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Research article

Fused high b-value diffusion weighted and T2-weighted MR images in staging of pediatric Hodgkin's lymphoma: A pilot study

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ABSTRACT

Purpose: To evaluate the value of fused high b-value diffusion weighted and T2-weighted MRI compared to T1-weighted imaging, T2-weighted imaging and DWI for staging pediatric Hodgkin's lymphoma.
Method: 21 consecutive pediatric patients who underwent whole-body MRI at Hodgkin's lymphoma staging were included. Fused, colorized DWI/T2-weighted images were created. Image sets consisting of (a) T1-weighted, T2-weighted and DWI images and (b) T1-weighted, T2-weighted, DWI and DWI/T2-weighted fused images were reviewed by a radiologist using a cross-over design with blinding and randomization. Scoring was performed using a standardized form, based on detection, characterization and reading time, using a FDG-PET/CT based reference standard. Test characteristics, test agreement to a FDG-PET/CT based reference standard and reading times were calculated.
Results: Agreement for whole-body MRI without fused images and FDG-PET/CT was very good for nodal staging (κ = 0.86, 95% CI 0.78-0.93) and extra-nodal staging (κ = 0.90, 95% CI 0.71–1.09). Agreement improved with the addition of the fused DWI/T2-weighted images (κ = 0.92 95% CI 0.87-0.97 (nodal staging), κ = 0.92 95% CI 0.76–1.08 (extra-nodal staging). Sensitivity and specificity for staging nodal disease were 99 % and 95% respectively for whole-body MRI including DWI/T2-weighted fused images (versus 88 % and 97 % without fused images) and 100 % and 99 % for extra-nodal disease (83 % and 100 % without fused images). Disease stage for MRI including fused DWI/T2-weighted images agreed with the reference standard in 18 out of 21 patients.
Conclusions: The addition of DWI/T2-weighted fusion images to T1-weighted, T2-weighted and DWI whole-body MRI might shorten reading times and might improve the diagnostic performance of whole-body MRI in staging pediatric Hodgkin's lymphoma.

1. Introduction

Imaging plays a central role in the staging of pediatric Hodgkin's lymphoma (HL). During the last decades, lymphoma imaging has evolved from using contrast-enhanced computed tomography (CT) alone, to the addition of 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET). More recently, whole-body magnetic resonance imaging (MRI) is preferred to contrast-enhanced CT in addition to FDG-PET for staging within the European study and treatment protocol for pediatric Hodgkin's lymphoma (Euronet-PHL-C2) [1–5].

The additional value of diffusion weighted imaging (DWI) for (pediatric) HL has already been described in the literature [6–8], but DWI images contain relatively poor anatomical detail compared to high resolution T2-weighted images. Combining the functional DWI information with the anatomic detail present in T2-weighted images by overlaying the high b-value DWI image upon the corresponding T2-weighted image might therefore be of additional value in HL imaging. Since both normal lymph nodes and malignant lymph nodes show restricted diffusion [9], the potential value of overlaying DWI and T2-weighted images for HL is to increase the detection rate rather than to improve characterization. An additional potential benefit of DWI/T2-weighted fusion imaging involves reading times. Reading of a whole-body MRI including DWI is known to be a time consuming task and might currently take up to 25 min [10,11]. Combining T2-weighted and

Abbreviations: DWI, diffusion weighted imaging; FDG-PET/CT, 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography; HL, Hodgkin's lymphoma; MRI, magnetic resonance imaging; STIR, short inversion time inversion recovery; TSE, turbo spin echo

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DWI images could potentially help limiting reading times and by doing so improving workflow efficiency.

Recent literature showed that fusion of DWI and T2-weighted images improved identification of pelvic lymph nodes in patients diagnosed with pelvic malignancies [12]. For detecting recurrence of pelvic malignancies DWI/T2-weighted fusion imaging was superior to T2-weighted and DWI alone as well [13]. In the pediatric population DWI/T2-weighted fusion imaging was studied in patients with bowel inflammation and showed similar results compared to post contrast imaging [14].

The use of DWI/T2-weighted fusion MR images for staging pediatric HL has, by our knowledge, not yet been previously described in the literature. The aim of this study was to assess the diagnostic ability and possible time saving opportunities of fused color map DWI/T2-weighted fusion images at staging of pediatric HL when compared to conventional MR sequences (T1-weighted, T2-weighted and DWI).

2. Materials & methods

2.1. Study population

This study was a retrospective review of acquired data in 21 patients (13 female, 8 male) at a single institution (University Medical Center Utrecht). Data were collected between 2014 and 2018. This study was approved by the local institutional research ethics board, formal consent was not required. Inclusion criteria were: pediatric patients with histologically proven HL who underwent whole-body MRI for staging. Patients without complete staging whole-body MRI and FDG-PET/CT studies made within a 15 days range of each other were excluded.

2.2. MRI technique

Imaging was performed on either a Philips 1.5 T MR system (18 patients) or a Philips 3.0 T MR system (3 patients) (Ingenia, Philips Medical Systems, Best, The Netherlands). Whole-body MRI included T1-weighted, T2-weighted and DWI of head and neck, chest, abdomen and pelvis. Detailed imaging parameters are shown in Table 1. Fusion images of the DWI and T2-weighted images were created by the researcher (S.S.) prior to the reading session using OsiriX Medical Imaging Software (free version, version 8.0.2). In these images the signal from the high b-value DWI was overlaid on the T2-weighted images. In case of initial misalignment, the correct alignment was manually adjusted.

2.3. Image interpretation

The MR images were analyzed by a board-certified pediatric radiologist (A.S.L. with 10 years of pediatric MRI experience) using OsiriX Medical Imaging Software. FDG-PET/CT images were analyzed by a nuclear medicine physician (B.d.K. with 12 years of FDG-PET/CT experience) using OsiriX Medical Imaging Software as well. All patient images were anonymized. The readers were aware of the diagnosis HL, but had no access to other information such as clinical data and other imaging findings. Analyses and scoring were performed using a standardized form based on the Lugano classification [15]. The MRI reader first evaluated the conventional sequences (T1-weighted, T2-weighted, DWI) followed by the conventional sequences plus the DWI/T2-weighted fusion images 4 months after the initial reading. Reading times for both reading sessions were recorded (the reading time for the set including the fused images did not include the time to fuse the images, which was performed by the researcher (S.S.) prior to the reading and was less than one minute per fusion). The discrepancies were defined as being either caused by incorrect interpretation of an abnormality (interpretation error) or failure of detection of the abnormality (perceptual error).

2.4. Statistical analysis

FDG-PET/CT was used as reference standard. Overall agreement (the proportion of correctly staged patients as compared to the reference standard), sensitivity and specificity were calculated against the reference standard. 95% Confidence intervals were calculated. Unweighted kappa statistics (defined as: poor (κ 0-0.2), fair (κ 0.21-0.4), moderate (κ 0.41-0.6), good (κ 0.61-0.8), very good (κ > 0.81)) were used to compare agreement between whole-body MRI staging results with and without DWI/T2-weighted fusion images. These analyses were performed for: disease stage, all nodal stations together, all extra nodal stations together and for all stations separately. Reading times were compared using related samples Wilcoxon signed rank test. The most diagnostic sequences (as chosen by the reader) were compared. Data were analyzed using Statistical Package for the Social Sciences (SPSS Inc., version 25 for Windows, Chicago, IL, USA). In all statistical analyses a P-value ≤0.05 was considered statistically significant.

Table 1
WB-MRI detailed imaging parameters. *DWI, diffusion weighted imaging; STIR, short inversion time inversion recovery; T, Tesla; T1W, T1-weighted; T2W, T2-weighted; TSE, turbo spin echo*.

	1.5 T			3 T		
	Pulse sequence					
	T1W TSE	T2W STIR	DWI STIR	T1W TSE	T2W STIR	DWI STIR
Orientation	Coronal	Coronal	Axial/coronal	Coronal	Coronal	Axial/coronal
Repetition time (ms)	573	2414	8056	685	8289	8388
Echo time (ms)	17.5	65	67	8	70	86
Inversion time (ms)	–	165	180	–	230	220
Slice thickness/ slice gap (mm)	6/1	6/1	6/0	6/1	6/1	7/0
Number of slices per station	30	30	60	30	30	40
Field of view (mm2)	530 × 265	530 × 265	450 × 365	549 × 230	549 × 230	450 × 295
Acquisition matrix	416 × 287	336 × 267	128 × 99	344 × 292	344 × 304	128 × 125
B-values (s/mm2)	–	–	0, 100, 800	–	–	0, 800
Number of signals averaged	1	1	1	1	1	1
Respiratory motion compensation	Breath hold thorax and abdomen	Breath hold thorax and abdomen	Free breathing	Breath hold thorax and abdomen	Breath hold thorax and abdomen	Free breathing
Total effective scan time	5 min 48 s	5 min 13 s	16 min 26 s	4 min 48 s	3 min 58 s	11 min 44 s

Table 2
Agreement between whole-body MRI and the FDG-PET/CT based reference standard. *CI, confidence interval; DWI, diffusion weighted imaging; K, kappa; MRI, magnetic resonance imaging; NA, not applicable.*

	K for MRI without DWI/T2-weighted fused images		K for MRI with DWI/T2-weighted fused images	
	K	95% CI	K	95% CI
All nodal stations	0.86	0.78-0.93	0.92	0.87-0.97
All extranodal stations	0.90	0.71-1.09	0.92	0.76-1.08
Nodal stations:				
Cervical	0.45	−0.19-1.09	0.64	0.03-1.28
Axillary	0.67	0.33-1.01	1.00	NA
Infraclavicular	1.00	NA	0.80	0.53-1.07
Mediastinal	0.64	0.03-1.28	1.00	NA
Hilar	0.71	0.41-1.00	0.80	0.54-1.06
Spleen	1.00	NA	0.83	0.51-1.15
Para-aortic	0.46	−0.14-1.06	0.83	0.51-1.15
Mesenteric	0.46	−0.14-1.06	1.00	NA
Pelvic	1.00	NA	0.65	0.03-1.27
Inguinal	1.00	NA	1.00	NA
Extranodal stations: Central nervous system	1.00	NA	1.00	NA
Lung	0.77	0.35-1.19	0.83	0.51-1.15
Liver	1.00	NA	1.00	NA
Bone marrow	1.00	NA	1.00	NA
Ann-Arbor stage	0.95	0.88-1.02	0.92	0.84-1.00

3. Results

3.1. Study population

A total of 21 pediatric HL patients were included. All were diagnosed and treated between 2014 and 2018. The mean age was 14.4 years (standard deviation (SD): 2.3, age range 8–17). 13 female (61.9 %) and 8 male (38.1 %) patients were included. 20 patients were diagnosed with classical HL (75 % nodular sclerosing HL, 20 % classical HL not otherwise specified and 5% mixed cellularity HL) and 1 patient was diagnosed with nodular lymphocyte predominant HL (nodular paragranuloma).

3.2. Staging agreement

Both the staging results of the whole-body MRI examinations including DWI/T2-weighted fused images and those without fused images were compared to a FDG-PET/CT based reference standard (Table 2). A minor improvement in agreement was shown by the addition of fused DWI/T2-weighted images for staging HL, both nodal and extranodal. For both sets of sequences the agreement for both nodal and extra nodal staging was very good (κ values ranging from 0.86 to 0.92). When comparing the separate stations, agreement was good or very good for all stations, including reading of fused images. For MRI without fused DWI/T2-weighted images agreement was moderate for the cervical, para-aortic and mesenteric lymph node stations. In all other stations agreement was good or very good. In three of the nodal stations (infraclavicular nodes, the spleen and pelvic nodes) the addition of fused images resulted in a lower agreement. In all other stations the agreement was either comparable (4 stations) or higher (7 stations) for the reading set including fused images.

3.3. Sensitivity, specificity and agreement for staging HL

The sensitivity and specificity for whole-body MRI including fused DWI/T2-weighted images for detecting nodal disease involvement were 99 % (95% CI 0.93–1.00) and 95% (95% CI 0.90-0.98) respectively, compared to 88 % (95% CI 0.78-0.94) and 97 % (95% CI 0.93-0.99) without fused images. For extranodal staging a sensitivity of 100 % (95% CI 0.54–1.00) and a specificity of 99 % (95% CI 0.93–1.00) were found for whole-body MRI including fused images compared to a sensitivity of 83 % (95% CI 0.36–1.00) and a specificity of 100 % (95% CI 0.95–1.00) for whole-body MRI without fused images. The overall agreement for staging was 86 % (95% CI 0.65-0.95) for staging with and 90 % (95% CI 0.71-0.97)for staging without fused DWI/T2-weighted images.

For the set of MRI sequences without fused images disease stage agreed with the reference standard in 19 out of 21 patients. In two patients the MRI underestimated disease stage (stage 2 versus stage 3, one was considered a perceptual error, the other an interpretation error). For those two patients the reference standard and the MRI reading including fused DWI/T2-weighted images did agree on disease stage.

For the set of MRI sequences including fused images disease stage agreed with the reference standard in 18 out of 21 patients comparable to the reference standard. Discrepancies were as follows; in one patient the addition of fused images resulted in finding an E-lesion (direct extension of a nodal disease site into extra-lymphatic organs or structures) in the lung where both the reference standard and the set of MRI sequences without fused images did not (stage 3E versus stage 3; interpretation error). In two patients the addition of fused images resulted in stage 3 compared to stage 2 for the reference standard (both interpretation errors). For those two patients the reference standard and the MRI reading without fused DWI/T2-weighted images did agree on disease stage (both stage 2). Fig. 1 and 2 show examples of the DWI/T2-weighted fusion compared to separate T2-weighted and DWI MRI.

3.4. Reading times

The mean reading time of the T1-weighted, T2-weighted and DWI sequences together was 8.5 min (range 4–19 minutes) compared to 7.0 min (range 3–12 minutes) for the T1-weighted, T2-weighted, DWI and DWI/T2-weighted fused images. This difference of 1.5 min was statistically significant with a p-value of 0.048.

3.5. Most diagnostic sequences

Fig. 3 shows the distribution of sequences chosen as most diagnostic in the evaluation of the whole-body MRI. In all cases a combination of sequences was chosen as most diagnostic rather than one separate sequence. For the series without fused DWI/T2-weighted images a combination of T2-weighted images and DWI was chosen most diagnostic in 19/21 patients (90.5%). For the series including fused DWI/T2-weighted images, the fused images were chosen as being part of the most diagnostic sequences in 16/21 patients (76 %). This was always in combination with other sequences.

4. Discussion

This pilot study in 21 pediatric HL patients evaluated the staging performance and possible additional value of the addition of DWI/T2-weighted fusion images to the currently used sequences (T1-weighted, T2-weighted, DWI) in whole-body MRI. By combining the functional DWI information with the anatomic detail of the T2-weighted sequence the aim of this study was to evaluate the detection rates and reading times. It was demonstrated that the staging results from whole-body MRI including DWI/T2-weighted fusion images were similar compared to whole-body MRI without fused images. With comparable specificities and improved sensitivities for staging, the addition of fused DWI/T2-weighted images resulted in better detection of affected lymph nodes. On the other hand, this high sensitivity resulted in overstaging in three patients. For one of these three patients this would not have caused treatment differences (stage 3E versus stage 3). However, in the other two cases the overstaging (stage 3 in stead of stage 2) would have

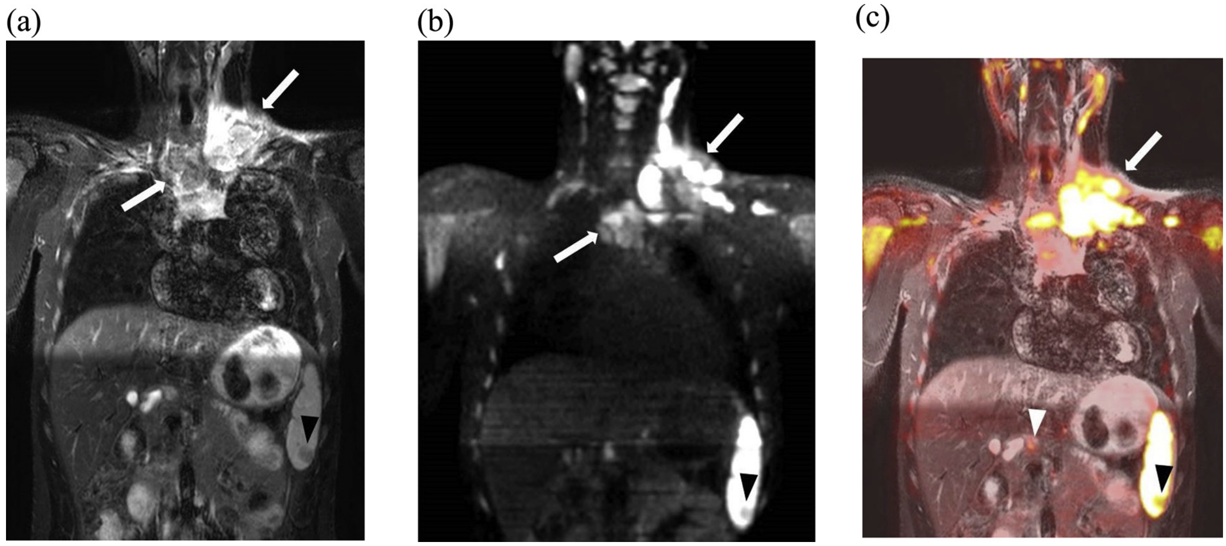

Fig. 1. A 15-year-old girl with stage III Hodgkin's lymphoma. Coronal T2-weighted (a), DWI (b) and DWI/T2-weighted fused MR images show involvement of cervical, mediastinal and hilar lymph node stations (arrows) and spleen (black arrowhead). For the para-aortal lymph node station, FDG-PET/CT (not shown) and WB-MRI including fused images were scored positive (white arrowhead), whereas the separate sequences were scored false-negative for this station.

resulted in a treatment protocol involving more cycles of chemotherapy, according to the European treatment protocol for pediatric Hodgkin's lymphoma (EuroNet-PHL-C2 protocol) [5]. This is in contrast with the set of MRI sequences without fused images in which two patients were staged lower compared to the reference standard and no patients were overstaged. This understaging in two patients, stage 2 in stead of stage 3, would have resulted in a different, less intensive, treatment protocol. Both under- and overtreatment are of course undesirable. Undertreatment on the one hand most likely will result in an insufficient amount of treatment and therefore high risk of relapses. Overtreatment on the other hand might result in an unnecessary increase in side-effects and long term complications. Independent of the staging differences found in the present study between whole-body MRI and the FDG-PET/CT based reference standard, one should realize that, although sensitivity and specificity for staging are high, the FDG-PET/CT might also show false positive or negative results [16].

When assessing all stations separately, the agreements in most stations were the same or better for whole-body MRI including fused images compared to MRI without fused images (11 out of 14 stations). In the three remaining stations agreement was lower due to overstaging in whole-body MRI including fused images. Compared to the set of MRI sequences without fused images, the overall detection rate was higher when including DWI/T2-weighted fused images. But since the set including fused images identified more lesions compared to FDG-PET/CT as well, the fused images might have been too sensitive. On the other hand, for abdominal lymph nodes the detection rates improved with the addition of fused images, resulting in an increased agreement with the FDG-PET/CT reference standard (from moderate to very good in both para-aortic and mesenteric lymph node stations).

The results of the present study show a shortened mean reading time. The addition of fused DWI/T2-weighted images might potentially help to limit reading times and improve workflow efficiency. Despite the mean shorter reading times, all sequences had still to be assessed separately. Although the fused sequence was not suitable for isolated use, it neither did act as a full additional sequence to review. The fused images could be used to easily detect the areas of interest and these areas could be further explored in the separate sequences.

The fused images were chosen to be amongst the most diagnostic sequences in 76 % of the patients. However, this was always in combination with other sequences (in all patients combined with T2-weighted images, and in 43 % with the separate diffusion weighted images as well). Therefore, the fused DWI/T2-weighted images were

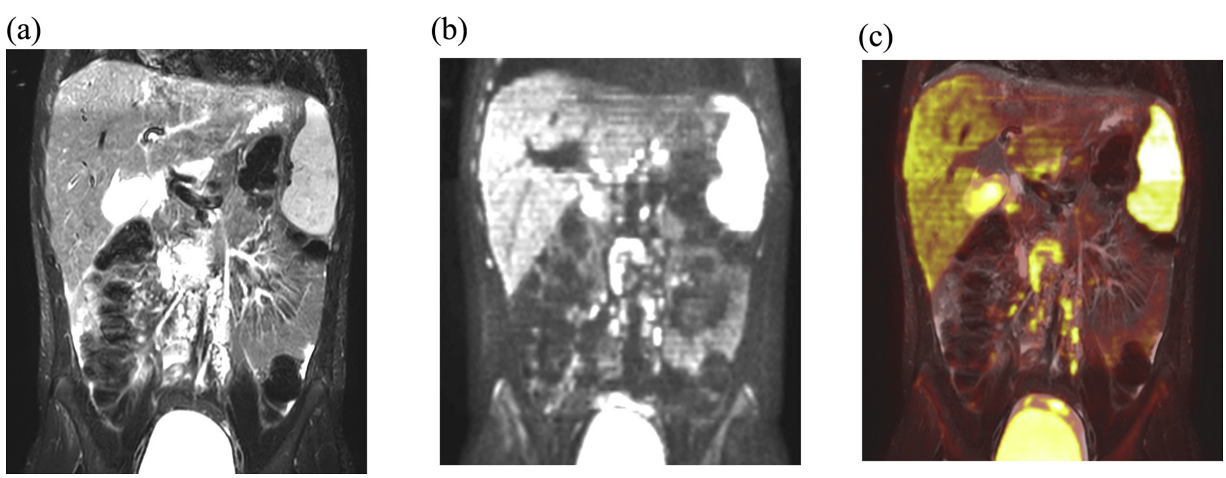

Fig. 2. A 13-year-old boy with stage IV Hodgkin's lymphoma. Lymphoma localizations for this patient included several lymph node stations both above and below diaphragm as well as involvement of bone marrow and spleen. Coronal T2-weighted (a), DWI (b) and DWI/T2-weighted fused MR images show involvement of several mesenteric lymph nodes. The affected lymph nodes are better visualized on the fused image (c) compared to the separate sequences (a and b).

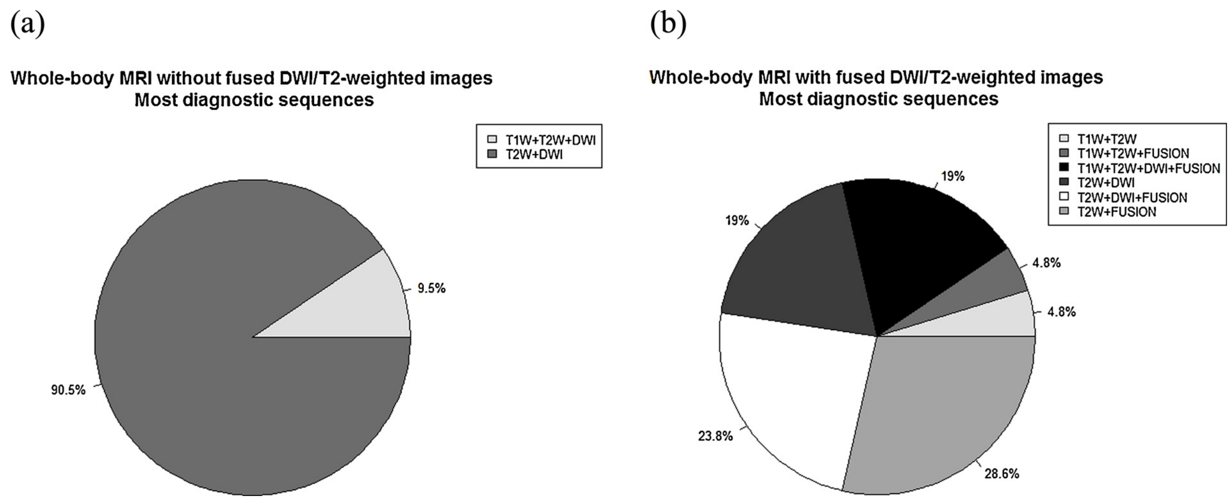

Fig. 3. Pie charts showing the combinations of sequences chosen as most diagnostic for (a) whole-body MRI without fused DWI/T2-weighted images and (b) whole-body MRI with fused DWI/T2-weighted images. *T1W, T1-weighted MRI, T2W, T2-weighted MRI, DWI, diffusion weighted imaging, fusion = fused T2-weighted and diffusion weighted images.*

found to be useful as an addition to the separate sequences rather than a replacement. Compared to the reading without the fused images, a wider variation of sequences was chosen as most diagnostic for the reading including the fused images. The addition of the fused sequence could have influenced the readers opinion of the other sequences.

Although the additional value of fused DWI/T2-weighted images in HL has not yet been described in literature, our findings are in line with previous studies in other diseases [12–14,17]. For instance, in pelvic malignancies it was shown that fused DWI/T2-weighted images improved the identification of lymph nodes and the fused images outperformed separate DWI and T2-weighted images in recurrent malignancies [12].

Limitations of this study are the small sample size (and consequently limited statistical options and relatively large confidence intervals) and the fact that only one reader assessed all images for this pilot study. In further assessment of the value of fused images we would also take interrater variability into account. Furthermore, the reader performed the two separate readings (without and with fused DWI/T2-weighted images) for the whole dataset. Although the time between the first and second review was 4 months, recall bias could still have influenced the results. Not all fused images were of sufficient quality (e.g. good alignment of the images was in some cases difficult to achieve, amongst others possibly due to geometric distortion and movement of the patient between sequences [17]). Improved fusing techniques might contribute to improved results. Finally, another limitation is the fact that imaging findings could not be confirmed by pathology since obtaining tissue of all lesions for pathological examination is not possible and ethical acceptable. FDG-PET/CT was therefore used as reference standard since this imaging modality is still considered the gold standard for staging HL.

In conclusion, this study shows that the addition of fused DWI and T2-weighted images to whole-body MRI protocols for staging of pediatric HL might potentially be of additional value. Especially for the detection of abdominal lymph nodes there seems to be a benefit of using fused images, and, additionally, DWI/T2-weighted fusion images seem to limit reading times as well. However, this first pilot study consisted of a small sample size and the fusing technique was not yet sufficient enough to fully rely on the fused images alone for staging.

Declaration of Competing Interest

None.

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