ACTA ONCOLOGICA
2022, VOL. 61, NO. 2, 239–246
https://doi.org/10.1080/0284186X.2021.1974554

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Baseline FDG PET/CT in free breathing versus deep inspiration breath-hold for pediatric patients with mediastinal lymphoma

Anni Young Lundgaard[a], Danijela Dejanovic[b], Anne Kiil Berthelsen[a,b], Flemming Littrup Andersen[b], Laura Ann Rechner[a], Lise Borgwardt[b], Lisa Lyngsie Hjalgrim[c], Lena Specht[a] and Maja Vestmø Maraldo[a]

[a]Section of Radiotherapy, Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [b]Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [c]Department of Pediatric Haematology and Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Introduction: The prospective TEDDI protocol investigates the feasibility of radiotherapy delivery in deep inspiration breath-hold (DIBH) for pediatric patients. To secure optimal radiotherapy planning, a diagnostic baseline FDG PET/CT in free breathing (FB) and DIBH was acquired. The anatomical changes in the mediastinum and the effect on PET metrics between the two breathing conditions were assessed for pediatric patients with mediastinal lymphoma.

Material and methods: Ten patients aged 5–17 were included and had a PET/CT in FB and DIBH. Metabolic active lymphoma volumes were manually delineated with a visually based segmentation method and the PET metrics were extracted. The anatomical lymphoma, lung and heart volumes were delineated on CT.

Results: The lung volume increased while the heart was displaced caudally and separated from the lymphoma in DIBH compared to FB. Both the anatomical and the metabolically active lymphoma volumes appeared different regarding shape and configuration in the two breathing conditions. The image quality of the DIBH PET was equal to the FB PET regarding interpretation and delineation of lymphoma lesions. All PET metrics increased on the DIBH PET compared to the FB PET with the highest increase observed for the maximum standardized uptake value (33%, range 7–56%).

Conclusion: Diminished respiratory motion together with anatomical changes within the lymphoma increased all PET metrics in DIBH compared to FB. The anatomical changes observed in DIBH compared to FB are expected to reduce radiation doses to the heart and lungs in pediatric patients with mediastinal lymphoma referred for radiotherapy delivery in DIBH and, thereby, reduce their risk of late effects.

Trial registration: The Danish Ethical Committee (H-16035870, approved November 24th 2016), the Danish Data Protection Agency (2012-58-0004, approved 1 January 2017). Registered retrospectively at clinicaltrials.gov (NCT03315546, 20 October 2017).

ARTICLE HISTORY
Received 22 June 2021
Accepted 25 August 2021

Introduction

Hodgkin lymphoma (HL) is highly curable with combination chemotherapy followed by consolidating radiotherapy [1–4]. However, long-term survivors experience treatment-induced late effects [5–8] and optimizing treatment to reduce the risk of late effects is of outmost importance. In the past, patients with HL received standard extensive radiation fields [9]. Today irradiated patients receive personalized radiotherapy that only encompasses the original lymphoma volume in each individual patient, known as involved site (ISRT) or involved node radiotherapy (INRT) [10]. Modern highly conformal radiotherapy delivers the prescribed radiation dose almost exclusively to the contoured target volume and minimizes the radiation doses to the normal tissues [10]. To further reduce radiation doses to the critical organs, most importantly the heart and lungs, radiotherapy in deep inspiration breath-hold (DIBH) is standard in adult patients with mediastinal HL [11,12].

Defining an accurate target volume for this highly conformal radiotherapy is challenging since significant changes in the lymphoma volume, and possibly also in the patient anatomy, may happen during the time from diagnosis to radiotherapy planning (2–6 months). Consequently, high quality imaging plays a pivotal role in modern radiotherapy planning [13] and baseline prechemotherapy imaging should, ideally, be acquired with the patient in the same position using the same breathing condition as planned for later radiotherapy enabling image fusion between the prechemotherapy scan and the postchemotherapy treatment planning scan [10].

Lymphomas are highly 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) avid and positron emission tomography with computer

CONTACT Anni Young Lundgaard anni.young.lundgaard@regionh.dk Section of Radiotherapy, Department of Oncology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, Copenhagen Ø 2100, Denmark

Supplemental data for this article can be accessed here.

tomography (PET/CT) imaging with FDG as a radiotracer is now recommended for optimal staging [14–16]. At our institution, a baseline PET/CT in DIBH is standard procedure in adult patients with mediastinal HL, whereas image acquisition and radiotherapy delivery in DIBH for pediatric patients has not been routinely used.

Respiratory motion is a source of error when standardized uptake values (SUVs) are obtained from a combined FDG PET/CT if the PET and the CT, used for attenuation correction, are obtained in different respiratory phases [17]. The effects of respiratory motion on the PET metrics in lymphoma have not previously been analyzed.

In 2017, we initiated a combined feasibility study and the first prospective clinical trial to introduce radiotherapy delivery in deep inspiration for pediatric patients – the TEDDI protocol (NCT03315546) [18]. The protocol aims to investigate the dosimetric benefit (a surrogate marker for the potential clinical benefit) of radiotherapy delivery using DIBH compared to free breathing (FB). In adult patient the reduced radiation doses to the heart and lungs with radiotherapy in DIBH are primarily due to the anatomical changes in DIBH, i.e. an inflation of the lungs and a caudal and posterior displacement of the heart [12,19]. However, for young children the anatomical changes or the breathing patterns might be less pronounced than for adults diminishing the dosimetric advantage of DIBH for children.

Here, we describe the acquisition of a baseline PET/CT performed in FB and DIBH during the same session for pediatric patients with mediastinal lymphoma. Furthermore, we assess the anatomical changes in the mediastinum and the effect on PET metrics between the two breathing conditions.

Material and methods

Patients

Ten consecutive pediatric patients age 5–17 with a mediastinal lymphoma with a possible later need of consolidating radiotherapy, were included. All patients were enrolled in the TEDDI protocol (cf. Supplemental material for SPIRIT reporting guidelines for study protocols according to EQUATOR) and, upon enrollment, the patients' parents provided written, informed consent.

Workflow

A whole-body diagnostic FDG PET/CT scan in FB together with a mediastinal scan in DIBH was performed in a joint session. First, the patients had a training session where their ability to perform DIBH was assessed [20]. The DIBH was voluntary but monitored with the noninvasive optical Real-Time Position Management (RPM) surface system (Varian Medical Systems, Palo Alto, CA). Using an infrared camera, the RPM system tracked the patients' respiratory motion by an optical marker placed on the patients' sternum (a surrogate marker for the position of the internal structures). To aid reproducibility of the DIBH level during the image acquisition, the patients received a visual feedback showing the level of inspiration on a video screen. The DIBH level was set individually ensuring a comfortable and reproducible level.

Prior to the FDG injection, the patients rested under a warm blanket for 30 min to decrease brown fat activity and thereby minimizing the risk of a false positive PET interpretation. The injected activity was 3 MBq/kg in patients $\leq$15 years and 4 MBq/kg in older patients. After another hour of resting, the patients were asked to empty their bladder before being positioned in the scanner (Siemens Biograph 64 mCT with an axial field of view (FOV) of 216 mm; Siemens Healthineers, Erlangen, Germany). The patients were immobilized on a flat chest-board device (ConChest Aps, Gislev, Denmark) and scanned in the supine position with arms raised above the head. Should the patient later require consolidating radiotherapy, their planning CT scan and radiotherapy delivery would be performed with the patient in the same position.

Image acquisition

The whole-body diagnostic FB PET/CT was acquired first and extended from the vertex to the middle of the thigh. The FB CT was performed with intravenous contrast (Optiray 300 mg iodine/ml, dosage 1.5 ml/kg, maximum 75 ml administered immediately before the CT scan), supplemented with oral contrast (Ioxitalamat 12.6 mg iodine/ml, dosage 250 ml administered after the FDG injection) in patients suspected of having infra-diaphragmatic disease. A contrast-enhanced CT is mandatory to distinguish lymph nodes from blood vessels when contouring for radiotherapy planning. The FB PET scan was acquired in a total of 4–8 bed positions with an acquisition time of three minutes per bed position.

The mediastinal DIBH PET/CT was performed immediately after the FB PET/CT using the same FDG dose, and the RPM surface system with the same DIBH level as during the training session. The DIBH CT was non-enhanced and acquired over 15 s. The DIBH PET was limited to one bed position (21.5 cm in the cranio-caudal direction). The field of view was set manually, to encompass as much of the visual mediastinal tumor as possible. The DIBH PET scan was acquired over six consecutive 20 s DIBHs (total DIBH acquisition time 2 min) and the information was post-processed and combined by averaging the raw counts using an in-house software. The individual DIBH scans were decay corrected to match the first DIBH scan.

Both CT scans were acquired with CarekV (100-120 kVp) and CareDose settings (226 quality reference mAs). All PET images were attenuation corrected using the CT information in the same breathing condition. The PET data were reconstructed iteratively using 3D-OP with point spread function including time-of-flight information (527 ps) using the vendor supplied TrueX algorithm (Siemens Healthineers, Erlangen, Germany). The settings were: 3 iterations, 21 subsets, smoothed by a 2 mm Gaussian filter, matrix size 400×400 voxels. The pixel size/slice thickness in the reconstructed PET image was approximately 2×2 mm/2 mm.

Lymphoma volumes

A cranial and caudal border were defined for lymphoma delineation for the purpose of this study as the DIBH PET/CT was confined to one bed position. The cranial border was defined as the suprasternal notch just above the manubrium of the sternum for both scans, and the caudal border for both scans matched the length of the DIBH scan. Therefore, only the lymphoma volume present on both the FB and the DIBH scans were delineated. However, should a patient later be referred to radiotherapy, all visible lymphoma at baseline would be delineated and the limited DIBH scan would be extended using the FB scan.

A nuclear medicine physician, with experience in DIBH PET/CT for radiotherapy planning, delineated the FDG avid lymphoma volume on both the FB PET and the DIBH PET. This was designated the gross tumor volume PET (GTV_{PET}). All delineation on PET images was completed on a Mirada XD® workstation (version 3.6, Mirada Medical, Oxford, UK) with standardized window level and display settings in side-by-side collaboration with a specialist in radiology (the same approach as used in clinical cases). The GTV_{PET} was manually delineated using a visually based segmentation method according to departmental guidelines. The SUV_{max}, SUV_{mean}, and SUV_{peak} together with the total metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were extracted automatically based on the GTV_{PET}.

The FB and DIBH CT scans and the respective GTV_{PET} delineations were imported into the Eclipse treatment planning system (version 13.7, Varian medical Systems, Palo Alto, CA). The anatomical lymphoma volume (GTV) was delineated on the CT scans in FB and DIBH and included both the GTV_{PET} and the PET-negative parts of the lymphoma (cf. Figure 1). To aid in contouring the GTV on the non-enhanced DIBH CT the FB scan was rigidly co-registered with the DIBH scan. Because of the anatomical changes, the lymphoma or the large blood vessels were the focus of the fusion and not bony landmarks. The GTV was delineated by the same radiation oncologist and subsequently validated by an experienced radiologist.

The total heart and lung volumes were not always included on the DIBH scan. To quantify the anatomical changes between FB and DIBH in the lungs, all visible lung volume was delineated on both scans. This method could underestimate the lung volume in DIBH in some cases and therefore underestimate the increase in lung volume when comparing the techniques (a conservative estimate for the purpose of the present study). For the heart, the cranial border was delineated according to Feng *et al.* [21], and the caudal border was delineated 1 cm below the caudal border of the lymphoma on both scans indicating the inferior border of the volume that would be irradiated in case the patient had radiotherapy.

Statistics

The relative differences between PET metrics and anatomical volumes in FB and DIBH were compared using the non-parametric Wilcoxon signed-rank test. A two-sided *p*-value $<.05$ was considered statistically significant. Analyses were performed in SPSS (version 24.0, IBM Corp., Armonk, NY).

Approvals and ethics

The TEDDI protocol was approved by the Danish Ethical Committee (H-16035870) and the Danish Data Protection Agency (2012-58-0004). The patients were exposed to an extra ~5 mSv (corresponding to ~1.5 year of exposure to the natural background irradiation) from the CT scan in DIBH. The potential benefit from reduced radiation doses to the heart and lungs with a later radiotherapy course was estimated to outweigh the additional exposure from the CT scan.

Results

Patients

The 10 patients were enrolled in the TEDDI protocol between July 2017 and April 2019. Their median age was 14.5 years (range 11–16 years). Nine patients were diagnosed with HL and one patient with non-Hodgkin lymphoma. The patients were equally divided into early and advanced stage (five clinical stage [CS] II, three CS III, two CS IV). Seven patients (of the nine HL patients) had risk factors (according to the EuroNet-PHL C2 trial [NCT02684708]), such as B-symptoms, localized extranodal disease, bulky disease ($\geq$200 ml), and/or elevated erythrocyte sedimentation rate ($\geq$30 mm/h).

Anatomical changes

On the DIBH CT scan, the lung volume increased compared to the FB CT, despite the total lung volume only being included in one out of ten patients (the youngest age 11). The relative difference was 47.2% (range 9.3–105%). Median FB lung volume was 2.222 cm^3 (range 1.317–4.045 cm^3) versus a median DIBH lung volume of 3.290 cm^3 (range 2.207–4.424 cm^3). In DIBH, the heart was displaced caudally and posteriorly, and the mediastinum was elongated and narrower (cf. Figure 1). The heart was separated from the lymphoma in DIBH, which in all patients resulted in a decreased median of the volume of the heart delineation on the DIBH CT (226 cm^3, range 0–722 cm^3) compared to the FB (292 cm^3, range 14–797 cm^3). The relative difference was −18.1% (range −100 to (−0.9)%). The difference in the lung volumes and the delineated heart volumes between the two breathing conditions were significant (cf. Figure 2). The lymphoma changed position and appeared anatomically more homogeneous on the DIBH CT compared to the FB CT (cf. Figures 1 and 3). In some cases, the lymphoma separated from the chest wall, demonstrating that there was no direct extension into the chest wall or sternum (which was suspected on the FB scan) and involvement of the internal mammary lymph nodes could be assessed (Figure 3). The GTV_{PET} volume comprised 29% (range 2–71%) and 34% (range 3–76%) of the GTV volume in FB and DIBH,

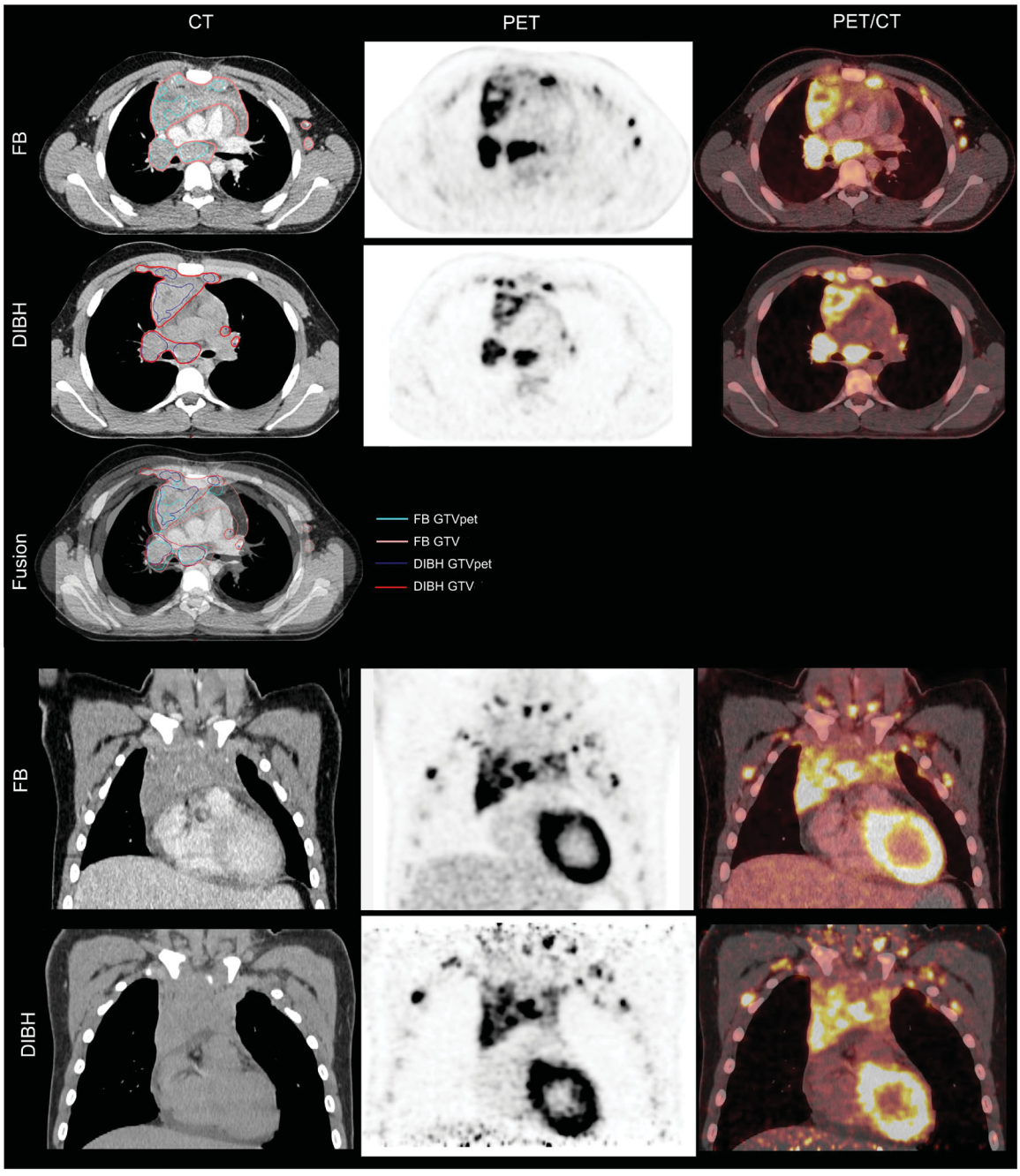

Figure 1. Illustrates the lymphoma volumes on a baseline PET/CT scan in free breathing (FB) and deep-inspiration breath-hold (DIBH) in the axial and coronal plane. The GTV_{PET} represents the FDG avid lymphoma volumes and the GTV represents the anatomical lymphoma volumes including both GTV_{PET} and the PET-negative parts of the lymphoma. The fusion with the contrast-enhanced FB CT scan aids in the contouring of the GTV on the non-enhanced DIBH CT scan. In DIBH, the heart and the large vessels used for the fusion are displaced caudally, hence, the lymph nodes in the left axilla are situated more cranially and not present on the axial DIBH image. Notice, that the lung volume is larger, the heart is displaced caudally and separated from the lymphoma, and the mediastinum narrower on the DIBH scan.

respectively. The volume of the GTV did not change on the DIBH compared to the FB scans (357 cm^3 [range 53.9–570] versus 357 cm^3 [range 49.2–536]) despite an increased GTV_{PET} volume and anatomical changes within the lymphoma (cf. Figure 2 and Table 1).

PET metrics

The median time from FDG injection to FB PET acquisition start was 66 min (range 54–88 min) and the median time between the FB PET and the DIBH PET, measured from the beginning of both scans, was 28 min (range 19–69 min). The prolonged time of 69 min between the FB and the DIBH PET in one session was caused by technical scanner problems. The range without the one outlier was 19–30 min.

There was no discrepancy between the number of lymphoma lesions seen on both PET scans although the FDG uptake appeared somewhat different with regard to shape and configuration in the two breathing conditions (cf. Figures 1 and 3). The image quality (visually assessed) of the DIBH PET was found to be equal to the FB PET regarding interpretation and delineation of lymphoma lesions.

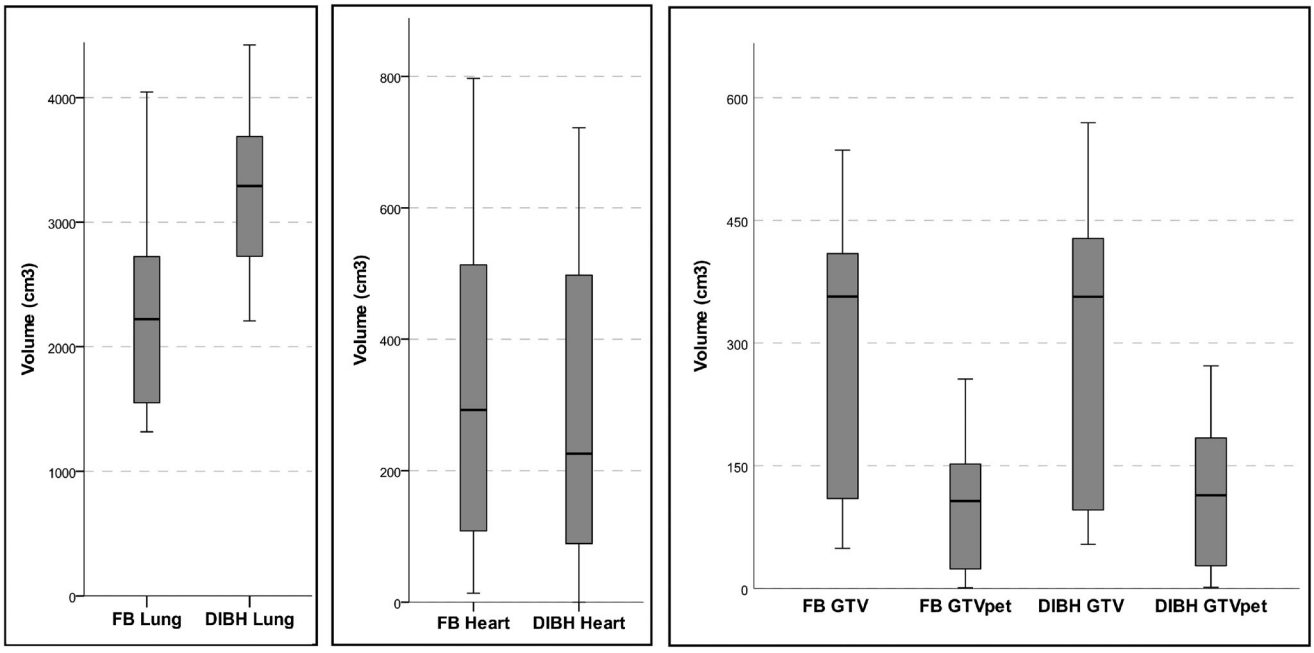

Figure 2. Boxplots of the lung volume, the delineated part of the heart volume, the FDG avid lymphoma volume (GTV_{PET}), and the anatomical lymphoma volume (GTV) in free breathing (FB) and deep inspiration breath-hold (DIBH). The volume differences between the two breathing conditions were compared using the Wilcoxon signed-rank test and, except for GTV, all differences were significant.

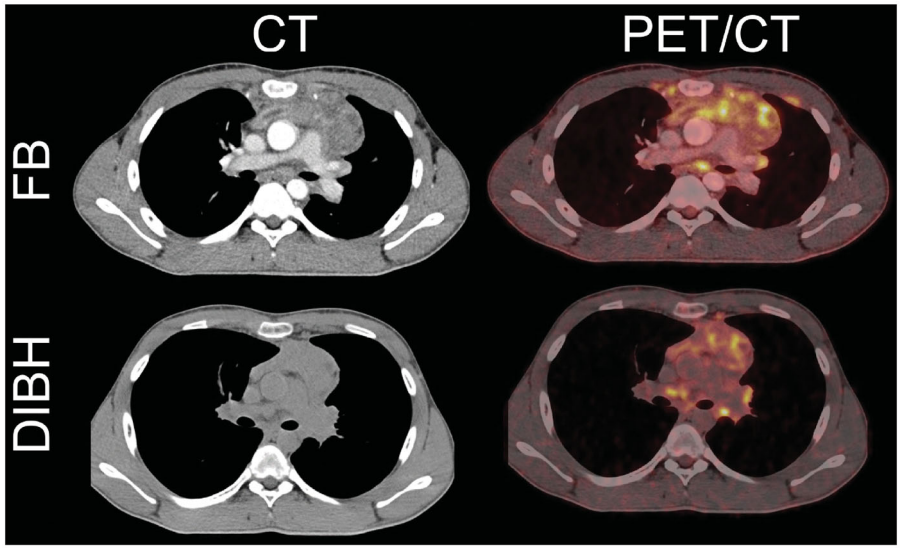

Figure 3. Notice the anatomical changes in the lymphoma in deep inspiration breath-hold (DIBH) compared to free breathing (FB). The lymphoma separates from the chest wall and extension into the chest wall or sternum and involvement of the internal mammary lymph nodes can be assessed in DIBH.

The DIBH PET was limited to one PET bed and due to limited sensitivity at the edge of the axial FOV, an increase in noise and a decrease in image quality was observed (cf. Figure 1, coronal plane). The PET metrics were not affected since it was outside of the predefined borders used for delineation.

Patient characteristics and the lymphoma characteristics in FB and DIBH together with the relative differences are displayed in Table 1. All SUVs, the TLG, and the MTV were significantly higher on the DIBH PET compared to FB. Figure 4 illustrates the difference in SUV_{max}, SUV_{mean}, and SUV_{peak} between the two breathing conditions. While all SUV values were statistically different when comparing FB and DIBH, SUV_{peak} had the smallest magnitude of difference when compared to SUV_{max} and SUV_{mean}. The patient with the 69 min between the FB and the DIBH scan had the largest differences in SUV_{max} and SUV_{peak} of 55% and 11.5%, respectively. Removing this patient (represented by a black dot in Figure 4) from the analyses did not change the overall outcome.

Discussion

To our knowledge, this is the first study to describe the anatomical changes in the mediastinum and the effect on PET metrics between the two breathing conditions in pediatric patients with mediastinal lymphoma. The present study demonstrates how a diagnostic baseline FDG PET/CT in FB and DIBH can be acquired in a joint session with minimal inconvenience and limited extra radiation exposure for pediatric

Table 1. Patient and lymphoma characteristics in median and range.

Patient characteristics, $N = 10$							
Gender							Male: 6; female: 4
Age (years)							14.5 (11–16)
Height (mm)							176 (152–185)
Weight (kg)							60 (36–78)
$\Delta time_{FDG\ inj\text{-}FBscan}$ (min)							66 (54–88)
$\Delta time_{FBscan\text{-}DIBHscan}$ (min)							28 (19–69)[b]
Lymphoma characteristics	FB		DIBH		Relative difference %[a]		*p* Value[a]
SUV_{max}	16.5	(12.8–19.4)	20.8	(16.9–27.5)	33.3	(7.2–55.5)	<.01
SUV_{mean}	7.2	(6.2–8.6)	7.60	(6.40–8.90)	5.0	(3.2–11.3)	<.01
SUV_{peak}	12.2	(6.2–13.9)	12.4	(7.6–14.9)	4.2	((−5.4) to 22.6)	.03
TLG	779	(7.0–1,827)	886	(15.1–2,017)	19.6	(8.6–116)	<.01
MTV (cm^3)	109	(1.0–256)	117	(2.1–270)	13.9	(3.7–110)	<.01
GTV (cm^3)	357	(49.2–536)	357	(53.9–570)	0.4	((−12.7) to 12.1)	.70

[a] Relative difference = (DIBH-FB)/FB x 100%.
[b] $\Delta time_{FBscan\text{-}DIBHscan}$ prolonged in one patient due to technical problems at the scanner.
[a]The difference between the two breathing conditions were compared using the Wilcoxon signed-rank test.

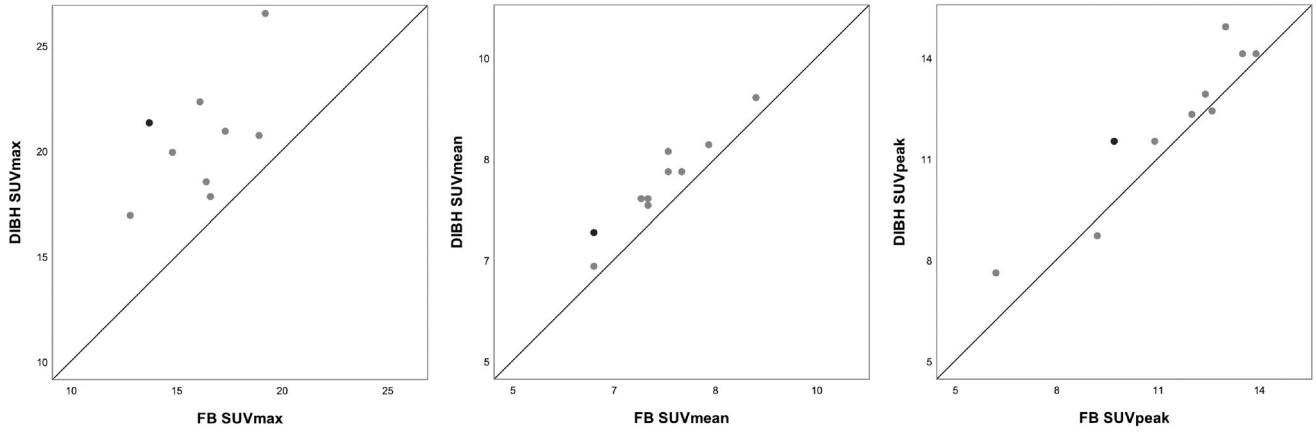

Figure 4. Scatterplots of deep inspiration breath-hold (DIBH) versus free breathing (FB) in standardized uptake value (SUV) max, mean, and peak. The black dot represents the patient with a prolonged time (69 min) between the FB and DIBH PET acquisition. The difference in SUVs between the two breathing conditions were compared using the Wilcoxon signed-rank test and all differences were significant. A reference line ($y = 1 * x + 0$) has been added.

patients with mediastinal lymphoma. This will provide optimal conditions for radiotherapy planning and delivery in DIBH with the INRT technique, which reduces the irradiated volume to a minimum.

Dosimetric benefits from radiotherapy delivery in DIBH to the lungs, heart, and cardiac substructures have been demonstrated in adult patients with HL and breast cancer [11, 12, 22]. The TEDDI protocol will investigate if the same applies to children. The present study shows that anatomical changes in DIBH in children appear similar to those observed in adults, although very young patients were not included. The lung volume increased by nearly 50% on the DIBH CT compared to the FB CT, even though the total lung volume was rarely included on the limited DIBH scans. During radiotherapy this may decrease the proportion of lung tissue being irradiated, depending on the applied radiotherapy technique. The heart was displaced caudally and separated from the lymphoma in all 10 patients and in some patients the median volume included in the heart delineation on the DIBH CT was zero. Hence, INRT in DIBH is expected to reduce the heart volume receiving radiation.

Respiratory motion uncertainties warrant attention when measuring PET metrics in mediastinal lymphomas. Respiratory motion becomes a source of error when SUVs are obtained from a combined PET/CT, if the PET and the CT used for attenuation correction are obtained in different respiratory phases [17]. Without the use of respiratory motion management this is often the case since PET emission acquisition is required in minutes and a CT scan in seconds [17]. In the present study, the DIBH PET and CT scans were obtained at the same respiratory level, hence, the respiratory motion artifacts were diminished. This contributed to increased values of all PET metrics in DIBH compared to FB. SUV_{max} was the most sensitive to respiratory motion and increased by a median of 33% (range 7–56%). A variation in SUV_{max} of 30% caused by attenuation correction to CT data acquired in different respiratory phases has also been reported in lung cancer patients [23].

The total tumor burden is a well know prognostic factor in HL [24]. The MTV and TLG represent quantitative measurements correlated with the individual total disease burden. Hence, the MTV and TLG have been investigated as prognostic factors and found to be associated with progression-free survival [25–28]. However, the referenced studies did not use the same SUV threshold for delineating MTV (SUV $\geq$ 2.5 or 41% of SUV_{max}). The optimal method for MTV segmentation

is debated and, therefore, the use of the metabolic volume for risk stratification in clinical trials has not yet been implemented [29]. Importantly, the MTV (delineated visually) and the TLG increased significantly in mediastinal lymphoma lesions when measured in DIBH compared to FB in our small study. This should be considered when MTV and TLG are investigated as prognostic factors. An association between advanced PET radiomics and refractory disease status in early-stage adult HL patients has also been demonstrated [30]. However, this study was not performed in DIBH, and it is therefore uncertain how much of the variation in radiomics may be attributed to motion artifacts.

In the present study, PET/CT images were interpreted on workstations dedicated for this purpose in side-by-side collaboration with a specialist in radiology. The GTV_{PET} was then delineated using a visually based segmentation method in accordance with departmental guidelines adopted in the clinical setting. Although basic, this intuitive approach is not necessarily suboptimal compared to a fixed threshold segmentation approach [31]. In patients with lung cancer, it has been demonstrated that an automatic tumor segmentation defined by 40% of the SUV_{max} leads to visually inadequate coverage of the tumor volume defined on CT [32]. This was especially found in lung tumors with markedly heterogeneous FDG uptake [32] as is often the case with large mediastinal lymphomas. Malignant lymphomas, unlike lung tumors, occur as numerous individual or confluent tumors with a wide range of volumes (generally larger) and uptakes with heterogeneous tumor/background ratios [33]. Also, large tumors are often seen with necrotic regions. The FDG avid lymphoma volumes often comprise a minor part of the anatomical lymphoma volumes. In the present study, the GTV_{PET} comprised approximately one-third of the GTV, which has also been reported in another lymphoma study [34]. The improved conditions in PET DIBH led to larger areas within the tumor to be included in the DIBH GTV_{PET} that were not included in the FB GTV_{PET}. For radiotherapy, precise delineation of the lymphoma is of outmost importance and an absolute threshold or percentage threshold excluding visible lymphoma or including normal tissue is therefore not optimal. However, the visually based GTV_{PET} delineation is a limitation to the present study, since the method is prone to intra-and interobserver variability making the PET metrics harder to reproduce. But using contouring tools (and not manually contouring) to delineate only the metabolic active components of the tumor aids to lessen variability.

Several patient-related and technical factors affect the SUVs measured [35]. For the present study, especially the longer time period from FDG injection until the DIBH PET scan influences the DIBH SUVs. The median time difference between the FB and the DIBH PET was 28 min, however, in one patient it was 69 min and the highest difference in SUVs between the two breathing conditions were seen in just that patient. Conversely, the post-process with combining the six DIBH images could decrease the SUVs on the DIBH PET. The SUVs on the FB PET scan could be increased (by ~3–5% for SUV_{max}) compared to the DIBH PET scan since the CT scan used for attenuation correction was contrast-enhanced in FB and non-enhanced in DIBH [36]. To investigate how those factors may affect the PET metrics, we would have to scan the patients again, this time acquiring the DIBH PET first with a contrast-enhanced CT and the FB PET afterwards with a non-enhanced CT. This would, however, subject the patients to unnecessary radiation dose and would be unethical in children. Other limitations are the small number of patients and the single institution set-up, and our results should be validated in a larger data set. Nonetheless, the present study is the first to quantify the effect on PET metrics between FB and DIBH in patients with mediastinal lymphoma demonstrating that the PET metrics were consistently increased on the DIBH PET/CT for all patients.

In conclusion, diagnostic baseline PET/CT can be acquired in both FB and DIBH for pediatric patients with mediastinal lymphoma. The image quality of the DIBH PET was equal to the FB PET regarding interpretation and delineation of lymphoma lesions. Diminished respiratory motion as well as the anatomical changes within the lymphoma increased all PET metrics in DIBH compared to FB. The anatomical changes observed in DIBH compared to FB are expected to reduce the irradiation of the heart and lungs in pediatric patients with mediastinal lymphoma referred for radiotherapy delivery in DIBH and, thereby, reduce their risk of late effects.

Acknowledgments

The authors want to thank the participating children and their families.

Ethics approval

The TEDDI protocol was approved by the Danish Ethical Committee (H-16035870, approved 24 November 2016) and the Danish Data Protection Agency (2012-58-0004, approved 1 January 2017).

Disclosure statement

Professor Lena Specht is on advisory boards and received honoraria from Takeda, Kyowa Kirin, MSD, and Janssen. She has research grants from Varian and ViewRay. The remaining authors report no conflict of interest.

Funding

This study was supported by the Danish Childhood Cancer Foundation [grant no. 2015-9] and the Danish Cancer Society [Grant no. R150-A10066].

ORCID

Anni Young Lundgaard http://orcid.org/0000-0001-5800-888X
Laura Ann Rechner http://orcid.org/0000-0002-0623-4495
Lisa Lyngsie Hjalgrim http://orcid.org/0000-0001-5186-3365
Lena Specht http://orcid.org/0000-0002-6902-2190

References

[1] André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II

Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2017;35(16):1786–1794.
[2] Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016;374(25):2419–2429.
[3] Dörffel W, Rühl U, Lüders H, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: final results of the multinational trial GPOH-HD95. J Clin Oncol. 2013;31(12):1562–1568.
[4] Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the children's oncology group study AHOD0031. J Clin Oncol. 2014;32(32):3651–3658.
[5] Aleman BMP, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol. 2003;21(18):3431–3439.
[6] Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the childhood cancer survivor study. Blood. 2011;117(6):1806–1816.
[7] Schaapveld M, Aleman BMP, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med. 2015;373(26):2499–2511.
[8] Maraldo MV, Giusti F, Vogelius IR, European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group, et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials. Lancet Haematol. 2015;2(11):e492–e502.
[9] Specht L. Radiotherapy for Hodgkin lymphoma: reducing toxicity while maintaining efficacy. Cancer J. 2018;24(5):237–243.
[10] Specht L, Yahalom J, Illidge T, ILROG, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89(4):854–862.
[11] Paumier A, Ghalibafian M, Gilmore J, et al. Dosimetric benefits of intensity-modulated radiotherapy combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 2012;82(4):1522–1527.
[12] Petersen PM, Aznar MC, Berthelsen AK, et al. Prospective phase II trial of image-guided radiotherapy in Hodgkin lymphoma: benefit of deep inspiration breath-hold. Acta Oncol. 2015;54(1):60–66.
[13] Mikhaeel NG, Milgrom SA, Terezakis S, et al. The optimal use of imaging in radiation therapy for lymphoma: guidelines from the international Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2019;104(3):501–512.
[14] Cheson BD, Fisher RI, Barrington SF, United Kingdom National Cancer Research Institute, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–3067.
[15] Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol. 2014;32(27):3048–3058.
[16] Kluge R, Kurch L, Georgi T, et al. Current role of FDG-PET in pediatric Hodgkin's lymphoma. Semin Nucl Med. 2017;47(3):242–257.
[17] Paulino AC, Teh BS. PET-CT in radiotherapy treatment planning. 1st ed. Philadelphia (PA): Saunders Elsevier; 2008. Chapter 4, Biological Target Volume; p. 52–89.
[18] Lundgaard AY, Hjalgrim LL, Rechner LA, et al. TEDDI: radiotherapy delivery in deep inspiration for pediatric patients – a NOPHO feasibility study. Radiat Oncol. 2018;13(1):56.
[19] Aznar MC, Maraldo MV, Schut DA, et al. Minimizing late effects for patients with mediastinal Hodgkin lymphoma: deep inspiration breath-hold, IMRT, or both? Int J Radiat Oncol Biol Phys. 2015;92(1):169–174.
[20] Lundgaard AY, Josipovic M, Rechner LA, et al. The feasibility of implementing deep inspiration breath-hold for pediatric radiation therapy. Int J Radiat Oncol Biol Phys. 2020;106(5):977–984.
[21] Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2011;79(1):10–18.
[22] Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. Radiother Oncol. 2013;106(1):28–32.
[23] Erdi YE, Nehmeh SA, Pan T, et al. The CT motion quantitation of lung lesions and its impact on PET-measured SUVs. J Nucl Med. 2004;45(8):1287–1292.
[24] Specht L, Nordentoft AM, Cold S, For the Danish National Hodgkin Study Group, et al. Tumor burden as the most important prognostic factor in early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. Cancer. 1988;61(8):1719–1727.
[25] Kanoun S, Rossi C, Berriolo-Riedinger A, et al. Baseline metabolic tumour volume is an independent prognostic factor in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2014;41(9):1735–1743.
[26] Akhtari M, Milgrom SA, Pinnix CC, et al. Reclassifying patients with early-stage Hodgkin lymphoma based on functional radiographic markers at presentation. Blood. 2018;131(1):84–94.
[27] Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. Blood. 2018;131(13):1456–1463.
[28] Pike LC, Kirkwood AA, Patrick P, et al. Can baseline PET-CT features predict outcomes in advanced Hodgkin lymphoma? A prospective evaluation of UK patients in the RATHL trial. Hematol Oncol. 2017;35:37–38.
[29] Barrington SF, Meignan M. Time to prepare for risk adaptation in lymphoma by standardizing measurement of metabolic tumor burden. J Nucl Med. 2019;60(8):1096–1102.
[30] Milgrom SA, Elhalawani H, Lee J, et al. A PET radiomics model to predict refractory mediastinal Hodgkin lymphoma. Sci Rep. 2019;9(1):1322.
[31] Bayne M, MacManus M, Hicks R, et al. Can a mathematical formula help define a radiation target volume using positron emission tomography? In regard to black et al. Int J Radiat Oncol Biol Phys 2004;60:1272–1282). Int J Radiat Oncol Biol Phys. 2005;62(1):299–300.
[32] Nestle U, Kremp S, Schaefer-Schuler A, et al. Comparison of different methods for delineation of18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-small cell lung cancer. J Nucl Med. 2005;46:1342–1348.
[33] Meignan M, Itti E, Gallamini A, et al. FDG PET/CT imaging as a biomarker in lymphoma. Eur J Nucl Med Mol Imaging. 2015;42(4):623–633.
[34] Girinsky T, Ghalibafian M, Bonniaud G, et al. Is FDG-PET scan in patients with early stage Hodgkin lymphoma of any value in the implementation of the involved-node radiotherapy concept and dose painting? Radiother Oncol. 2007;85(2):178–186.
[35] Keyes JW. SUV: standard uptake or silly useless value? J Nucl Med. 1995;36:1836–1839.
[36] Berthelsen AK, Holm S, Loft A, et al. PET/CT with intravenous contrast can be used for PET attenuation correction in cancer patients. Eur J Nucl Med Mol Imaging. 2005;32(10):1167–1175.