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ORIGINAL ARTICLE

Imaging children suffering from lymphoma: an evaluation of different ^{18}F-FDG PET/MRI protocols compared to whole-body DW-MRI

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Abstract
Objectives The objectives of this study were to evaluate and compare the diagnostic potential of different PET/MRI reading protocols, entailing non-enhanced / contrast-enhanced and diffusion-weighted ^{18}F–FDG PET/MR imaging and whole-body diffusion-weighted MRI for lesion detection and determination of the tumor stage in pediatric lymphoma patients.
Methods A total of 28 ^{18}F–FDG PET/MRI datasets were included for analysis of four different reading protocols: (1) PET/MRI utilizing sole unenhanced T2w and T1w imaging, (2) PET/MRI utilizing additional contrast enhanced sequences, (3) PET/MR imaging utilizing unenhanced, contrast enhanced and DW imaging or (4) WB-DW-MRI. Statistical analyses were performed on a per-patient and a per-lesion basis. Follow-up and prior examinations as well as histopathology served as reference standards.
Results PET/MRI correctly identified all 17 examinations with active lymphoma disease, while WB-DW-MRI correctly identified 15/17 examinations. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 96%, 96.5%, 97%, 95%, and 96% for PET/MRI$_1$; 97%, 96.5%, 97%, 96.5%, and 97% for PET/MRI$_2$; 97%, 96.5%, 97%, 96.5%, and 97% for PET/MRI$_3$ and 77%, 96%, 96%, 78.5% and 86% for MRI-DWI.
Conclusion ^{18}F–FDG PET/MRI is superior to WB-DW-MRI in staging pediatric lymphoma patients. Neither application of contrast media nor DWI leads to a noticeable improvement of the diagnostic accuracy of PET/MRI. Thus, unenhanced PET/MRI may play a crucial role for the diagnostic work-up of pediatric lymphoma patients in the future.

Keywords Pet/MRI · Pediatric lymphoma · Contrast agent administration · Diffusion-weighted imaging

Introduction

Lymphomas account for 10–15% of cancers in children, resulting in being the third most common pediatric neoplasm after leukemia and central nervous system tumors [1]. Lymphomas are broadly subdivided into Hodgkin and Non-Hodgkin lymphoma with a slightly higher incidence for Non-Hodgkin lymphoma in children [1].

^{18}F–Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F–FDG PET/CT) has been established for staging of most types of lymphoma and sarcoma in pediatric patients [2–4]. Advances in diagnostics and therapy go hand in hand with dramatic improvements of prognosis for children suffering from lymphoma resulting in a 5-year survival of 97% for Hodgkin lymphoma and 85% for Non-Hodgkin lymphoma, respectively [5, 6].

Thus, special attention must be paid towards the applied ionizing radiation dosage associated with (PET)CT imaging as a potential cause of second-line malignancies, particularly in patients of young age [7–9]. The "As Low As Reasonable Achievable" (ALARA) principle is a keypoint of imaging safety. The implementation of integrated PET/Magnetic

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Resonance Imaging (PET/MRI) offers the opportunity to reduce radiation exposure up to 65%, while still preserving high-quality morphologic imaging and staging of lymphoma patients [10–12]. Initial observations have shown similar performance of PET/CT and PET/MRI in the clinical work-up of pediatric lymphomas [13, 14]. Especially in children, the markedly prolonged examination time, caused by the acquisition of a variety of MR sequences still constitutes a major disadvantage of this modality. The prolonged examination time of up to more than one hour is stressful, time consuming, expensive and in the special setting of pediatric imaging may require anesthesia [15]. Apart from PET/CT imaging, whole-body diffusion-weighted MRI (WB-DW-MRI) has been established as a radiation-saving and promising alternative / add-on (to PET imaging) for staging children suffering from lymphoma [16]. Due to the lack of data regarding the comparison of ^{18}F–FDG PET/MRI and WB-DW-MRI for staging pediatric lymphoma patients and the necessity to shorten PET/MRI examination time, we had two aims for this study: First, determining whether PET/MRI or WB-DW-MRI is more suitable for staging pediatric lymphoma patients. Secondly, assessment and comparison of different PET/MRI protocols concerning their diagnostic accuracy to identify the ideal protocol for future clinical routine use. Thus, we compared whether (1) unenhanced PET/MR imaging, (2) contrast enhanced PET/MR imaging, (3) contrast enhanced PET/MR imaging with additional DWI information or (4) WB-DW-MR imaging is more suitable for detecting active lymphoma lesions and determining the tumor stage in pediatric lymphoma.

Material and methods

Patients

This study was approved by the institutional review board. All patients underwent a clinically indicated whole-body PET/MRI after informed written consent of the parents was obtained. Histopathological verification of lymphoma subtypes was available in all patients. A total of 28 examinations were performed in 12 patients (15 ± 2 years; range 9–17 years) enrolled in this study, including scans for initial staging ($n = 11$) and restaging during treatment or at the end of treatment ($n = 17$) as recommended in the ESMO Guidelines [17, 18].

Pet/MRI

^{18}F–FDG PET/MRI examinations were performed on an integrated 3 Tesla PET/MRI scanner (Biograph mMR, Siemens Healthcare GmbH, Erlangen, Germany) with an average delay of 68 ± 21 min after ^{18}F–FDG injection. To ensure blood glucose levels below 150 mg/dl, blood samples were obtained prior to injection of a body-weight adapted dosage of ^{18}F–FDG (4 MBq/kg bodyweight), resulting in a mean activity of 168 ± 64 MBq. A whole body scan (including head and limbs) was performed for initial staging. The scan volumes of follow-up imaging covered skull base to mid-thigh if head and limbs were unsuspicious in initial staging. PET data acquisition was performed in up to five bed positions, depending on children's height. Acquisition time was 4 min per bed position. PET images were reconstructed using the iterative ordered-subset expectation maximization (OSEM) algorithm (three iterations, 21 subsets, Gaussian filter 4 mm, matrix size 344 × 344) [19]. To investigate possible differences between (1) unenhanced PET/MRI, including unenhanced T2w and T1w imaging, (2) additional contrast enhanced T1w VIBE, (3) contrast enhanced PET/MRI including DWI or (4) whole body MRI including T2w imaging and DWI, the readers were asked to exclusively read the corresponding sequences in different combinations out of a longer protocol. In accordance with previous publications, the protocol for whole-body MRI-DWI consisted of a non-enhanced T1w, T2w and diffusion-weighted sequence [20]. The MR protocols were set up in accordance with clinical (age-dependent) standards, entailing different kinds of T1w- and T2w-sequences. For contrast enhanced imaging, a transverse volume interpolated breath-hold examination (VIBE) after intravenous administration of intravenous administration of a gadolinium-based contrast medium (Dotarem; Guerbet, France; 0.05 mmol/kg bw) was acquired. For diffusion-weighted imaging, a transversal diffusion-weighted (DWI) echo-planar imaging (EPI) (b-values: 0, 500 and 1000 s/mm^2) was obtained.

Image analysis

The following imaging datasets of the ^{18}F–FDG PET/MRI examination were analyzed in consensus and in random order by two experienced radiologists in hybrid and MR imaging interpretation on a dedicated OsiriX Workstation (Pixmeo SARL, Bernex, Switzerland) in four different reading sessions comprising the following sequence combinations: (1) PET/MRI$_1$ comprising unenhanced T2w and T1w imaging and ^{18}F–FDG PET (2) PET/MRI$_2$ comprising an additional contrast enhanced VIBE, (3) PET/MRI$_3$ comprising unenhanced T2w and T1w imaging, contrast enhanced VIBE and additional diffusion-weighted imaging and (4) WB-MRI-DWI including T2w imaging and DWI. Each dataset was evaluated in a dedicated reading session in random order with a minimum of two weeks apart to avoid recognition bias. Both readers were blinded to patient identity and results of prior or follow-up imaging. Readers were informed about suspicion for lymphoma and regarding the purpose of the scans, by means of initial staging or restaging.

For each dataset the readers were asked to identify lymphoma manifestations in lymph nodes and extra-nodal regions.

The maximum diameter of all suspicious lesions was determined, and the maximum standardized uptake value (SUV_{max}) was measured by placing a manually drawn polygonal volume of interest (VOI) over each lesion on attenuation-corrected PET images. Using DWI as a part of MR imaging, an ADC map was generated utilizing a dedicated hybrid imaging system software (syngo VB18P, Siemens Healthcare GmbH, Germany) using three b -values (b = 0, 500 and 1000 s/mm^2).

Up to current status, no universally applied morphologic criteria for pediatric lymphoma manifestation have been established. Thus, in accordance with previous publications for adult lymphoma and, as recommended by the Lugano classification, the morphologic criteria for lymphoma manifestation were considered nodal lesions with a nodal long-axis diameter greater than 1.5 cm (unidimensional measurement), cluster formation or mass-like lesions and distinctive contrast enhancement [21–24]. In DWI-sequences high signal intensity on high b-value (b = 1000 s/mm^2) with signal drop in the corresponding ADC map indicated malignancy.

The five-point scale for interpretation of ^{18}F–FDG PET recommended as the standard reporting tool at the First International Workshop on PET in Lymphoma in Deauville and the revised staging and response criteria of the Lugano classification were entirely focused on adult lymphoma without reference to pediatric lymphoma entities [25, 26]. Nevertheless, for lesion characterization on PET, visually increased focal FDG-uptake in comparison to background and mediastinum and higher than liver activity was considered indicative for involvement with lymphoma in concordance with the five-point scale of the Lugano classification.

In accordance with previous publications reporting the superiority of PET uptake over morphology [27] as well as the high sensitivity for detection of malignant lesions in MRI when utilizing DWI [28], a consensus decision among the two readers was made based on all available data in case of discrepant findings on PET and MR datasets as well as in case of discrepancies between the two readers.

As therapy management depends on the distribution of the lymphoma manifestation, the tumor stage was determined in accordance with the revised international pediatric NHL staging system (IPNHLSS) [29] To evaluate the overall diagnostic capability in determining the tumor extent, the tumor stage was assessed in all four datasets separately by both readers. In case of any discrepancies between the two readers, the lesions were specifically evaluated and a consensus decision was made.

Reference standard

Data analysis was performed by two physicians with dedicated expertise in MR and hybrid imaging, performing a consensus interpretation on lesion- and patient-basis for the determination of the reference standard. As described in previous publications [30–32] a modified standard of reference was applied comprising previous cross-sectional imaging (mean interval 107 ± 103 days; ^{18}F–FDG PET/MRT: n = 16; ^{18}F–FDG PET/CT: n = 1; CT: n = 2) as well as follow-up cross-sectional imaging (mean interval of 98 ± 47 days; ^{18}F–FDG PET/MRT: n = 15; MRI: n = 8).

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22 (IBM Inc., Armonk, NY, USA) and Graphpad Prism 7 (GraphPad Software, La Jolla, CA, USA).

Data analysis was performed patient-based as well as lesion-based. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated for PET/MRI$_1$, PET/MRI$_2$, PET/MRI$_3$, PET/MRI$_4$ and WB-MR-DWI, respectively. The Friedman test was applied to test for significant differences between the different datasets. As post hoc test, the Wilcoxon signed-rank test was chosen and Bonferroni adjustment was applied. The McNemar test was applied to test for significant differences between the datasets for determination of tumor stage.

Results

PET/MRI was successfully completed in all 28 examinations. Based on the 28 examinations, Hodgkin lymphoma was diagnosed in 17 cases, Burkitt lymphoma in five cases, extramedullary B-cell lymphoblastic lymphoma in four cases and diffuse large B-cell lymphoma in two cases. For patients' details, see Table 1.

Patient-based analysis

According to the reference standard, active lymphoma was present in 17 out of the 28 examinations. PET/MRI$_1$, PET/MRI$_2$ and PET/MRI$_3$ correctly identified active lymphoma in all cases (100%), while WB-DW-MRI correctly identified active disease in 15 out of the 17 examinations (88%). In all datasets, one patient was classified as false positive (9%).

As described before, tumor stage was determined in accordance with the revised international pediatric NHL staging system. Based on the reference standard, stage 1 disease was present in 2/17 examinations, stage 2 in 1/17 and stage 3 in 14/17 examinations. In our collective, no patient suffered from stage 4 disease. In total, all PET/MRI datasets determined correct tumor stage in 27/28 examinations (96.5%) and overrated one patient (3.5%). WB-DW-MRI determined correct tumor stage in 23/28 patients (82%), overrating one patient (3.5%) and underrating four patients (14.5%). However, no statistically significant difference was seen between the

Table 1 Study patients' characteristics. Abbreviations: B-LBL = B-cell lymphoblastic lymphoma; DLBCL = Diffuse large B-cell lymphoma

Patient	Age in years	Sex	Diagnosis	PET/MRI indication
1	17	Female	Hodgkin Lymphoma	Treatment monitoring
2a	13	Male	Extramedullary B-LBL	Initial staging
2b	13	Male	Extramedullary B-LBL	Treatment monitoring
2c	14	Male	Extramedullary B-LBL	Treatment monitoring
2d	14	Male	Extramedullary B-LBL	Restaging after completion of chemotherapy
3a	9	Male	DLBCL	Initial staging
3b	10	Male	DLBCL	Restaging after completion of chemotherapy
4a	16	Female	Hodgkin Lymphoma	Initial staging
4b	16	Female	Hodgkin Lymphoma	Restaging after completion of chemotherapy
5a	14	Male	Hodgkin Lymphoma	Initial staging
5b	14	Male	Hodgkin Lymphoma	Treatment monitoring
5c	14	Male	Hodgkin Lymphoma	Restaging after completion of chemotherapy
6a	17	Female	Hodgkin Lymphoma	Initial staging
6b	17	Female	Hodgkin Lymphoma	Treatment monitoring
7a	15	Male	Hodgkin Lymphoma	Initial staging
7b	15	Male	Hodgkin Lymphoma	Restaging after completion of chemotherapy
8a	15	Female	Hodgkin Lymphoma	Initial staging
8b	16	Female	Hodgkin Lymphoma	Treatment monitoring
8c	16	Female	Hodgkin Lymphoma	Restaging after completion of chemotherapy
9	14	Male	Hodgkin Lymphoma	Initial staging
10a	14	Male	Burkitt lymphoma	Initial staging
10b	14	Male	Burkitt lymphoma	Treatment monitoring
10c	14	Male	Burkitt lymphoma	Treatment monitoring
10d	15	Male	Burkitt lymphoma	Treatment monitoring
10e	15	Male	Burkitt lymphoma	Restaging after completion of chemotherapy
11a	13	Male	Hodgkin Lymphoma	Initial staging
11b	13	Male	Hodgkin Lymphoma	Treatment monitoring
12	15	Male	Hodgkin Lymphoma	Initial staging

different datasets regarding determining the tumor stage in accordance with the revised pediatric NHL staging system. The rated tumor stages in the different datasets are given in Fig. 1.

Lesion-based analysis

In accordance with the reference standard, a total of 132 lesions were detected, comprising 75 active lymphoma manifestations and 57 benign lesions. Distribution of the different benign lesions is given in Table 2.

Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 96%, 96.5%, 97%, 95%, and 96% for PET/MRI_1 respectively. The corresponding results were 97%, 96.5%, 97%, 96.5%, and 97% for PET/MRI_2; 97%, 96.5%, 97%, 96.5%, and 97% for PET/MRI_3 and 77%, 96%, 96%, 78.5% and 86% for MRI-DWI. This resulted in a significantly higher diagnostic accuracy of all PET/MRI datasets compared to WB-DW-MRI ($p < 0.005$) while no statistically significant difference was seen between the different PET/MRI readings.

Discussion

The present study confirms the feasibility and high diagnostic accuracy of PET/MRI in pediatric lymphoma patients and its superiority to whole-body DW-MRI.

PET/CT has been well-established as the imaging method of choice for adult lymphoma diagnosis, as integrating high resolution anatomical and metabolic information has been shown beneficial for staging and therapy monitoring as well as for differentiation between active and non-active disease [26, 33, 34]. Due to brown fat tissue, a large proportion of the red bone marrow and different tumor biology, the findings in evaluation of adult lymphomas cannot be unreservedly transferred to pediatric imaging. But numerous studies have also confirmed the high diagnostic value of PET/CT for staging children suffering from lymphoma [3, 35]. Nevertheless,

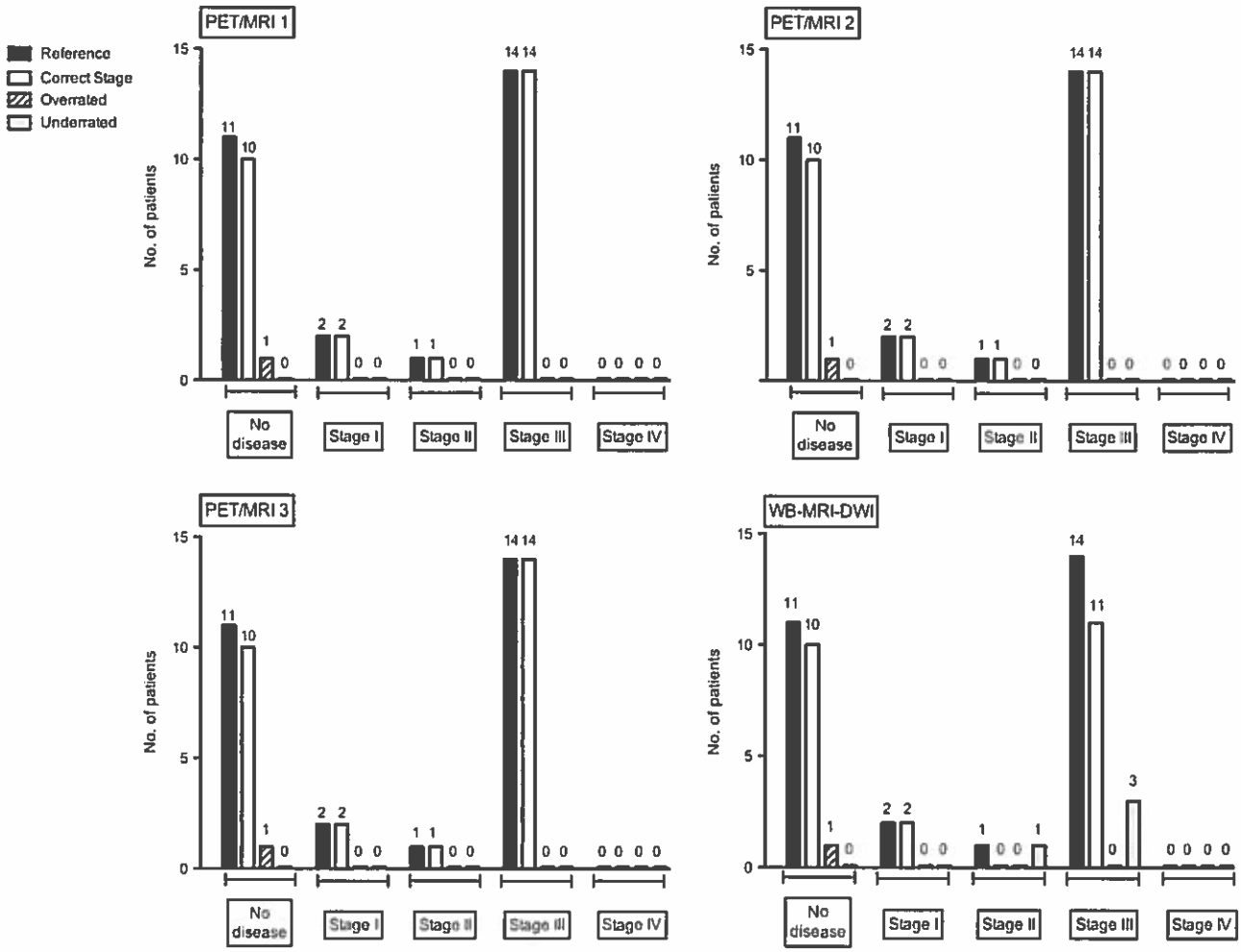

Fig. 1 PET/MRI is superior to WB-DW-MRI. Based on the revised IPNHLSS, all PET/MRI datasets were rated superior to WB-DW-MRI regarding determination of the tumor stage, while no difference could be detected between the different PET/MRI datasets including (1) unenhanced T2w and T1w imaging, (2) additional contrast enhanced sequences or (3) contrast enhanced sequences and DWI

the associated increase in radiation exposure associated with ^{18}F-FDG PET/CT (when compared to conventional imaging) as well as potential repetitive scans for therapy monitoring and post-remission surveillance, demands special attention [36].

Currently, there are two different approaches to reconcile the reduction of ionizing radiation exposure, while preserving high diagnostic accuracy. The first is the utilization of an integrated PET/MRI system, combining the high spatial resolution and soft-tissue contrast of MRI with the metabolic information based on PET, which has shown promising results for the evaluation of children with lymphoma [14]. Initial studies put the focus on the general feasibility of PET/MRI for whole-body staging in pediatric patients. But as prolonged examination times in PET/MRI may result in discomfort and potential termination of the exam, particularly in pediatric imaging, one of the aims of our study was to specifically analyze different reading protocols differing in their total examination time. Furthermore, recent publications raised awareness on gadolinium deposition in the brain after repetitive application of gadolinium-based contrast agents [16]. As lymphoma patients commonly undergo multiple contrast-enhanced examinations for staging, therapy monitoring and surveillance of their disease, the likelihood to be affected by potential gadolinium deposition is increased. While the clinical consequences of this side effect are yet to be investigated, the raised awareness puts the emphasis on the actual need for contrast agent / potential omission. Hence, the second aim of

Table 2 Distribution of the benign lesions

Kidney cyst	23
Posttherapeutic bone marrow changes	11
Non-viable lymphoma	6
Liver cyst	3
Follicular cysts	2
Others	12
Total	*57*

this trial was to compare the diagnostic value of unenhanced versus contrast-enhanced PET/MR imaging. The second approach to reduce the amount of applied ionizing radiation is to perform whole-body MRI including DWI combined with unenhanced morphological imaging or combined with ferumoxytol-enhanced T1 images [20, 37]. Considering this recent data, the third aim of this study was to investigate the diagnostic potential of different PET/MRI reading protocols and of whole-body DW-MRI including T2w imaging for morphological correlation (Fig. 2).

This publication comprises two main messages we believe to be important: First, even unenhanced PET/MRI, just comprising T2w and T1w imaging and ^{18}F-FDG PET shows highest diagnostic accuracy and neither application of contrast media nor DWI leads to a noticeable improvement. Secondly, PET/MRI is significantly superior to WB-MR-DWI for the evaluation of pediatric patients suffering from lymphoma (Fig. 3).

On a patient-based and lesion-based analysis, our results regarding the high diagnostic potential of PET/MRI for evaluation of pediatric lymphoma patients are concordant with recently published results by Schafer et al. and Ponisio et al. [14, 38]. Yet, both authors investigated PET/MRI protocols comprising unenhanced morphologic sequences and DWI. Thus, this is the first publication to assess the role of DWI and the potential benefit of additional contrast media application as part of a PET/MRI examination. Contrary to observations in adults, no increasing diagnostic accuracy resulted from acquiring additional contrast enhanced sequences or diffusion-weighted imaging [39]. Previous publications showed that the use of DWI might be highly beneficial and potentially superior to PET imaging in staging specific lymphoma subtypes, in particular for mucosa-associated lymphoid tissue lymphoma, which is known to yield varying FDG-avidity, constraining the diagnostic value of PET imaging [40]. But this lymphoma subtype is very rare in children and not included in our cohort. Our results may be of particular importance as the total examination time could be remarkable reduced due to the omission of contrast media application and DWI acquisition in combination with a potential reduction of the PET acquisition time to two minutes as described by Hartung-Knemeyer et al. [41]. Waiving the contrast media application is not only of highest interest in regard to the examination time, but also regarding a potential gadolinium retention in the dentate nucleus and globus pallidus due to the repetitive application of linear gadolinium-based contrast agents as reported by Radbruch et al. [16]. Although there are no valid hints concerning effects of macrocyclic gadolinium-based contrast agents or clinical implications so far, our results indicate that any risk could be avoided in this group of young patients without decreasing the diagnostic accuracy.

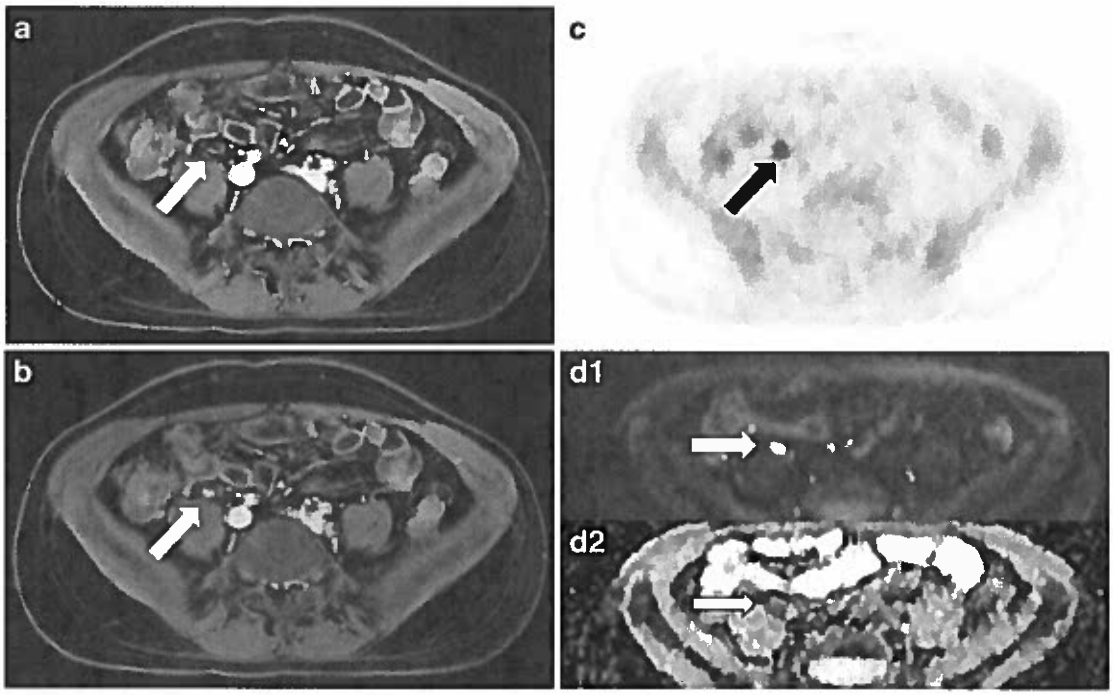

Fig. 2 Nodal lymphoma manifestations in a 14-year old boy suffering from Hodgkin lymphoma. The arrows mark a small lymph node ventral the right M. iliopsoas with unsuspicious morphology in ceT1w MR image (A) but pathological glucose metabolism in FDG PET imaging (C) that is clearly visible as active lymph node in fused PET/MRI (C) and restricted diffusion [distinctive diffusion restriction in DWI (D1; b = 1000 s/mm^2) and signal drop in corresponding ADC-map (D2)]

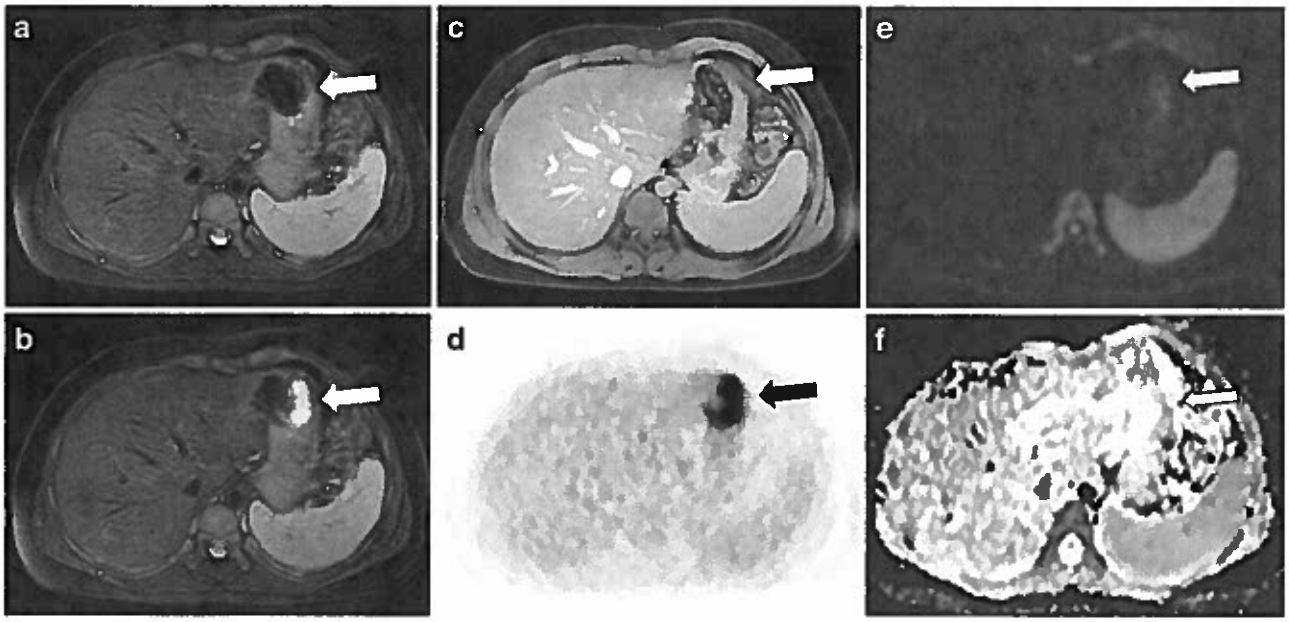

Fig. 3 Gastric lymphoma manifestation in a 15-year old boy suffering from Burkitt lymphoma. While unenhanced (A: T2w TSE) and contrast enhanced (C: T1w VIBE) MR imaging shows an unsuspicious gastrointestinal tract, a strong pathological glucose metabolism in the abdomen is seen in FDG PET imaging (D). The fused PET/MR imaging reveals the location in the gastric wall (B). No distinctive diffusion restriction in DWI (E: b = 1000 s/mm^2) or signal drop in ADC map (F) can be detected. Diagnosis of gastric lymphoma manifestation was confirmed by histopathology after gastroscopy was performed

This is the first publication comparing PET/MRI and WB-DW-MRI for staging pediatric lymphoma patients. Our findings demonstrate the superiority of PET/MRI over WB-DW-MRI, particularly in terms of sensitivity and diagnostic accuracy, and go in line with the observations of Herrmann et al. [21]. The authors compared PET/MRI and WB-DW-MRI for clinical work up of lymphomas in adults with comparable results to ours (sensitivity 67% vs 77%). Klenk et al. published promising results with ferumoxytol-enhanced WB-DW-MRI. Nevertheless, this emerging technique also offered slightly inferior results when compared to PET/CT [37]. So far, ferumoxytol is used as an off-label contrast agent and no data about potential long-time risks are available.

Our study is not without limitations. First, although histopathological sampling for subtype determination was available in all patients, not every detected lesion could be sampled due to ethical reasons and in accordance with current clinical guidelines. Hence, as published in numerous previous trials on hybrid imaging, a modified reference standard was applied [30, 32]. Secondly, lymphoma is known to comprise a heterogeneous group of cancers entailing different subtypes. Thus, although a dedicated subtype evaluation would have been desirable, the rather small number of included patients restricted further subtype categorization due to potentially underpowered statistical analyses. Hence, as the number of pediatric lymphoma patients is inherently limited, future trials involving multi-center approaches should be the focus of studies.

In conclusion, the present study shows the very high diagnostic accuracy of PET/MRI in staging pediatric lymphoma and underlines the lack of additional benefit of contrast-enhanced or diffusion-weighted imaging. Furthermore, PET/MRI was shown to be superior versus WB-DW-MRI considering sensitivity and diagnostic accuracy. Thus, with regard to a decrease in radiation exposure, manageable examination time and high diagnostic accuracy unenhanced PET/MRI, solely including T2w and T1w imaging may play a crucial role for the diagnostic work-up of pediatric lymphoma patients.

Compliance with ethical standards

Funding None.

Conflict of interest None.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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