffuse large B cell lymphoma. **A** Axial post-gadolinium T1-weighted MRI (post-Gd T1WI), (**B**) fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) PET, (**C**) color-coded fused [^{18}F]FDG/MRI, (**D**) whole-body diffusion-weighted imaging (DWI), (**E**) apparent diffusion coefficient (ADC) map of the brain, (**F–G**) the neck, and (**K–O**) the liver demonstrating multiple rim-enhancing lesions with peripheral FDG uptake in the right temporal lobe, right internal jugular chain, bilateral parapharyngeal spaces, and right lobe of the liver (arrows). These lesions show peripheral restricted diffusion on whole-body DWI and low signal intensity on the ADC map (arrows)

AC = 0.72; 95% confidence interval [CI] 0.44, 0.996; and Gwet's AC = 0.83; 95% CI 0.62, 1, respectively; Table S2).

Therapy response assessment on end-of-therapy scans

[^{18}F]FDG PET/MRI and WB-DWI scans at the end of therapy were not available for nine patients due to an adequate clinical response to induction therapy ($n = 8$) and death ($n = 1$). Of the remaining 36 patients (15 with HL and 21 with NHL), 97% (35 of 36) showed concordant responses between [^{18}F]FDG PET/MRI and WB-DWI at the end of therapy (Gwet's AC = 0.97; Table 4). One patient with NHL (Fig. 4) was assigned a partial response on [^{18}F]FDG PET/MRI and a complete response on WB-DWI on the first imaging investigation after completion of chemotherapy, followed by complete remission on subsequent 4-month off-therapy imaging.

The ADCmin and SUVmax of all lymphomas showed a strong inverse correlation (Spearman's rho = −0.71, $p < 0.001$, $n = 309$; Fig. S2A). There was a moderate inverse correlation between the relative degree of changes in

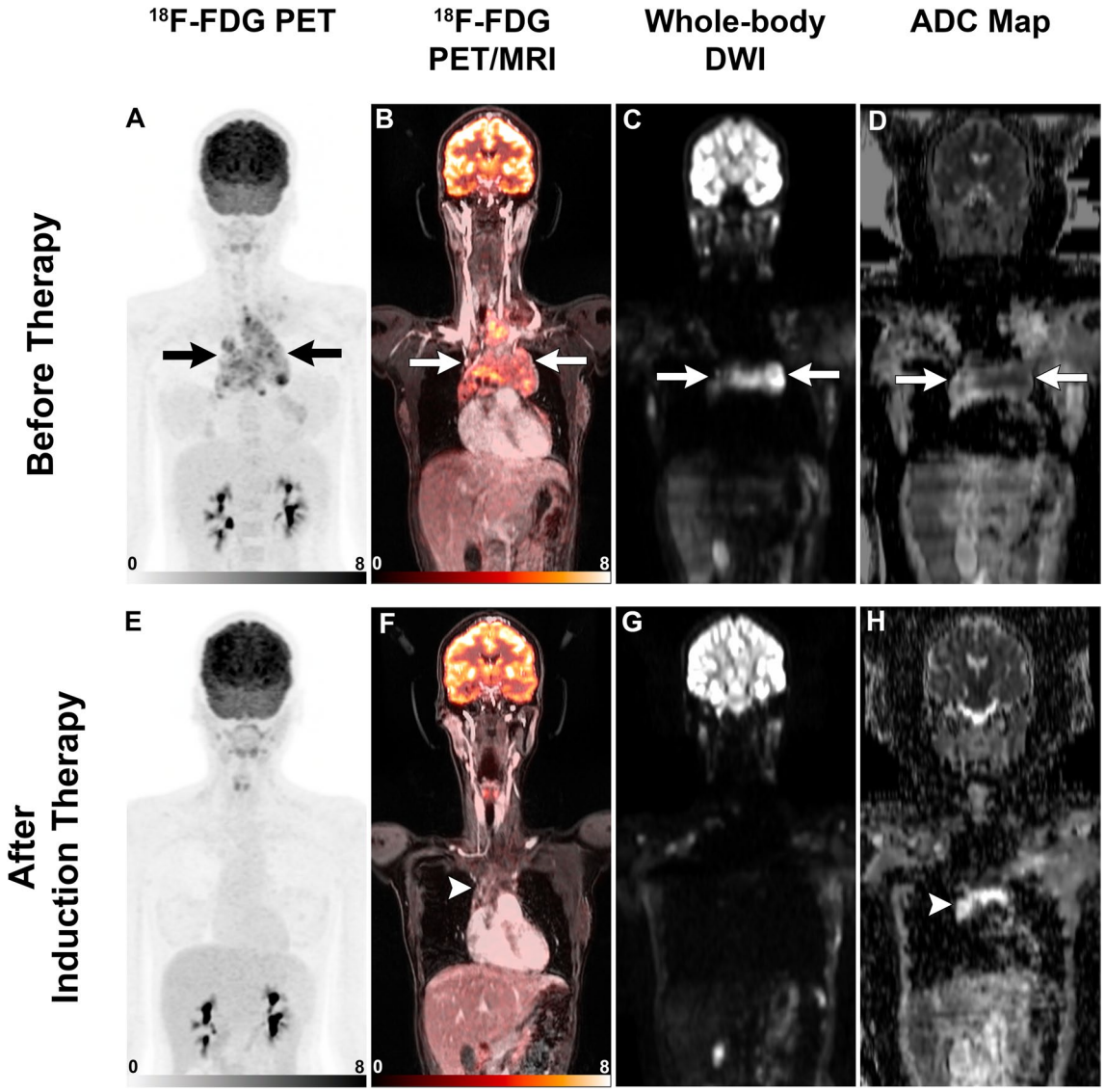

Fig. 3 A 16-year-old female with Hodgkin lymphoma and a concordant complete response on fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) PET/MRI and whole-body diffusion-weighted imaging (DWI). **A–D** Before therapy, **(A)** [^{18}F]FDG PET maximum intensity projection (MIP) image and **(B)** coronal color-coded fused [^{18}F]FDG PET/MRI demonstrating an anterior mediastinal mass with increased FDG uptake. The mass shows restricted diffusion on **(C)** coronal reformatted whole-body DWI, and a low signal on **(D)** the apparent diffusion coefficient (ADC) map (arrows). **E–H** After induction therapy, the mass decreased in size and showed no abnormal FDG uptake on **(E, F)** [^{18}F]FDG PET/MRI, no restricted diffusion on **(G)** whole-body DWI, and a high signal on **(H)** the ADC map (arrowheads)

Table 4 Agreement between whole-body DWI and [^{18}F]FDG PET/MRI therapy response assessment

	Gwet's agreement coefficient (95% confidence intervals)	
Patient group	Interim scan	End-of-therapy scan
All patients	0.80 (0.66, 0.94)	0.97 (0.91, 1)
Hodgkin lymphoma	0.94 (0.82, 1)	1
Non-Hodgkin lymphoma	0.66 (0.43, 0.90)	0.95 (0.83, 1)

DWI, diffusion-weighted imaging; [*^{18}F]FDG*, fluorine-18 fluorodeoxyglucose

SUVmax and ADCmin (Spearman's rho = −0.45, $p < 0.001$, $n = 200$; Fig. S2B). Therapy-induced changes in tumor ADCmin were more variable than those in SUVmax (Fig. S3).

The log-rank test demonstrated different progression-free survivals between responders and non-responders, classified based on either [^{18}F]FDG PET/MRI or WB-DWI ($p = 0.009$ and $p = 0.01$, respectively; Fig. 5).

Discussion

Our data show that the therapeutic response of Hodgkin lymphoma can be assessed by either [^{18}F]FDG PET/MRI or WB-DWI after induction therapy, whereas patients with non-Hodgkin lymphoma may benefit from a combined approach.

Several studies have compared WB-DWI and [^{18}F]FDG PET for treatment monitoring of lymphoma [17–19, 21, 26, 28–30]. However, most previous studies were conducted in adults [17, 18, 26, 28, 29]. Lin et al reported that the ADC analysis reduced false-positive findings in adult patients with NHL on WB-DWI [26]. Mayerhoefer et al found a 97% agreement between [^{18}F]FDG PET/CT and WB-DWI on follow-up examinations in 64 adults with HL and NHL [18]. Theruvath et al reported an agreement between [^{18}F]FDG PET/MRI and WB-DWI at interim follow-up in 30 of 37 (81%) pediatric patients with lymphoma [19]. This is in accordance with our study, which found 82% agreement for interim scans and 97% agreement for end-of-therapy examinations.

Theruvath et al observed that the tumor metabolic activity declined first and the tumor cell density decreased afterwards in lymphoma patients who showed a mismatch in tumor response between [^{18}F]FDG PET/MRI and WB-DWI [19]. In the present study, we examined the type of tumor and found a higher agreement between interim [^{18}F]FDG PET/MRI and WB-DWI in patients with HL than in those with NHL. In a few patients, we noted a complete response on interim WB-DWI and partial response on interim [^{18}F]FDG PET/MRI. We hypothesized that these tumors might have shown an

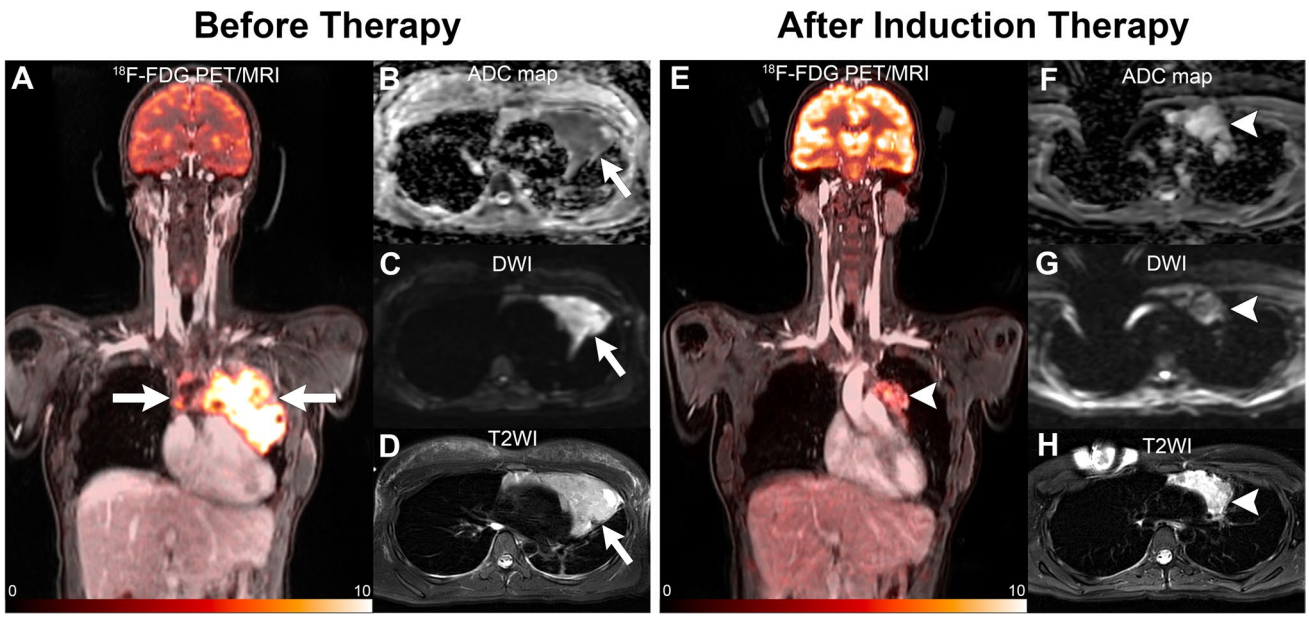

Fig. 4 A 17-year-old female with primary mediastinal large B cell lymphoma and a discordant response on fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) PET/MRI and whole-body diffusion-weighted imaging (DWI). **A–D** Before therapy, (**A**) coronal [^{18}F]FDG PET/MRI shows a heterogeneous anterior mediastinal mass with high metabolic activity (arrows). The lesion shows a low signal on (**B**) the apparent diffusion coefficient (ADC) map with a hyperintense signal on (**C**) axial DWI and (**D**) T2-weighted MRI (T2WI) (arrows). **E–H** After induction therapy, the mass decreased in size but demonstrated a remaining high metabolic activity on **E**.[^{18}F]FDG PET/MRI, consistent with a partial metabolic response (arrowhead). However, the lesion shows a high signal on (**F**) the ADC map, which is higher than that of the muscle as an internal reference standard, compatible with a complete response according to the modified criteria for DWI (arrowhead). The mild hyperintense signal of this lesion on (**G**) DWI is likely due to the T2-shine-through effect since it demonstrates a markedly hyperintense signal on (**H**) T2WI (arrowheads)

Table 5 [^{18}F]FDG PET/MRI– and whole-body DWI-based therapy response assessment of Hodgkin lymphoma ($n=20$)/ non-Hodgkin lymphoma patients ($n=25$)

[^{18}F]FDG PET/MRI	Whole-body DWI				
	Progressive disease	Stable disease	Partial response	Complete response	Total
Progressive disease	0/2	0/0	0/0	0/0	0/2
Stable disease	0/0	0/1	0/0	0/1	0/2
Partial response	0/0	0/1	1/1	0/2	1/4
Complete response	0/0	0/0	1/3	18/14	19/17
Total	0/2	0/2	2/4	18/17	20/25

Data are numbers of patients

DWI, diffusion-weighted imaging; *[^{18}F]FDG*, fluorine-18 fluorodeoxyglucose

inflammatory response rather than a residual tumor metabolic activity. This is compounded by the fact that follow-up scans of all tumors with this pattern demonstrated a complete response at the end of the therapy scans. An experimental study also reported that the ADC analysis helped distinguish between inflammatory and malignant lymph nodes in a rabbit model of VX2 carcinoma [31]. An inflammatory reaction in a residual mass causing an increased metabolic activity in the absence of histologically viable tumor cells has been described in patients with NHL in both interim and end-of-therapy assessments [32–34]. In these cases, adding information from DWI scans may increase the predictive accuracy of interim scans.

Few studies investigated the ability of WB-DWI to predict the long-term survival of patients with lymphoma [28, 35, 36], and none was conducted in pediatric patients. Tsuji et al reported that the absence of restricted diffusion predicted recurrence-free survival in adults [36]. In our cohort of pediatric NHL patients, interim WB-DWI provided a superior agreement with end-of-therapy outcomes compared with interim [^{18}F]FDG PET (88% vs. 80%). De Paepe et al reported 86.7% agreement between interim DWI and clinical outcome and 71.4% agreement between interim [^{18}F]FDG PET and clinical outcome in adult patients with NHL. Therefore, they suggested using an increase in ADC ratio greater than − 0.23% for nodal lesions, less than 67.8% for bone lesions, and greater than 36.1% for extranodal lesions to predict a longer progression-free survival [28]. We found a significantly longer progression-free survival in patients whose tumors demonstrated increased ADC values compared to those with stable or decreased ADC values on interim WB-DWI. Thus, the ADC semiquantitative analysis could be considered an independent criterion for the prediction of progression-free survival.

Our study has several limitations. Since we investigated data from a single center, our study population was limited. However, this approach ensured consistent high-quality MRI and PET data and minimized the risk that the observed differences could be due to technical reasons. Further studies with larger prospective cohorts are required to validate our results. According to the power analysis in our study, we were able to compare the results for patients with HL and NHL. However, we did not have a sufficiently large number of patients to further

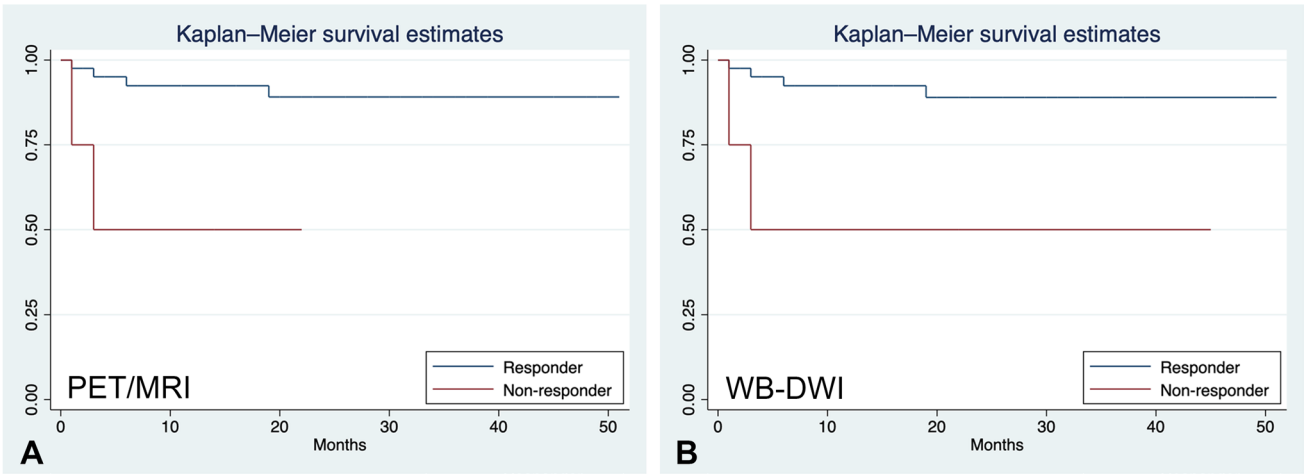

Fig. 5 Kaplan–Meier curves for the progression-free survival of responders and non-responders, defined based on (**A**) interim fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) PET/MRI ($p=.009$) and (**B**) interim whole-body diffusion-weighted imaging (DWI) response assessment ($p=.01$)

evaluate NHL subtypes. DWI has been proven to be comparable to [^{18}F]FDG PET in adult DLBCL [17, 26]. Further studies are required to investigate the role of DWI in NHL subtypes. However, from a practical point of view, our data provide initial evidence to suggest an abbreviated [^{18}F]FDG PET/MR protocol for patients with HL, and a more comprehensive [^{18}F]FDG PET/MR protocol for patients with NHL, including DWI. In addition, a complete protocol of WB MRI including DWI might be considered an alternative for patients with HL in hospitals where [^{18}F]FDG PET/CT or PET/MRI is not available.

In conclusion, WB-DWI is comparable to [^{18}F]FDG PET/MRI for response assessment in patients with Hodgkin lymphoma, whereas patients with non-Hodgkin lymphoma will benefit from an integrated imaging approach.

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Declarations

Guarantor The scientific guarantor of this publication is Heike E. Daldrup-Link, MD, PhD.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent All patients or their legally authorized representative signed a written informed consent, and all children between 7 and 18 years of age signed an assent form.

Ethical approval Institutional Review Board approval was obtained (IRB-44706).

Study subjects or cohorts overlap There is no overlap with previously published work.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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