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^{18}F-FDG uptake of the non-tumour-specific sites on the PET/CT examinations of onco-haematological paediatric patients

PhD thesis

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List of Abbreviations:

Acc: accuracy

bPET: baseline PET examination

BAT: brown adipose tissue

CI: confidence interval

CIM: conventional imaging modalities

CR/CMR: complete response/complete metabolic response of the lymphoma

CSM: conventional staging methods

CT: computed tomography

DLBCL: diffuse large B-cell lymphoma

DS: Deauville score

EFS: event-free survival

ERA: early response assessment

FDG: fluorodeoxyglucose

G-CSF: granulocyte-colony stimulating factor

HL: Hodgkin lymphoma

H/RS: Hodgkin/Reed-Sternberg cells

IHP: International Harmonization Project

iPET: interim PET examination

MRI: magnetic resonance imaging

NHL: non-Hodgkin lymphoma

NPV: negative predictive value

OS: overall survival

PET: positron emission tomography

PFS: progression-free survival

PPV: positive predictive value

RFS: relapse free survival

ROC analysis: receiver-operating-characteristic analysis

RRI: relapse risk index

Se: sensitivity

Sp: specificity

SUV: standardised uptake value

SUVmax: maximum value of SUV

SUVmean: mean value of SUV

ΔSUVmax%: reduction in the maximum value of SUV

TLG: total lesion glycolysis

TMTV: total metabolic tumour volume

US: ultrasonography

WAT: white adipose tissue

I. Introduction

I visited the university hospital Tenon, Paris, in 2012 to enhance my knowledge regarding ^{18}F-fluorodeoxyglucose (FDG) imaging in preparation for the FDG positron emission tomography (PET) examinations planned at our department in Budapest. Prof. Jean-Noel Talbot was the Chief of the Department of Nuclear Medicine at the Hôpital Tenon, and Prof. Francoise Montravers was the Deputy. After commencing clinical FDG imaging with a coincidence gamma-camera in 1997, this department acquired a PET machine in 1999. The first article published by Prof. Talbot and the Lymphoma Working Party (research and education regarding the role of stem cell transplantation in the management of patients with lymphoid malignancies) of the Assistance-Publique Hôpitaux de Paris PET centre in 2001 reported its added value in the exploration of lymphoma [1]. The diagnosis of lymphoma is made based on the findings of histological examination owing to the lack of specificity of FDG for lymphoma. According to the data available in 2001, FDG PET can detect more lesions than computed tomography (CT) or clinical examination, elucidating the extension of lymphoma that resulted in upstaging in 13% of cases [1]. FDG PET has been used to select an optimal site for biopsy in cases wherein the site selected initially is difficult to access. One of the most promising indications for FDG PET is the staging of lymphoma, which provides baseline images for the subsequent evaluation of the efficacy of therapy. A negative result indicates a response to therapy and subsequent remission with a predictive value of 89% [1]. In contrast, a positive result indicates resistance or predicts relapse with a predictive value of 83%. FDG imaging has facilitated the early detection of recurrence and viable tissue in residual masses that remain for several months after treatment. Notably, its sensitivity (Se; 84%) and specificity (Sp; 95%) are superior to those of conventional imaging modalities, such as CT and gallium-67 scintigraphy [1].

Montravers et al. published data assessing the clinical utility of FDG PET and its impact in case of paediatric patients compared with those of conventional imaging modalities

(CIM) in a series comprising 20 children with Hodgkin lymphoma (HL) and seven children with non-Hodgkin lymphoma (NHL) [2]. This was the first routine application of FDG PET in a paediatric population. HL and NHL constitute 15–18% of paediatric malignancies [3]. According to Philip et al., advances in the treatment of these malignancies at the beginning of the 21st century, such as the introduction of aggressive chemotherapy for NHL and combined modality treatment with chemotherapy and radiotherapy for HL, have prolonged survival and reduced mortality rates [4]. The diagnosis of lymphoma is guided by the clinical history, findings of the physical examination, and initial laboratory data; however, appropriate histological examination of the pathological lymph nodes or bone marrow biopsy must be performed to confirm the diagnosis.

CIM comprises CT, magnetic resonance imaging (MRI), ultrasonography (US), and gallium-67 scintigraphy. These modalities exhibit a limited ability to differentiate malignant lymph nodes from benign lymph nodes and detect viable malignant tissue within residual masses. Furthermore, CIM may fail to differentiate cancer from fibrosis, especially in cases wherein the patients present with bulky masses, which remain large in approximately 40% of patients with HL after first-line therapy [5, 6].

This pilot study revealed that FDG PET (PET/CT was unavailable at the time of conducting the study) exhibited high Se (12/12) for staging and restaging of the illness, detecting a greater number of more lesions than CIM. Furthermore, it exhibited a patient upstaging rate of 50% (6/12). FDG PET has been used to accurately monitor the response to therapy and characterise residual masses. False-positive results were observed in two patients with NHL with thymic uptake, whereas false-negative results were observed in a patient with NHL who relapsed 1 month after exhibiting negative FDG PET results. The questionnaire survey emphasised the effect of FDG PET on clinical management, which was modified based on the FDG PET results of 23% of the patients. Thus, FDG PET is a very sensitive imaging technique for staging and restaging of lymphoma in children, exhibiting efficacy similar to that observed in the adult population. Furthermore, it can be used to monitor the response to therapy.

Hermann et al. [7] compared the FDG PET and CT results of 25 children with histologically-confirmed HL (n = 18) or NHL (n = 7) using a dedicated PET (without using gamma-cameras which were in use at that time). A total of 662 regions, comprising 470 nodal and 192 extranodal regions, were compared. From these regions 91 (14%), comprising 81 nodal and 10 extranodal regions, were concordant positive, whereas 517 (78%) regions, comprising 347 nodal and 170 extranodal regions, were concordant negative. In case of 47 regions, 48 (7%) discordant findings were observed. Twenty-seven findings (22 nodal and 5 extranodal) could be detected using FDG PET but not on the CT images, whereas 21 findings (17 nodal and 4 extranodal) could be detected using CT but not on PET images. In total 7 (1%) regions were judged equivocal for one imaging modality (FDG-PET [n=1] and CT [n=6]). These findings indicate that compared with CT, FDG PET yielded higher staging in 4 and lower staging in 2 of the 25 patients.

The favourable outcomes of FDG PET in childhood lymphoma were confirmed by Hernandez-Pampaloni et al. 1 year later [8], who conducted a similar study involving 24 patients with histologically-confirmed lymphoma (HL [n=18] and NHL [n=6]) who underwent FDG PET and CT examinations. In the study, 7 PET acquisitions were performed for initial staging, 12 for monitoring therapy response, and 9 for detecting recurrence. A histopathological examination was conducted to confirm the initial diagnosis. The standard of truth at follow-up was established by clinical follow-up, additional imaging modalities, and/or biopsy. PET and CT were concordant in 366 of the 441 regions analysed (positive in 16 regions and negative in 350 regions). Discordance was observed in 48 regions. The diagnostic performance of FDG-PET was as follows: Se, 78%; Sp, 98%; positive predictive value (PPV), 94%; and negative predictive value [NPV], 90%. The diagnostic performance of CT was as follows: Se, 79%; Sp, 88%; PPV, 90%; and NPV, 46%.

Kabickova et al. [9] compared a staging work-up using conventional staging methods (CSM; CMI + bone marrow biopsy) and FDG PET in 55 children and adolescents with HL. They studied 61 FDG PET images. Discordance was resolved through magnetic resonance imaging or clinical follow-up (range 2–47 months). FDG PET correctly

predicted the changes in the staging in 15% of patients (upstaging in seven cases and downstagings in two cases). FDG PET could not accurately stage two (3%) of the 61 patients, owing to the absence of FDG uptake in small parenchymal lung nodules detected on CT. The Se of PET and CSM were 96.5% and 87.5%, respectively. The Sp of PET and CSM were 100% and 60%, respectively. The accuracy (Acc) of PET and CSM were 96.7% and 85.2%, respectively. The diagnostic accuracy of the combination of FDG PET and lung CT reached 100%.

Meany et al. [10] demonstrated the limited value of FDG PET performed at the end of initial treatment to predict subsequent recurrence in their study involving 33 paediatric patients with HL. Twenty two of the 23 patients had negative FDG PET results at the end of therapy. However, positive FDG PET results were observed in 10 patients subsequently, yielding a total of 11 (47.8%) patients with a positive post-treatment FDG PET results. Five patients underwent six tissue biopsies. Four of these specimens were negative for disease, whereas two specimens revealed HL relapse. Six patients who were monitored clinically remained asymptomatic. Repeated PET examinations revealed resolution of abnormalities in four cases; in contrast, persistently positive, but stable PET findings were observed in two patients who continued to be in remission 11 and 40 months following treatment. Twelve (52.2%) patients belonging to the original cohort who exhibited consistently negative FDG PET findings did not exhibit relapse. Consequently, the authors concluded that FDG PET is a sensitive (100%) but not a specific (57%) method for evaluating the post-treatment status of paediatric patients with HL with a strong negative predictive value (100%), but poor PPV (18%).

In the same year, Lin et al. [11] published a prospective study involving 92 patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) that aimed to assess the prognostic value of early FDG PET using standardised uptake value (SUV) compared with that of visual analysis. The patients underwent FDG PET (PET/CT in the case of 11 patients) before and after receiving two cycles of chemotherapy (midtherapy). The maximum and mean values of SUV (SUVmax and SUVmean, respectively) normalised to body weight and the body surface area, as well as tumour-to-normal ratios, were computed for the areas that exhibited the most intense uptake. Visual analysis

comprising receiver-operating-characteristic (ROC) analysis of the SUVs, tumour-to-normal ratios, and the changes in these parameters over time was performed to predict the event-free survival (EFS) and overall survival (OS). Survival curves were estimated through Kaplan–Meier analysis and compared using the log-rank test.

Visual analysis revealed that the accuracy of early PET to predict EFS was 65%. The 2-y EFS estimate was 51% (95% confidence interval [CI], 34–68%) and 79% (95% CI, 68–90%) in the FDG-positive and FDG-negative groups, respectively ($p = 0.009$). ROC analysis yielded an optimal cutoff value of 65.7% for reduction in SUVmax from baseline to midtherapy, with an accuracy of 76% for predicting EFS. The 2-year EFS estimate was 21% (95% CI, 0–42%) and 79% (95% CI, 69–88%) in patients with SUVmax reduction of ≤65.7% and >65.7%, respectively ($p < 0.0001$). Fourteen patients with positive visual analysis results could be reclassified as good responders.

Thus, SUV-based assessment of therapeutic response at midtherapy, rather than at the end of first-line chemotherapy, improves the prognostic value of early FDG PET compared with that of visual analysis in DLBCL.

The first international workshop on the utility of PET in lymphoma was convened in April 2009 at Deauville to discuss strategies that target the lack of uniform and reliable criteria for interim PET scan interpretation [12]. The utility of applying a five-point scale to the visual analysis and the additional value of SUV analysis were investigated. These criteria are widely known as the Deauville criteria and have been incorporated into the Deauville five-point scale. The scale scores for the sites exhibiting the most intense FDG uptake in a site of initial disease, if present, were as follows:

1. No uptake
2. Uptake lesser than or equal to that observed in the mediastinum
3. Uptake greater than that in the mediastinum but lesser than or equal to that in the liver
4. Moderate increase in uptake compared with that observed in the liver
5. Marked increase in uptake compared with that observed in the liver and/or new sites of disease.

The guidelines issued by the European Society for Medical Oncology in 2011 [13] state that FDG PET may be considered in HL according to the revised response criteria.

FDG imaging has evolved in the years preceding my educational stay in Paris. Hybrid PET/CT machines (available at Hôpital Tenon since 2004) have replaced PET machines. The use of low-dose "non-diagnostic" CT has been favoured over the use of these machines as it facilitates the attenuation correction of PET images and the anatomical landmarking of the PET foci using the CT component of PET/CT fused images. The time of flight of annihilation photons of PET have been implemented in those machines, in particular, the Philips PET/CT machine available at Hôpital Tenon since 2009. These evolutions have resulted in an overall reduction in the total radioexposition burden, an important concern in the paediatric population. The total radioexposition burden was increased by the low-dose CT but decreased by the better PET signal with time of flight imaging, resulting in a reduction in the injected radioactivity without a loss in image quality.

Rhodes et al. addressed the added value of performing follow-up FDG PET/CT in their study involving 41 children with lymphoma who had completed treatment [14]. FDG PET/CT with uptake greater than that of the liver was considered positive. Uptake greater than that observed in the background but lesser than that observed in the liver was considered equivocal. Data regarding the clinical outcomes were extracted from the medical records. Positive FDG PET/CT results were observed in 13 (32%) patients. Notably, equivocal results were observed in an equal number of patients during a median follow-up of 2.3 years. Diagnostic CT images revealed new and persistent abnormalities in 13 (32%) and 21 (51%) children, respectively. Five children developed recurrent disease, and one child developed another cancerous lesion. No children with equivocal positivity developed recurrent disease. The SE and PPV of FDG PET/CT were 95% and 53%, respectively. The SE and PPV of diagnostic CT were 79% and 52%, respectively. Thus, the authors concluded that negative FDG PET/CT results obtained during routine follow-up is strongly suggestive of the absence of recurrence in children with lymphoma. In contrast, positive PET/CT and diagnostic CT images

indicate low PPV and should be interpreted with caution in this setting. This conclusion was confirmed by the findings of further studies.

London et al. [15] conducted a study involving 30 children with HL and 22 children with NHL who underwent a total of 209 FDG PET/CT acquisitions. The standard of truth comprised histopathological findings and a follow-up duration of > 6 months. Most of the sites were FDG-negative and considered to have true-negative results; however, the authors conducted an analysis to select a site based analysis owing to the relatively small number of patients. A total of 5,014 regions, comprising 3,342 lymph node and 1,672 extra-nodal regions, were analysed. FDG PET/CT exhibited a significantly better ability to detect malignant lesions than that of CIM. The Se and Sp of PET were 95.9% and 99.7%, respectively. The Se and Sp of CIM were 70.1% and 99.0%, respectively. The Se values of FDG PET and CIM for detecting HL were 98% (47/48) and 77% (37/48), respectively.

A study involving 30 patients with HL that evaluated FDG PET/CT images acquired for staging revealed that it could detect nodal disease in HL lesion-based with a Se of 88%, which was higher than that of diagnostic contrast-enhanced CT (69%) [16]. FDG PET/CT and diagnostic CT detected additional lesions in 50% and 17% of patients with HL, respectively, on a per patient level. FDG PET/CT led to upstaging in seven cases of HL and NHL each. In contrast, diagnostic contrast CT led to upstaging in two cases of NHL.

Prof. Montravers at Hôpital Tenon co-authored one article with two teams from Germany on the use of FDG PET/CT in children and adolescents with lymphoma [17]. Among the different forms of lymphoma, HL is particularly prevalent among adolescents.

Lymphomas account for 12.5% of the spectrum of childhood and adolescent cancer entities, with HL accounting for approximately 40% of cases according to the German Childhood Cancer Registry. Infants are rarely diagnosed with lymphoma; however, its prevalence increases with age, with adolescents aged 15–19 years accounting for 24.5% of all cases [18].

The World Health Organization (WHO) classification of lymphoid neoplasms [19, 20] classifies HL into four subtypes: nodular sclerosing, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. Classic HL can be distinguished from the lymphocyte-predominant type, another form of HL.

HL is highly sensitive to chemotherapeutic agents and radiotherapy, with childhood and adolescence HL exhibiting cure rates of 90–95% through a combination of intensive chemotherapy and radiotherapy [21].

Accurate initial staging plays an important role in correct stratification according to the chemotherapy dose and the irradiation fields. The major conclusions of this review article were as follows:

- The role of FDG PET in HL and NHL must be evaluated separately owing to the substantial differences between these entities in terms of histology, disease manifestation, and treatment.
- Classic HL exhibits high FDG-uptake and prompt response to chemotherapy; in contrast, the FDG-uptake is generally lower in lymphocyte-predominant HL.
- Regional tumour involvement in patients with classic HL can be diagnosed through FDG PET. The Se and Sp of FDG PET exceed those of CIM.
- Bone marrow involvement in patients with classic HL, which is often overlooked during bone marrow biopsy, can be easily detected with FDG PET.
- Evaluation of treatment response by early interim PET after 1–2 cycles of chemotherapy can be used to predict the prognosis of patients with classic HL and aggressive NHL. Several large, multi-centre studies have evaluated treatment adaptation (intensification or reduction) based on the interim PET results.

I. 1. Context that led to the selection of this topic for clinical research

Prof. Francoise Montravers has served as an investigator of the EuroNet-PHL-C1 trial (Eudra-CT-No:2006-000995-33), the largest European multicentric study on childhood and adolescent classic HL. All children undergo FDG PET/CT for initial staging and

after completing two cycles of chemotherapy. Radiotherapy is omitted if the early interim PET is negative. Over 2000 paediatric patients with low, intermediate, or advanced stages of classical HL were recruited from 18 European countries between 2007 and 2013 to participate in this trial.

The rich experience of the team in Hôpital Tenon in this field and the potential for improving the diagnostic approach for HL led me to join its investigational team assessing the role of FDG PET/CT in paediatric HL.

The European Association of Nuclear Medicine (EANM) dedicated its 2012 Young Investigators Meeting to "The multimodality approach in paediatric oncology: impact on therapy and patient management" [22], emphasising that paediatric oncology is a major domain of research for young investigators.

Prof. Jean-Noel Talbot and Prof. Francoise Montravers proposed evaluating the FDG PET/CT images of patients with HL prospectively included in the French cohort of the EuroNet-PHL-C1 trial through an innovative point of view: the FDG uptake is more likely to be affected by the inflammatory organ reaction induced by HL rather than the HL lesions.

I.2. Rationale and published data supporting the investigation of non-tumour-specific FDG uptakes

The HL tumour mass comprises only approximately 1% of malignant Sternberg–Reed cells, which can attract a large number of non-neoplastic mononuclear cells producing various cytokines to maintain malignancy.

Non-tumour-specific FDG uptake by structures without tumour invasion, which has been reported by previous studies, is considered a potential pitfall during initial staging (infrequently) and during/after treatment (more frequently) [10, 23, 24] (Figure 1), despite the Sp of FDG PET being better than that of conventional imaging such as contrast-enhanced MRI, ultrasounds, contrast-enhanced CT [26, 27].

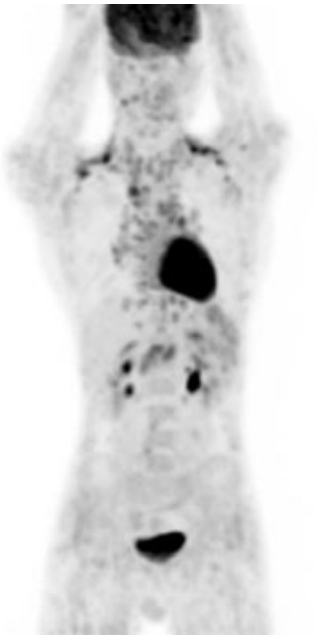

Figure 1. Baseline PET examination of a 15-year-old boy with HL, initial stage IIIBb (participant from our study). Wide HL involvement is visible in cervical, thoracic and abdominal lymph nodes. BAT activation is also present [25].

Several articles have aimed to describe the patterns of non-specific and lymphoma-specific FDG uptake in the thymus [28], spinal cord [29], bone marrow [28, 29, 30], and spleen [29, 30] in adult patients.

Salaun et al. [30] demonstrated that diffuse bone marrow uptake at the time of initial staging of HL could be attributed to bone marrow invasion but is more likely to be attributed to inflammatory changes in the bone marrow, and that diffuse spleen uptake may be associated with microscopic disease involvement, rather than inflammatory change.

Focal FDG uptake in the spleen of patients with lymphoma indicates lymphomatous involvement in most cases, given that other focal splenic pathologies are relatively rare [30, 31]. De Jong et al. reported high Se and Sp values of 75% and 99%, respectively,

of FDG PET for detecting the involvement of the spleen in case of diffuse uptake more intense than that of the liver [31]. However, it is unclear whether the small spleens with normal FDG PET were truly normal owing to the lack of pathologic correlation. Furthermore, the diffuse and intense FDG uptake in the spleen could decrease after the treatment of lymphoma without the involvement of the spleen.

FDG uptake by brown adipose tissue (BAT) has been observed in children. It is a well-recognised source of pitfalls in the evaluation of HL extent, particularly in cases of HL involving the cervical region. However, FDG uptake by BAT has also been reported to be a predictor of HL disease status in children [32].

The actual incidence and the signification of diffuse and intense FDG uptake by selected organs of children with HL may have been overlooked owing to information available in the same FDG PET/CT examination being missed.

FDG uptake by large inflammatory structures without tumour invasion has been hypothesised to be the consequence of the abnormal inflammation-inducing agents produced by malignant Sternberg-Reed cells. The inflammatory reaction of large structures, which is promoted by the substances released by the HL lesion, may provide relevant information regarding HL:

- an “integrator” in the case of widespread or bulky disease, reflecting the overall activity level at all HL sites better than the tumour uptake of FDG by the most active HL focus;
- an “amplifier” facilitating easier detection of signals by PET; however, very small clusters of Sternberg-Reed cells may not be detectable through non-invasive imaging.

We aimed to evaluate the frequency and intensity of visually diffuse FDG uptake by selected organs on baseline PET/CT (bPET) and interim PET/CT (iPET) images of children with HL and evaluate the correlation of the FDG uptake of these organs with the metabolic response and evolution of disease with treatment.

We performed an observational ancillary study and a validation study with larger cohort using images that had been collected from patients treated at the French centres who provided written consent for the use of their anonymised images and follow-up data for

further research (Table 1). Additional examinations were not performed for this study, and the radiation exposure of the children was confined to the two PET/CT examinations scheduled in the EuroNet-PHL-C1 trial only.

I.3. Additional studies on the significance of FDG uptake by brown adipose tissue (BAT) on baseline PET: "BAT on bPET studies"

Metabolically activated BAT takes up FDG [33]. The resulting FDG foci or masses represent a well-recognised source of pitfalls in the evaluation of the extent of cancer [34]. This is particularly true in the case of cancer involving the cervical region, a frequent localisation of HL invasion of lymph nodes. FDG uptake by the fat in the supraclavicular area was originally called "USA-Fat" [35]. Cohade et al. [35] reported that the prevalence of activated BAT was highest during the January/March period (38/278; 13.7%), which is characterised by low outside temperatures. Notably, the prevalence of activated BAT was significantly lower (30/739; 4.1%) during the rest of the year and greater in females (53/504; 10.5%) than that in males (15/513; 2.9%). Furthermore, patients with activated BAT were younger than those without activated BAT (46.9 ± 15 y vs. 58.9 ± 15 y), observed on 23.8% (10/42) of FDG PET/CT images of patients aged ≤18 years and 5.9% (58/975) = 5.9% of FDG PET/CT images of patients aged >18 years. Another study published in the same year [34] reported that FDG PET revealed that the presence of activated BAT in the neck in the paediatric population (4/26; 15%) was significantly more frequent than that in the adult population (16/837; 1.9%).

Ouellet et al. [36] reported that FDG revealed the presence of activated BAT in 328 of the 4842 adult patients (6.8%) involved in their study. The mass and FDG-uptake of BAT decreased with the increase in outdoor temperature, age, and body mass index. Furthermore, the mass and FDG-uptake of BAT in men and patients with diabetes were lower than those in women and adult patients without diabetes.

Brendle et al. [37] studied the FDG uptake by BAT in adult patients with lymphoma by performing PET/CT at different stages of disease evolution. HL exhibited the highest frequency of BAT visualisation (36/206; 17%) among all types of lymphoma; however, no association between BAT and lymphoma metabolic activity was observed.

Drubach et al. [38] analysed the FDG PET/CT images of 172 patients aged 5–21 years and reported that the epidemiology of BAT in paediatric patients varies from that in adult patients. In contrast to the results confirmed by several studies on adults, a very high prevalence of BAT visualisation (76/172; 44.2%) that did not differ significantly between boys (42/97; 43.3%) and girls (34/75; 45.3%) was observed. Furthermore, the BAT activity showed no correlation with the outdoor temperature.

Gilsanz et al. [32] studied the FDG PET/CT images of a smaller but more homogeneous paediatric population comprising 31 paediatric patients (age range: 3.7–18.2 y). Twenty-one of these 31 patients had HL, whereas the remaining 10 patients had NHL. They aimed to compare the prevalence of metabolically active BAT at the time of diagnosis with that after treatment (when there was no evidence of disease) in the same cohort of patients. The overall prevalence of BAT visualisation on FDG PET/CT images was 10% (3/31) and 77% (24/31) at the time of diagnosis and at the time point showing without evidence of active lymphoma, respectively. The corresponding prevalence values in the group with HL were 14% (3/21) and 86% (18/21), respectively.

BAT was considered one of the sites without invasion in paediatric HL in our pilot and validation study. Previous studies have reported conflicting results upon the prevalence of BAT in HL [32, 37]. Therefore, we aimed to elucidate the relation between BAT visualisation on FDG PET/CT at the time of diagnosis in children with HL and the main determinants reported in adults, beyond temperature, sex, age, and the metabolic activity of HL lesions.

Table 1. Summary of the different methodologies performed

* BAT activation was determined on a per-patient basis, irrespective of the extent and intensity

	Paediatric patients involved (n)	**Diagnosis of the patients**	**Evaluation of the diffuse, non-tumour-specific sites**	**Evaluation of the tumour lesion**	**Evaluation of the outcome of the disease**
Pilot study on non-tumour-specific FDG uptakes	30	Hodgkin lymphoma	Visual and quantitative analysis	Visual analysis	Follow-up data
Validation study on non-tumour-specific uptakes	112	Hodgkin lymphoma	Visual and quantitative analysis	Quantitative analysis	Deauville Criteria
Study on BAT on bPET with French cohort	135	Hodgkin lymphoma	Visual analysis*	Quantitative analysis	n/a
Study on BAT on bPET with Hungarian cohort	92	Hodgkin lymphoma; sarcoma	Visual analysis*	Quantitative analysis	n/a

II. Objectives

II.1. Objectives of the pilot study on non-tumour-specific FDG uptake in paediatric patients with Hodgkin lymphoma

The first objective of the pilot study was to evaluate the frequency and intensity of visually diffuse FDG uptake by BAT and four selected organs on the bPET and iPET images of children with HL.

The second objective was to evaluate the correlation between the FDG uptake of these sites, the metabolic response of the HL sites, and evolution of the disease with treatment. For this purpose, we evaluated whether complete response (CR) was achieved at the end of the scheduled treatment (two, four, or six cycles of chemotherapy according to the group of therapy with or without complementary radiotherapy) or intensification was required during or at the end of the scheduled therapy in patients with refractory disease. Relapse-free survival (RFS) was determined as well.

II.2. Objectives of the validation study on non-tumour-specific FDG uptake in paediatric patients with Hodgkin lymphoma

Similar to the pilot study, the first objective of the validation study was to evaluate the frequency and intensity of visually diffuse FDG uptake by BAT and four selected organs without tumour invasion on the bPET and iPET images in a larger series of children with HL.

The second objective was to evaluate the relation between FDG uptake by the four organs without tumour invasion (SUVmax) and the HL lesions (maxSUVmax, total

metabolic tumour volume [TMTV], and total lesion glycolysis [TLG]) on bPET images prior to commencing treatment.

The third objective was to evaluate the relation between FDG uptake by BAT and the four organs without tumour invasion and the remaining metabolic activity of HL on iPET after two cycles of treatment according to Deauville Score (DS).

II.3. Objective of the studies focusing on brown adipose tissue activation

One objective of the studies focusing on brown adipose tissue (BAT) activation was to elucidate the relation between BAT visualisation on bPET in children with oncological disease (HL or sarcoma) and the main determinants reported in adults (i.e. temperature, sex, age) and non-tumour-specific FDG uptake of organs without tumour invasion.

Other objective of these studies was to evaluate the correlation between the BAT activation and the metabolic activity of the tumour lesions, and identify any significant difference between the results of the patients with HL and those with sarcoma.

III. Methods

III.1. Methods of the pilot study

Data collection was performed by me, a MD personnel of the department. Thus, no authorisation from an Ethics Committee was necessary according to the guidelines.
The study was commenced in 2012 [23]. The collection of the 2-year follow-up data from the patients was completed in 2015, corresponding to the end of the treatment of the last included patient.

Patients of the pilot study

Thirty children with HL (15 boys and 15 girls, age range 3–17 years, median = 14) examined between June 2006 and July 2012 with FDG PET/CT at baseline (bPET) and after two cycles of chemotherapy as an interim examination (iPET) were included in this study (Table 2). FDG PET/CT images of a given patient were acquired using the same machine.

Table 2. Characteristics of the patients included in the pilot study

Number of patients:	n = 30
Sex:	Boys (n = 15)
	Girls (n = 15)
Age at the time of baseline FDG PET:	Median = 14 years, range = 3–17
Stage of Hodgkin lymphoma:	Stage I–IIA (n = 5)
	Stage IIB–IIIA (n = 8)
	Stage IIIB–IV (n = 17)
Response after two cycles of OEPA chemotherapy EuroNet-PHL-C1 criteria:	
	Adequate response (n = 23)

	Inadequate response (n = 7)
Deauville score:	1–3 (n = 25)
	4–5 (n = 5)

Response to the treatment scheduled according to the treatment group after two cycles of OEPA chemotherapy:

	Complete response (CR): (n = 25)
	Refractory: (n = 5)

Follow-up after the end of treatment:

	Overall (n = 30, median = 36.5 months, range = 1–61)
Relapse:	(n = 9)
Time to relapse:	(median = 7 months, range = 1–50)
Persistence of CR:	(n = 21)
Follow-up:	(median = 43 months, range = 28–61)

PET/CT practice in the pilot study

FDG PET/CT acquisitions were performed at five different PET centres across France, as specified in the protocol of the trial summarised as follows: 3–5 MBq/kg of body mass of ^{18}F-FDG was administered intravenously to well-hydrated patients after fasting for at least 4 h; image acquisition was commenced at least 60 min after the injection. The actual delay between FDG injection and the acquisition of bPET images of each patient was recorded such that the acquisition of the iPET images could be commenced after the same delay. The difference of delay (Ddelay) between bPET and iPET was calculated for each patient. The median Ddelay was 0 min (mean −2.7 min). Acquisition was commenced with low-dose CT without contrast enhancement, followed by PET acquisition from mid-thigh to the skull.

PET/CT reading in the pilot study

All FDG PET/CT analyses and review were performed as masked reading at the Nuclear Medicine Department of Hôpital Tenon. All images were displayed on the same workstation and examined with and without attenuation correction and with and without PET/CT fusion.

Visualisation of activated BAT was determined based on the high FDG uptake in adipose tissue corresponding to negative Hounsfield Units (HU) on CT, whereas the surrounding regions of soft tissue took up FDG with a lesser intensity.

The diffuse FDG uptake was visualised at four sites:

- the thymus
- the bone marrow at the iliac crest
- the spleen
- the spinal cord at the level of the twelfth thoracic (or dorsal) vertebra (Th12).

Only those sites at which the FDG uptake was diffuse and homogeneous within the organ were considered. If this criterion could not be fulfilled, such that the uptake was inhomogeneous with some more active parts within the organ, the site was considered to be probably invaded by HL and was not considered as harbouring non-specific inflammation.

The intensity of diffuse FDG uptake at those sites was quoted according to the following visual scale [30]:

- 1 = less than the liver uptake
- 2 = similar to the liver uptake
- 3 = greater than the liver uptake, considered “intense.”

The FDG uptake at each site, including the lower pole of the liver, was also quantified using the standardised uptake value in the pixel with maximum intensity (SUVmax) in a

volumic region of interest of 20 mm in diameter; except for the spinal cord, which required a visually-adapted region of interest.
FDG uptake by activated BAT corresponds to very extensive and non-contiguous foci; thus, this quantification was not performed for BAT.

The visual interpretation for each site were compared, and the SUVmax values were measured and computed to determine the relative variation of SUVmax using the following equation to evaluate the evolution of diffuse uptake between bPET and iPET: (iPET - bPET) / bPET.

According to the "classical" approach, a comparator in the present study, the masked reading of the overall metabolic disease response of those foci, which is considered to correspond to HL, was also performed. The patient was classified as having achieved complete metabolic response (CMR) or in-complete metabolic response by comparing the bPET and iPET images according to the following response criteria of the EuroNet-PHL-C1 trial:

- no persistent enhanced FDG uptake on iPET in all initially involved regions on bPET
- minor FDG uptake on iPET lower than or equal to the uptake in the mediastinal blood pool in at least one of the initially involved regions with residual lesion size of ≥ 2 cm or FDG uptake on iPET lower than or equal to the surrounding background uptake in residual lesions with a size of <2 cm [39].

The masked reader quoted a lack of CMR if these criteria were not fulfilled.
The metabolic disease response was also evaluated using the Deauville Criteria and the corresponding five-point scale on iPET images only [12]. Refinements to the Deauville Criteria that were included in 2014 [40] stating that areas of the body with high physiological FDG uptake could have uptake higher than that of normal liver, yet still be considered to represent CMR, were taken into account. This refinement is applicable to Waldeyer's ring, the bowel, the spleen, and the bone marrow activated by chemotherapy and/or granulocyte colony-stimulating factor (G-CSF). Uptake at a site of

initial disease that does not exceed that of the surrounding normal tissue can be regarded as CMR in such cases. MR, biopsy, or an interval scan should be considered in areas exhibiting a persistent focal abnormality in the bone marrow in the context of a nodal response, as changes in the bone marrow may take longer to resolve [42].
A score of 1, 2, or 3 corresponded to CMR, whereas a score of 4 or 5 corresponded to a lack of CMR.

Follow-up and relapse-free survival in the pilot study

It was recorded whether CR was obtained at the end of the scheduled treatment (two, four or six cycles of chemotherapy according to the group of therapy with or without complementary radiotherapy), or if additional therapy was needed during or at the end of the scheduled treatment to obtain CR in case of refractory disease. Patients were then followed-up according to the standard procedure for paediatric HL, to confirm whether or not the patient was still in CR, and with complementary medical visits in case of suspected relapse. Relapse-free survival (RFS) was determined from the date of the end of treatment reaching CR until the date of the last medical visit if the patient was still in CR or until the visit when relapse was diagnosed.

Statistics

The non-parametric Mann–Whitney U or Wilcoxon test was used to compare quantitative data, respectively unpaired or paired, and the Fisher's exact test to compare proportions. The McNemar's test was used to compare sensitivity, specificity and predictive values of the different criteria. A p value less than 0.05 was considered significant.
Receiver operating characteristics (ROC) analysis was performed to determine the best cutoff value for the criterion according to the Youden index, and the area under the curve was compared to 0.5. The analysis of RFS was performed according to the Kaplan-Meier method.

III.2. Methods of the validation study

An independent and larger series involving the FDG PET/CT images of 112 children and adolescents with HL was collected according to a well-established practice to validate the results of the pilot study (Table 3). The study design was similar to that of the pilot study: patients aged < 18 years underwent two FDG PET/CT acquisitions (at baseline before commencing treatment [bPET] and at the interim evaluation after two cycles of treatment [iPET]). The FDG PET/CT acquisitions were performed between September 2010 and February 2015 at various PET centres in France and submitted for masked reading at Hôpital Tenon.

Differences from the study variables and end points of the pilot study

The methods used in this larger study were identical to those used in the pilot study (please refer to Chapter III.1. "Methods of the pilot study" for further details). However, some additions were made in this "validation" study in terms of the study variables to better reflect the metabolic mass and activity of HL lesions. In addition, some changes in the statistical analysis and the secondary objectives were also made.

Table 3. Characteristics of the patients included in the validation study

Number of patients:	n = 112
Sex:	Boys (n = 47)
	Girls (n = 65)
Age at baseline FDG PET:	Median = 14.4 years (range = 4.5–17.9)
DS on iPET:	1 (n = 34)
	2 (n = 24)
	3 (n = 23)
	4 (n = 27)
	5 (n = 4)

The comparator, i.e., the FDG uptake by the HL lesions was evaluated visually according to two criteria in the pilot study: the response criteria of the EuroNet-PHL-C1 study and the Deauville criteria. The EuroNet-PHL-C1 criteria scores were derived based on the differences between bPET and iPET; in contrast, the Deauville criteria scores were derived from iPET only.

Three quantitative parameters reflecting the uptake and the extent of the HL lesions on bPET, prior to interference from the treatment, were introduced in the validation study as follows: maxSUVmax, TMTV, and TLG.

In the prediction of disease outcome Deauville Score (DS) was serving as a reference.

Statistics

The non-parametric Wilcoxon test was used to compare quantitative data. The McNemar's test was used to compare sensitivity, specificity and predictive values of the different criteria. Pearson correlation was used to evaluate the correlation of FDG uptake by HL on bPET and the FDG uptake at the sites without tumour invasion.

ROC analysis was performed by reducing the DS to two levels, "complete metabolic response" or "non-complete metabolic response". Stepwise logistic regression was performed with the dependent variable CR selected according to the Deauville score, a combination of all quantitative variables set to predict CR.

A p value less than 0.05 was considered significant.

III.3. Methods for the "BAT on bPET" studies

Patients

The first study evaluating BAT on bPET involved paediatric patients from French institutes. The data of 135 children and adolescents with HL, comprising 62 boys and 73 girls, who underwent FDG PET/CT at the time of diagnosis (baseline bPET) were

extracted (Table 4). This study focused on BAT activation on bPET, in contrast to the pilot study. Therefore, the data of 10 patients of the pilot study were included in the "BAT on bPET" study as the raw PET/CT images of these patients were available for the quantification of active volume of HL on bPET. The mean age of the patients at the time of undergoing FDG PET/CT was 13.6 year (median = 14.3, range 4.5–17.9). The patients were referred to undergo FDG PET/CT by the Paediatric Oncology Departments of various hospitals most frequently (n > 10) Hôpital Trousseau (n = 26), Institut Gustave Roussy (n = 26), Hôpital Robert Debré (n=22), and Institut Curie (n = 14). The outside temperatures in the town and on the day of each PET/CT acquisition and the minimum, maximum, and mean values were obtained from the dedicated website: infoclimat.fr.

A study involving 92 paediatric patients from Hungary, comprising 48 boys and 44 girls with the mean age 12.9 years (median age = 14 years; range 3–17 years) was performed to analyse the FDG PET/CT examination data obtained at the time of diagnosis (bPET). The patients were diagnosed with HL or sarcoma (osteosarcoma [n = 18], Ewing sarcoma [n = 4], rhabdomyosarcoma [n = 6], and monophasic synovial sarcoma [n = 1]) based on the findings of histological evaluation. Ninety-one patients underwent FDG PET/CT examination using a GE Discovery IQ5 PET/CT device; one patient underwent FDG PET/CT examination using a Siemens TruePoint HD PET/CT device. Patients were treated at the Paediatric Oncology Station, Semmelweis University, Budapest, or at the Heim Pál National Paediatric Institute, Budapest. The outside temperatures in the town and on the day of each PET/CT acquisition were obtained from the dedicated website: timeanddate.com/weather/hungary/budapest.

Table 4. Characteristics of the patients included in "BAT on bPET studies"

Cohort with French patients:	
Number of patients:	n = 135
Sex:	Boys (n = 62)
	Girls (n = 73)
Age at baseline FDG PET:	Median = 14.3 years (range = 4.5–17.9)
Diagnosis of the patients:	Hodgkin lymphoma (n=135)
Cohort with Hungarian patients:	
Number of patients:	n = 92
Sex:	Boys (n = 48)
	Girls (n = 44)
Age at baseline FDG PET:	Median = 14 years (range = 3–17)
Diagnosis of the patients:	Hodgkin lymphoma (n=63)
	sarcoma (n=29)

FDG PET/CT practice

FDG PET/CT was performed in a manner similar to that in the pilot study. The method can be summarised as follows: well-hydrated children or adolescents received an intravenous injection of FDG after fasting for at least 4 h. Image acquisition was commenced at least 60 min after injection.

FDG PET/CT reading

All FDG PET/CT analyses and reviews were performed as masked reading at the Department of Nuclear Medicine, Hôpital Tenon, in the case of patients from France. These analyses were performed by the Department of Nuclear Medicine, Semmelweis University, in the case of Hungarian patients. The analyses were performed by a nuclear medicine physician experienced in FDG PET/CT reading. Activated BAT was detected

based on the presence of a high FDG uptake in the adipose tissue corresponding to negative Hounsfield Units (HU) on CT and the lesser intensity of the FDG uptake of soft tissue in the surrounding regions.
BAT activation was determined on a per-patient basis, irrespective of the extent and intensity of the hyperfunctioning foci or masses on FDG PET/CT (Figure 2).
The metabolic activity of the HL lesions was determined as reflected by the following variables [42].

- Maximum value of the SUVmax of all HL lesions (maxSUVmax) – measured only on the data of the group with 135 patients from France
- Total metabolic tumour volume (TMTV)
- Total lesion glycolysis (TLG)

A volume of interest was set around each HL lesion (lymph node or organ). TMTV was defined as the sum of the volume of all nodal and extranodal HL lesions. Bone marrow and/or spleen involvement was included in HL volume measurement only if focal uptake was observed. TLG is defined as the sum of the products of the metabolic volume divided by the SUVmean of each HL lesion.
Furthermore, similar to the pilot study, the SUVmax was measured in the structures without tumour invasion in the cohort comprising 135 patients. The sites with enhanced glucose metabolism compared with the HL activity included the liver, spinal cord at the Th12 vertebra, and iliac crest reflecting the bone marrow. Similar to the pilot study, only the sites with diffuse and homogenous FDG uptake within the organ were considered.

The TMTV and TLG of the tumour lesions were the focus of the study conducted in Hungary. The primary intention was to visualise the possible correlation between the BAT activation and the TMTV and TLG values of the tumour lesions and identify any significant difference between the results of the patients with HL and those with sarcoma.

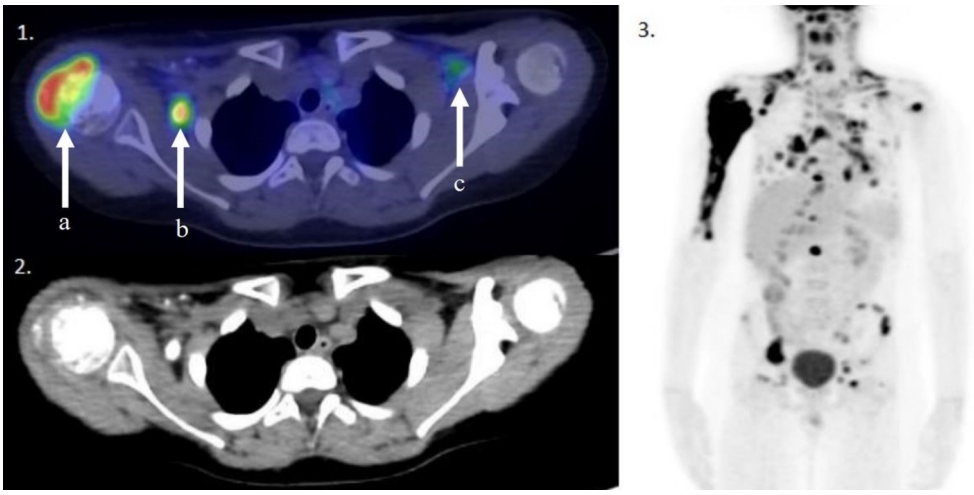

Figure 2. PET/CT fused images (1), CT images (2) and PET MIP image (3) of a 9-year-old patient with osteosarcoma. Visualisation of FDG uptake in the primary tumour of the right humerus (a), metastatic lymph node in the right axillary region (b), and brown adipose tissue (BAT) in the left axillary region (c) [43].

Statistics

The non-parametric Mann–Whitney test was used to compare the quantitative data of the 135 paediatric patients from France. The chi-square test was used to compare proportions.

The Mann–Whitney, chi-square, and Fisher's exact tests were used to analyse the data of the 92 patients from Hungary. The logistic regression model was fitted to further analyse the relationship between BAT activation and other variables.

A p-value of <0.05 was considered significant in both studies.

IV. Results

IV.1. Results of the pilot study of non-tumour-specific FDG uptake in children with Hodgkin lymphoma

IV.1.1. Presence of diffuse FDG uptake and evolution of its intensity

Brown adipose tissue (BAT)

Activation of BAT was noted on bPET and iPET images of two and five patients, respectively. Activation of BAT was visible on both PET/CTs in only one patient.

Other sites

Focal uptake was observed in the spleen in one case and in the thymus in five cases, which was considered to correspond to HL invasion. FDG uptake by the thymus could not be evaluated in six and three cases on bPET and iPET images, respectively, owing to the presence of the large bulk of HL tissue in the upper mediastinum.

Diffuse uptake that was visually quoted as 3 and considered “intense” (i.e., more intense than liver uptake) on bPET was observed more frequently in the spleen (48%) than in the spinal cord at the thoraco-lumbar junction (43%), bone marrow (37%), or thymus (21%). At least one site exhibited diffuse and intense uptake on bPET in the large majority of patients (77%).

The number of cases where at least one site exhibited diffuse uptake that were visually quoted as 3 decreased on iPET compared with that on bPET (to 23%). This decrease was statistically significant for the spleen and spinal cord at Th12 (Fisher’s exact test; Table 5).

Table 5. Pilot study. Detection of sites of non-tumour-specific FDG uptake visually more intense than the liver FDG uptake (quoted 3 by the visual scale)

	Baseline PET/CT (bPET)	Interim PET/CT (iPET) (Fisher's exact test vs. bPET)
Brown adipose tissue (BAT) activation	2/30 = 7%	5/30 = 17% (p = 0.4 NS)
Diffuse thymus hyperactivity *	4/19 = 21%	1/22 = 5% (p = 0.16 NS)
Diffuse bone marrow hyperactivity in iliac crests	11/30 = 37%	4/30 = 13% (p = 0.07 NS)
Diffuse spleen hyperactivity *	14/29 = 48%	1/29 = 3% (p < 0.001)
Spinal cord non-nodular hyperactivity at Th12	13/30 = 43%	4/30 = 13% (p = 0.04)
Hyperactivity at least one site (except BAT)	23/30 = 77%	7/30 = 23% (p < 0.001)

***** *The denominator takes into account that some of the sites were considered to be invaded by HL or could not be evaluated owing to the neighbouring HL bulk. Consequently, they were excluded from the visual analysis for non-tumour-specific uptake.*

Quantitative analysis revealed that the treatment induced a significant overall decrease in SUVmax at three sites (thymus, bone marrow in the iliac crest, and spleen), but not in the spinal cord at Th12 (Table 6). In contrast, an overall significant increase in the FDG uptake by the liver was observed after treatment (p = 0.002), with the median of the relative variation being +13% (Figure 3).

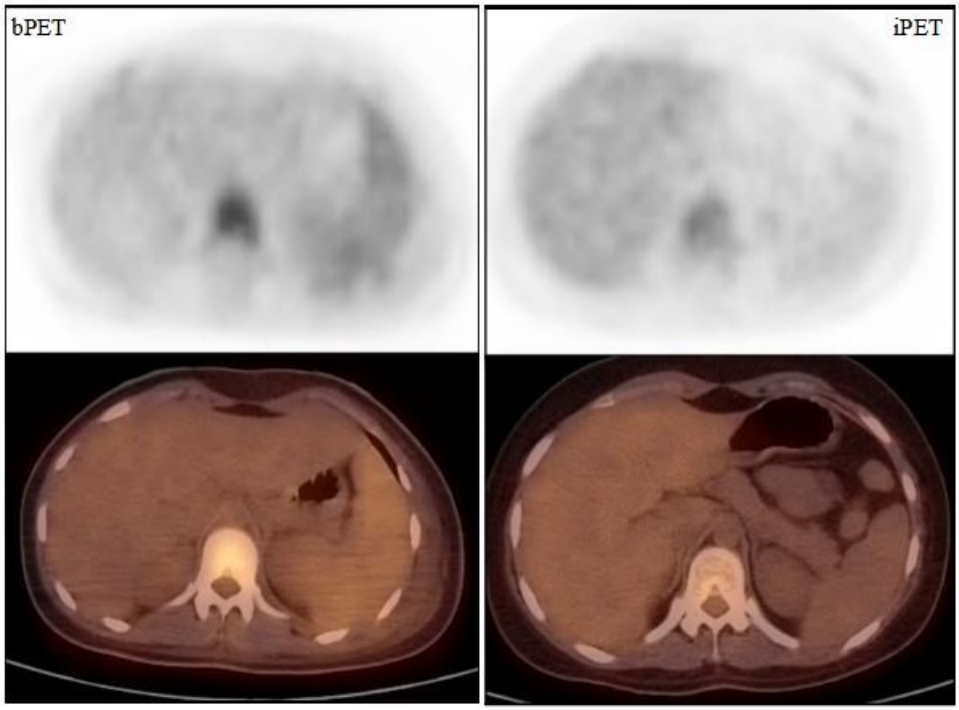

Figure 3. Representative image of a 14-year-old girl with HL in our pilot study, bPET and iPET transversal PET and PET/CT slices at the level of Th12. Visual and quantitative comparisons of bPET and iPET revealed that the liver uptake increased and the splenic uptake decreased after two cycles of treatment. The spinal cord uptake at Th12 also decreased [25].

Table 6. Pilot study. SUVmax of the sites where FDG uptake was quantified (median value [range]) and the influence of two cycles of chemotherapy

	Baseline PET/CT SUVmax: median value [range]	**Interim PET/CT SUVmax: median value [range]** (Wilcoxon's test for paired values)	**Relative variation: Median value [range]**
Thymus (non-invaded)	1.6 [0.9,3.0]	1.2 [1.0,1.7] ($p < 0.001$)	-25% [-43%,+11%]
Bone marrow in the iliac crest (non-invaded)	1.8 [0.4,3.8]	1.2 [0.5,2.7] ($p < 0.001$)	-29% [-61%,+100%]
Spleen (non-invaded)	1.8 [0.8,4.8]	1.3 [0.8,2.7] ($p < 0.001$)	-21% [-75%,+35%]
Spinal cord at Th12 (non-invaded)	1.7 [0.7,3.4]	1.5 [0.8,3.1] ($p = 0.5$ NS)	+1% [-47%,+60%]
Liver (non-invaded)	1.7 [0.8,2.5]	1.9 [1.2,2.9] ($p = 0.002$)	+13% [-16%,+75%]

Metabolic response of HL sites

The evolution of FDG uptake by HL tissue between bPET and iPET according to the EuroNet-PHL-C1 criteria was observed in 23 of the 30 patients (77%), indicating CMR. According to the Deauville criteria on iPET, 25 of the 30 patients (83%) were considered to have achieved CMR.

IV.1.2. Relation between diffuse uptake, metabolic response of the tumour, and evolution of the disease

Detection of refractory disease

Twenty-five of the 30 children (83%) achieved CR with the scheduled treatment. The remaining five children received complementary therapies before achieving CR, and their disease was considered to be refractory.

The performance of early metabolic response determination according to the EuroNet-PHL-C1 criteria to identify a refractory disease, considering the response to the scheduled initial management as a standard of truth, was as follows: Se, 60% (3/5); Sp, 84% (21/25); PPV, 43% (3/7); NPV, 91% (21/23); and accuracy, 80% (24/30). The corresponding values according to the Deauville criteria were as follows: Se, 60% (3/5); Sp, 92% (23/25); PPV, 60% (3/5); NPV, 92% (23/25); and Acc, 87% (26/30). ROC analysis confirmed that the initial choice of considering a DS of >3 as the criterion for the lack of CMR was optimal. The area under the ROC curve (AUC) was 0.73, with a difference of 0.5 being considered close to statistical significance ($p = 0.08$).

None of the six children with BAT activation on bPET or iPET experienced refractory disease. However, the implication of this finding is uncertain (Fisher's test $p = 0.6$) owing to the small number of children with BAT activation ($n = 6$) and those with refractory disease ($n = 5$).

ROC analysis was performed to determine whether the quantified diffuse uptake in these sites can be used to identify patients at risk of developing refractory HL. Only the relative variation of the liver SUVmax between bPET and iPET showed a significant difference between median values, with an AUC of 0.90, which was significantly >0.5 ($p < 0.0001$).

The performance for predicting the development of refractory HL with an optimal cut off value of 0% (no increase in SUVmax between bPET and iPET) was as follows: Se, 100% (5/5); Sp, 84% (21/25); PPV, 55% (5/9); NPV, 100% (21/21); and Acc, 87% (26/30).

The accuracy for predicting refractory HL using variation in the liver uptake was identical to that of the approach using the dual-point DS (1–3 vs. 4–5) at 87%. This accuracy was not significantly higher than that of the approach using EuroNet-PHL-C1 criteria (80%). However, the comparison of AUC revealed a trend favouring the variation of liver uptake vs. five-point scale Deauville criteria that did not reach statistical significance ($p = 0.15$).

Relapse after complete response

Complete response (CR) was reached at the end of initial treatment. CR was maintained in 21 of the 30 patients (70%) during the median follow-up period of 43 months (range = 28–61). The remaining nine patients relapsed after a median RFS of 7 months (range = 1–50). Six patients relapsed <12 months after the end of treatment, and three patients relapsed at 24, 25, and 50 months.

Relapse showed no significant association with previously refractory HL requiring complementary treatment.

Two of the five patients with initially refractory disease relapsed after 1 and 5 months. Seven of the 25 patients achieved CR with scheduled initial therapy (log rank test; $p = 0.22$).

ROC analysis was conducted to identify the factors predicting early recurrence within 12 months as the follow-up data were available for all patients.

The EuroNet-PHL-C1 or the Deauville criteria, which reflect the early metabolic response of HL lesions to treatment, exhibited poor PPV for detecting patients at risk of relapsing within 12 months. The PPV and Acc of the EuroNet-PHL-C1 criteria were 14% (1/7) and 63% (19/30), respectively. The corresponding PPV and Acc values for the Deauville criteria were somewhat better at 20% (1/5) and 70% (21/30), respectively.

A statistically significant predictor of relapse within 12 months of achieving CR could not be identified among the studied parameters at bPET or iPET, including BAT activation, which could be visualised on bPET or iPET for two patients who relapsed after 6 months. The criterion that achieved the best AUC in the ROC analysis (0.7, $p =$

0.07) was the variation in the spinal cord uptake at Th12 between bPET and iPET (Figure 4). An increase of > 5% between bPET and iPET was indicative of a higher risk of relapse. The Se, for predicting relapse using this cutoff value was 83% (5/6), Sp71% (17/24), PPV 42% (5/12), NPV 94% (17/18), and Acc 73% (22/30). However, a significant difference was observed in terms of the median values of spinal cord uptake at Th12 according to recurrence or prolonged response during the overall follow-up duration.

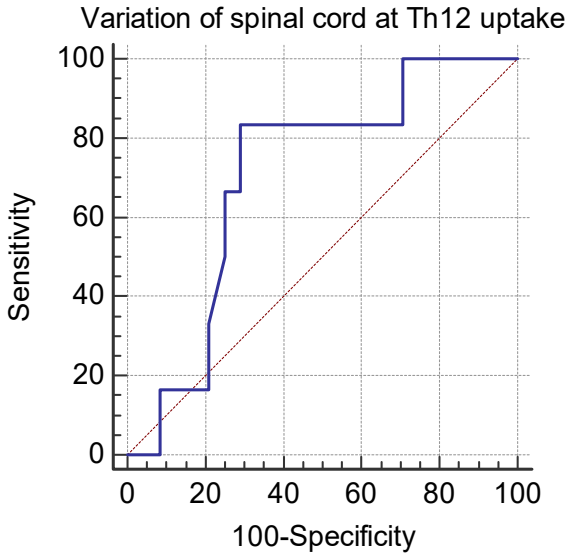

Figure 4. ROC curve depicting the ability of the variation in FDG uptake of the spinal cord, measured at Th12, between bPET and iPET to predict relapse within 12 months of completing treatment

Two unfavourable criteria were derived from this analysis of the evolution of diffuse FDG uptake in these sites between bPET and iPET: no increase in the liver FDG uptake and increase of > 5% in the spinal cord FDG uptake. The “relapse risk index” (RRI) corresponds to the number of unfavourable criteria (0, 1, or 2) that a given patient matches.

The RRI value was 2 in four patients, comprising three patients who required complementary treatment for refractory HL (two patients relapsed after 1 and 5 months) and one patient who relapsed after 10 months. Thus, the predictive value for an unfavourable outcome was 100%.

The RRI value was 1 in 13 patients, including two patients who required complementary treatment for refractory HL and four patients who relapsed after 6 (n = 2), 25 (n = 1), and 50 (n = 1) months.

The RRI value was 0 in 13 patients. None of the patients required complementary treatment for refractory HL. Two patients relapsed after 7 and 24 months.

Kaplan–Meier analysis revealed a significant difference in RFS according to the RRI (p = 0.005). The hazards ratios were 2.01 (95% confidence interval [CI] = 0.54–8.0) and 10.3 (CI = 0.72–147) for RRI of 1 and 2, respectively, considering an RRI of 0 as the reference. In contrast, no significant difference was observed in RFS according to the DS (p = 0.5), whose predictive values were superior to those of the EuroNet-PHL-C1 criteria. (Figure 5) (Figure 6)

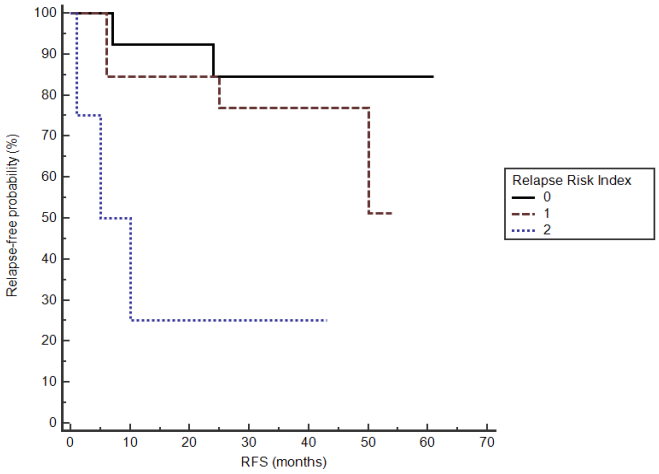

Figure 5. Kaplan-Meyer plot of the relapse-free survival (RFS) rate. RFS is plotted according to the value of "relapse risk index" (RRI) based on the evolution of diffuse FDG uptake in the liver and in the spinal cord at Th12 between bPET and iPET [25].

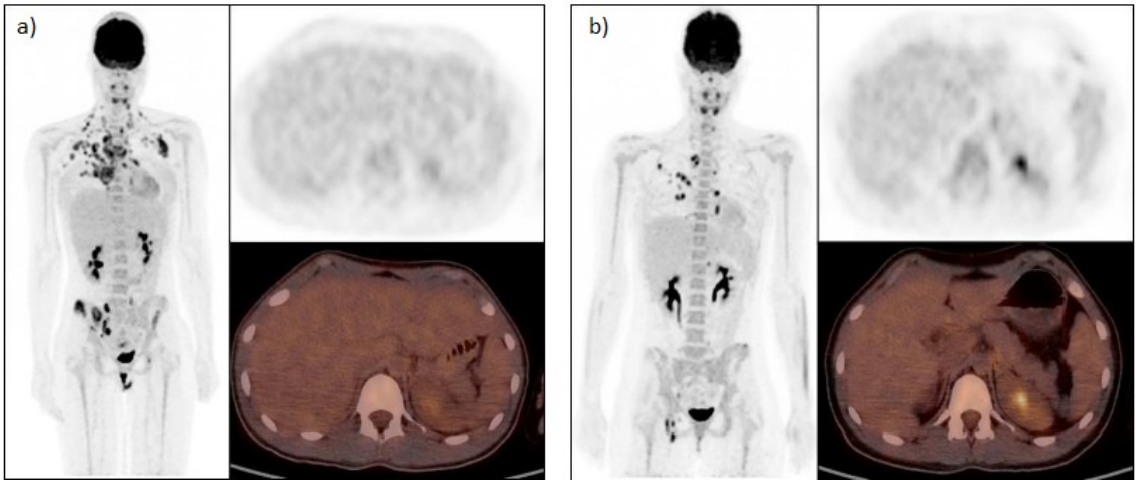

Figure 6. A 16-year-old girl participating in the pilot study with diagnosis of HL, initial stage IVBb. Baseline PET (a) and interim PET (b) images (maximal intensity pixel (MIP) visualisation, transversal PET and PET/CT slices at the level of Th12). BAT was not visualised on bPET or iPET. Incomplete metabolic response was on iPET. SUVmax of the lower pole of the liver decreased by 5 % (from 2.1 to 2) and SUVmax of spinal cord at the level of Th12 increased by 18 % (from 1.7 to 2). The "relapse risk index" was RRI=2, highest value. HL relapse was observed 5 months after the end of treatment [25].

IV.2. Results of the validation study of non-tumour-specific FDG uptake in children with Hodgkin lymphoma

IV.2.1. Presence of diffuse FDG uptake and the evolution of its intensity

Brown adipose tissue (BAT)

Activation of BAT was observed at bPET and iPET images in 12% and 20% of patients, respectively. Activation of BAT was observed on bPET and iPET in 7 patients, disappeared on iPET in 6 patients and appeared in 15.

Other sites

Focal or inhomogeneous uptake on bPET and/or iPET was observed in the spleen in 18 cases and the spinal cord at Th12 in 13 cases, which was considered evocative of HL invasion. Furthermore, it was not possible to evaluate FDG uptake by the thymus or to exclude its invasion by HL owing to focal uptake or heterogeneous uptake on bPET in 81 patients. As the activation of thymus was less frequent and intense on iPET, the thymus uptake was considered to be homogeneous more frequently after treatment.

Diffuse uptake visually quoted as 3 and considered “intense” (i.e., more intense than liver uptake) on bPET was observed at a similar frequency in the spleen (42%), bone marrow (44%), and thymus when the aspect was not evocative of HL invasion (45%). The frequency of hyperactivation was considerably reduced in these organs on iPET. The frequency of hyperactivation in the spinal cord at Th12 was lesser on bPET (31%); however, this status persisted on iPET more frequently (17%) compared with other sites. At least one site exhibited diffuse and intense uptake on bPET in the majority of patients (72%), but persisted on iPET in a minority of patients (27%) (Table 7).

Table 7. Validation study. Detection of sites of non-tumour-specific FDG uptake visually more intense than that of the liver uptake (quoted 3 according to the visual scale)

** The denominator of <112 takes into account that some of these sites were considered to have been invaded by HL or could not be evaluated owing to the neighbouring HL bulk. Therefore, they were excluded from the visual analysis of "non-specific" uptake for bPET and iPET.*

	Baseline PET/CT (bPET)	**Interim PET/CT (iPET) (McNemar test)**
Brown adipose tissue (BAT) activation	13/112 = 12%	22/112 = 20% (p = 0.08 NS)
Diffuse thymus hyperactivity *	13/29 = 45%	1/29 = 3% (p < 0.0005)
Diffuse bone marrow hyperactivity in iliac crests *	48/109 = 44%	2/109 = 2% (p < 0.0001)
Diffuse spleen hyperactivity *	38/94 = 42%	12/94 = 13% (p = 0.0001)
Spinal cord non-nodular hyperactivity at Th12 *	31/99 = 31%	17/99 = 17% (p = 0.02)
Hyperactivity at least one site (except BAT)	81/112 = 72%	30/112 = 27% (p < 0.0001)

Quantitative analysis revealed that treatment induced a significant overall decrease in the SUVmax in three sites without invasion (thymus, bone marrow of the iliac crests, and spleen) (all $p < 0.001$), but not in the spinal cord at Th12 (Table 8). In contrast, the FDG uptake by the liver exhibited a significant overall increase after two cycles of treatment ($p < 0.001$) in 85% (93/110) of cases.

Table 8. Validation study. FDG SUVmax (median value [range]) at baseline (bPET) and after two cycles of chemotherapy (iPET) at sites without tumour invasion. Variation between bPET and iPET

	Baseline PET/CT SUVmax: median value [range]	**Interim PET/CT SUVmax: median value [range]** (Wilcoxon's test for paired values)	**Variation between bPET and iPET: increase decrease**
Thymus (non-invaded)	1.35 [0.9,4.5]	0.7 [0.7,2.7] ($p < 0.001$)	Increase (n = 2) **Decrease** (n = 17)
Bone marrow in iliac crests (non-invaded)	1.9 [0.7,10.7]	1.5 [0.7,4.1] ($p < 0.001$)	Increase (n = 21) **Decrease** (n = 79)
Spleen (non-invaded)	2.1 [1.0,7.6]	1.8 [0.7,4.1] ($p < 0.001$)	Increase (n = 24) **Decrease** (n = 64)
Spinal cord at Th12 (non-invaded)	1.7 [0.9,3.2]	1.8 [0.8,4.1] ($p = 0.06$ NS)	**Increase** (n = 50) Decrease (n = 40)
Liver (non-invaded)	1.95 [1.0,3.8]	2.3 [1.2,2.9] ($p < 0.001$)	**Increase** (n = 93) Decrease (n = 17)

IV.2.2. Relation between diffuse uptake and metabolic response of the tumour

Table 9 illustrates the significant positive correlations between maxSUVmax of HL and the SUVmax of the sites without invasion before treatment. The volumic approach (TMTV and TLG) revealed no significant correlation with the SUVmax of the spinal cord and liver. A strong correlation was observed between bPET TMTV and TLG, but not with maxSUVmax (TMTV: $r = 0.08$ and $p = 0.4$; TLG: $r = 0.29$ and $p = 0.004$). Strong correlations between the SUVmax of the four sites without tumour invasion were observed on bPET and iPET, except for the spleen and spinal cord at Th12 on bPET ($r = -0.05$). The greatest correlations coefficients were observed between the bone

marrow and spleen on bPET (r = 0.78) and iPET (r = 0.67) and between the liver and spleen on bPET (r = 0.77) and iPET (r = 0.41).

Table 9. Validation study. FDG uptake by HL on bPET and its correlation with the uptake at the sites without tumour invasion

	Baseline HL maxSUVmax	**Baseline HL TMTV**	**Baseline HL TLG**
	Median value [range]	**Median value [range]**	**Median value [range]**
	11.7 [4.3–33.6]	182 [8.4–1254]	811 [29–8920]
	Pearson's correlation coefficient (significance vs. 0)	**Pearson's correlation coefficient (significance vs. 0)**	**Pearson's correlation coefficient (significance vs. 0)**
Bone marrow in iliac crests (non-invaded) SUV max	0.41 ($p < 0.001$)	0.20 ($p < 0.03$)	0.28 ($p < 0.003$)
Spleen (non-invaded) SUVmax	0.38 ($p < 0.0002$)	0.31 ($p < 0.003$)	0.34 ($p < 0.001$)
Spinal cord at Th12 (non-invaded) SUVmax	0.47 ($p < 0.001$)	-0.03 ($p = 0.7$ NS)	0.06 ($p = 0.5$ NS)
Liver (non-invaded) SUVmax	0.41 ($p < 0.001$)	-0.12 ($p = 0.22$ NS)	-0.02 ($p = 0.9$ NS)

IV.2.3. Prediction of complete metabolic response

Univariate analysis

Univariate analysis revealed a significant difference according to the Deauville five-point score (iPET) for bPET results on HL: maxSUVmax ($p = 0.007$), TMTV ($p = 0.009$), and TLG ($p < 0.001$). These bPET values were highest in the four patients with a subsequent DS of 5.

In contrast, no such significant difference according to the Deauville five-point score was observed in the SUVmax of any site without tumour invasion on bPET.

ROC analysis and logistic regression was performed by reducing the DS to two levels, "complete metabolic response" or "non-complete metabolic response."

As described in the study by Isik et al. [44], a "conservative" interpretation considering was tested, as in our pilot study: a DS of ≤3 was considered non-indicative of relapse, whereas a "sensitive" interpretation considering a DS of ≥3 was considered indicative of relapse.

The presence of CR according to Deauville interpretation was selected as the classification variable in the ROC analysis. The thymus SUVmax was not analysed as the number of patients with thymus that did not exhibit invasion was low.

Table 10 indicates that the patients whose iPET images were likely to correspond to an inadequate response can be delineated using the FDG uptake by HL on bPET (best with TLG, significant with TMTV, and borderline with maxSUVmax), as well as the SUVmax of the spinal cord at Th12 or the spleen without invasion on iPET.

Table 10. ROC analysis of the potential predictors of CR on iPET after two cycles of treatment determined according to the Deauville criteria. Variables and results in bold correspond to a significant rejection ($p < 0.05$) **of the null hypothesis (area under the ROC curve = 0.5).**

	Area under the ROC curve to predict CR on iPET, **"conservative" interpretation (Deauville 3 = CR)**	Area under the ROC curve to predict CR on iPET, **"sensitive" interpretation (Deauville 3 = no CR)**
Bone marrow in iliac crests (non-invaded) SUVmax on bPET	0.53	0.58
Bone marrow in iliac crests (non-invaded) SUVmax on iPET	0.61	0.57
Bone marrow in iliac crests (non-invaded) iPET - bPET	0.52	0.56
Spleen (non-invaded) SUVmax on bPET	0.54	0.51
Spleen (non-invaded) SUVmax on iPET	**0.65**	**0.64**
Spleen (non-invaded) iPET - bPET	0.59	**0.64**
Spinal cord at Th12 (non-invaded) SUVmax on bPET	0.55	0.57
Spinal cord at Th12 (non-invaded) SUVmax on iPET	**0.67**	**0.64**
Spinal cord at Th12 (non-invaded) iPET-bPET	0.61	0.61
Liver (non-invaded) SUVmax on bPET	0.52	0.53

Liver (non-invaded) SUVmax on iPET	0.52	0.57
Liver (non-invaded) iPET-bPET	0.51	0.53
HL maxSUVmax on bPET	0.60	**0.62**
HL total metabolic tumour volume (TMTV) on bPET	**0.69**	**0.66**
HL total lesion glycolysis (TLG) on bPET	**0.71**	**0.70**

Multivariate analysis

Stepwise logistic regression was performed with the dependent variable CR selected according to "conservative" or "sensitive" interpretation of the Deauville score, a combination of all quantitative variables set to predict CR.

The TLG on bPET ($p < 0.01$) and variation in the spinal cord uptake on Th12 ($p = 0.05$) were significant contributors for predicting CR according to the "conservative" interpretation of the Deauville score. The area under the ROC curve increased from 0.71 to 0.72 on combining the variation in the spinal cord uptake (iPET – bPET) on Th12 with the TLG on bPET.

Only TLG on bPET was identified as the single significant contributor for the prediction of CR according to the "sensitive" interpretation of the Deauville score.

IV.3. Results of the "BAT on bPET" studies

The frequency of BAT visualisation on FDG PET/CT at the time of the diagnosis was 19% (25/135; 95% confidence interval [CI] = 12–25%) in the first study that analysed BAT on bPET involving 135 paediatric patients.

Analysis of the patients based on whether FDG uptake by BAT was visible revealed no significant difference in terms of age; outside temperature on the day of PET/CT acquisition; SUVmax of the liver, the spleen, the spinal cord at Th12, and the bone marrow in the iliac crest; and maxSUVmax of the HL lesions (Table 11).

A trend toward lower values for TMTV and TLG was observed in the HL lesions of cases with visible FDG uptake by BAT; however, the result did not reach statistical significance ($p = 0.07$ and 0.06 respectively).

The prevalence of BAT visualisation did not differ between boys (15/62; 24%) and girls (10/73; 14%) according to a class of age, in particular, 13–14.9 years (Table 12).

The frequency of BAT visualisation on bPET was 23.9% (22/92; CI: 15.2–32.6%) in the study involving 92 patients from Hungary. Signs of BAT activation were observed in 19% (12/63) and 34.4% (10/29) of patients with HL and sarcoma, respectively. Fisher's exact test performed to determine the prevalence of BAT activation in patients with HL compare with that in patients with sarcoma revealed no significant difference ($p = 0.12$).

Table 11. Results of quantitative variables according to whether BAT was visualised on FDG PET/CT at baseline (study with 135 patients).

Potential determinant	NO FDG uptake by BAT, n = 110 Median, range	POSITIVE FDG uptake by BAT, n = 25 Median, range	p (Mann–Whitney test)
Age (years)	14.2, 4.5–17.9	14.9, 7.0–17.3	0.51
Outside temperature on the day of FDG PET/CT (°C)	Min = 10.2, -6.4 to 23.3	Min = 6.3, -0.5 to 17.8	0.22
	Max = 17.4, 1.0–35.0	Max = 14.0, 6.1–30.9	0.30
	Mean = 13.9, -2.1–29.2	Mean = 9.7, 2.9–24.0	0.28
Liver SUVmax	1.9, 1.0–3.8	2.1, 1.4–2.8	0.44
Spinal cord at Th12 SUVmax	1.7, 0.9–3.2	1.9, 1.1–2.9	0.17
Bone marrow at iliac crest SUVmax	1.9, 0.7–10.7	2.0, 0.7–4.5	0.65
HL lesions maxSUVmax	11.3, 4.3–33.6	11.1, 5.5–21.1	0.61
HL lesions TMTV (mL)	182, 12.7–1250	119, 8.4–894	0.07
HL lesions TLG (g)	782, 29.0–8920	502, 35.5–4370	0.06

Table 12. Prevalence of BAT visualisation on baseline FDG PET/CT images according to sex and age (study with 135 patients).

Potential determinant	NO FDG uptake by BAT, n = 110	POSITIVE FDG uptake by BAT, n = 25	p (chi-square test)
Sex	Boys: n = 47 Girls: n = 63	Boys: n = 15 (24%) Girls: n = 10 (14%)	0.18
Age (years)	< 13: n = 38 13–14.9: n = 34 ≥ 15: n = 38	< 13: n = 8 (21%) 13–14.9: n = 6 (17%) ≥ 15: n = 11 (29%)	0.65

For TMTV and TLG of the malignant tissue, the Mann–Whitney test revealed no significant association between BAT activation in the group that included paediatric patients with HL and sarcoma. However, analysing the subgroup of patients with HL revealed a trend towards significancy for TMTV ($p = 0.06$) and TLG ($p = 0.09$) (Table 13). Analysis of the connection between BAT activation and the TMTV and TLG values revealed a difference between the HL and sarcoma subgroups. The TMTV and TLG values of the patients with HL exhibiting BAT activation were lower than those of the patients not exhibiting BAT activation. The TMTV and TLG values of the patients with sarcoma exhibiting BAT activation were higher than those of the patients not exhibiting BAT activation. However, the Mann–Whitney test revealed no significant association between the TMTV and TLG values and BAT activation in the sarcoma subgroup. This could be attributed to the limited number of patients with sarcoma.

Logistic regression did not reveal the aforementioned trends for TMTV and TLG in any group; however, a significant correlation was observed between the age of the patient

and BAT activation in the HL subgroup (p = 0.04); a near significant correlation was observed in the whole group (p = 0.06).

Analysing the frequency of BAT activation on PET/CT images according to the season revealed that 45% (10/22) of the PET/CT examinations depicting signs of BAT activation were performed in autumn. Furthermore, 38% (10/26) of the total number of PET/CT examinations with signs of BAT were conducted in autumn. The logistic regression model revealed a significant inverse relation between the seasons of winter and autumn (reference) for FDG uptake by BAT in the whole group (Log. Odds -2.13; p = 0.02). A near significant trend was observed in the subgroup of patients with HL (Log. Odds -2.45; p = 0.08).

The prevalence of BAT visualisation in this study did not differ between boys and girls in the whole group (boys: 10/48 [20%] and girls: 12/44 [27%]; p = 0.63) or in the subgroups of HL (boys: 4/31 [13%] and girls: 8/32 [25%]; p = 0.36) or sarcoma (boys: 6/17 [35%] and girls: 4/12 [33%]; p = 1) (Table 14).

Table 13. Results of quantitative variables according to whether BAT was visualised on FDG PET/CT at baseline in the HL and sarcoma subgroups (study with 92 patients)

	NO FDG uptake by BAT Hodgkin lymphoma (n = 51) Median; mean; range	**POSITIVE FDG uptake by BAT** Hodgkin lymphoma (n = 12) Median; mean; range	**p (Mann–Whitney test)** Hodgkin lymphoma (n = 63)	**NO FDG uptake by BAT** Sarcoma (n = 19) Median; mean; range	**POSITIVE FDG uptake by BAT** Sarcoma (n = 10) Median; mean; range	**p (Mann–Whitney test)** Sarcoma (n = 29)
Age (years)	14; 12.58; 3–17	15; 14; 8–17	0.37	14; 12.53; 7–17	13; 12.9; 9–16	0.98
Outside temperature (C^{o}), mean	17; 18.23; 1–35	19.5; 17.33; 1–35	0.75	13; 14.84; -1 to 34	13; 11.9; 0–28	0.59
TMTV (cm^{3}) of the tumour lesions	268.66; 384.32; 1.44–1787.64	82.3; 166.58; 0–547.21	0.06	99.76; 180.19; 7–984.12	156.9; 263.89; 4.31–987.29	0.37

TLG (g) of the tumour lesions	1111.33; 1765.08; 4.07–8636.79	279.97; 760.24; 0–2356.22	0.09	425.86; 799.23; 30.27–3888.61	1033.41; 1352.87; 12.92–4539.97	0.24

Table 14. Prevalence of BAT visualisation on FDG PET/CT according to sex (study with 92 patients)

	POSITIVE FDG uptake by BAT (Whole group)	**p (Fisher's exact test)** (Whole group)	**POSITIVE FDG uptake by BAT** (Hodgkin lymphoma)	**p (Fisher's exact test)** (Hodgkin lymphoma)	**POSITIVE FDG uptake by BAT** (Sarcoma)	**p (Fisher's exact test)** (Sarcoma)
Sex	Boys: n =10 Girls: n =12	0.63	Boys: n = 4 Girls: n = 8	0.33	Boys: n = 6 Girls: n = 4	1

V. Discussion

V.1. Discussion of the pilot study on non-tumour-specific FDG uptake in children with Hodgkin lymphoma

The results of this pilot ancillary study were published in 2016 [25] in the *European Journal of Nuclear Medicine and Molecular Imaging*. This study has been cited in six articles [37, 44, 45, 46, 47, 48] and one letter to the Editor [49].

V.1.1. Prevalence of non-tumour-specific FDG uptakes

Non-tumour-specific FDG uptake by structures without tumour invasion is considered a potential pitfall during initial staging and during treatment. Diffuse and intense uptake on bPET was observed in at least one of the five evaluated areas without HL invasion in the majority of patients (77%). After 2 cycles of chemotherapy, on iPET, this ratio decreased (23%). Several studies addressed the frequency of this pattern of FDG uptake in patients with HL. The pilot study was referenced by Escudier et al. [45] who reported three cases of Kikuchi–Fujimoto disease, also known as histiocytic necrotising lymphadenitis, a rare cause of lymphadenopathy in children. Kikuchi–Fujimoto disease is a benign disease that mimics lymphoma. All three patients included in the study by Escudier were teenagers who presented with isolated lymphadenopathy or lymphadenopathy accompanied by fever, weakness, and weight loss. The hypermetabolic activity of the lymph node on FDG PET/CT led to the suspicion of lymphoma in all three patients; however, a non-specific FDG uptake was not observed in other organs. This pattern was noted in only 33% of patients with HL in our pilot study. The diagnosis of Kikuchi disease was made for all patients based on the findings of lymph node biopsy.

Brown adipose tissue

Gilsanz et al. [32] studied FDG uptake by BAT in 21 children with HL (median age = 14) and reported that the frequency of visible FDG uptake by BAT was 13% (3/21) and 86% (18/21) at baseline and during the follow-up period, respectively, when no evidence of disease was observed on PET/CT. BAT activation was observed in two (7%) and five (17%) patients on bPET and iPET, respectively, in the present study. All patients had achieved CR. A definite lower frequency of BAT visualisation on iPET, which was performed after administering only two cycles of chemotherapy, was observed in the present study compared with that reported in the study by Gilsanz et al. [32]. The duration of treatment was not specified in the study by Gilsanz et al. [32]; however, it is anticipated to be longer, considering the patients exhibited no evidence of disease. Nevertheless, the findings of the study by Gilsanz et al. [32], i.e., BAT visualisation with FDG exhibited an inverse correlation with the presence of active HL, are consistent with those of the present series. Active HL should be reduced at iPET. FDG uptake by BAT on bPET and iPET was not predictive of the persistence of CR in the present study, given that two patients with this pattern experienced early relapse.

Brendle et al. [37] who studied BAT in patients with lymphoma using FDG PET, reported that HL exhibited the highest frequency of BAT visualisation, with 21 and 15 of the 206 cases exhibiting low and high uptake, respectively. Lymphoma was considered active if vital manifestations with FDG uptake above the mean liver uptake were detected. No association between BAT and the metabolic activity of lymphoma was observed.

This discrepancy prompted further analysis of the context of BAT activation in a larger series of children and adolescents with HL. The “BAT on bPET” study is summarised in Chapter V.3. Discussion of the “BAT on bPET” studies.

Bone marrow

Salaun et al. [30] evaluated the significance of diffuse bone marrow FDG uptake in 106 patients with HL (median age = 31) who underwent FDG PET/CT imaging for initial staging. The iPET examination was not studied in their work. Comparison between the

results of this series and the bPET results of the present study revealed a difference in terms of the age range of the patients, i.e., adults constituted the majority of the participants in the study by Salaun et al. [30]. Bone marrow uptake was higher than liver uptake in 58% of patients in their study. In contrast, diffuse bone marrow hyperactivity in the iliac crests was observed in 37% of patients on bPET in the present study. The lower frequency observed in the present study (difference close to significance [p = 0.06 using Fisher's test]) could be attributed to the fact that we did not considered this phenomenon at the whole-body level, unlike in the study by Salaun et al. [30]. Furthermore, we used the criteria to exclude if the bone marrow was invaded by HL. In contrast, bone marrow invasion of HL, leading to a specific FDG uptake, was observed in 7% of patients in the study by Salaun et al. [30].

Spleen

Splenic uptake was higher than liver uptake in 25% of patients in the study by Salaun et al. [30]. In contrast, splenic uptake was higher than liver uptake in 45% of patients on bPET in the present study (p = 0.04). In addition to the younger age of the patients included in the present study, the higher frequency of intense spleen uptake observed in the present study can be attributed to more frequent diffuse HL involvement of the spleen that was missed.

Thymus

The evaluation of thymic uptake was hindered by the following issues:

- Data regarding the FDG uptake by non-pathologic thymus before the age of 18 years and the potential age dependence of the uptake of the thymus were incomplete [50]. Thus, differentiating diffuse non-tumour-specific activation from diffuse HL invasion is difficult.
- "Thymus rebound" increases the thymus FDG uptake after treatment; however, it may increase this uptake during the course of chemotherapy (iPET) in patients who achieved CR [28].

Patel et al. [51] reported a mean mediastinal SUV of 1.47 in 14 children and concluded that a mediastinal SUV of > 2.5 is suggestive of the onset of a malignant process. Notably, SUVmax, rather than SUVmean, was determined in subsequent studies, even when the term SUV was used in the results sections. Brink et al. [52] reported a mean SUVmax of 1.84 ± 0.68 in 11 children with malignant disease before chemotherapy (group Ia, mean age ± SD, 11.9 ± 3.7 year). Jerushalmi et al. [53] revealed a higher mean thymic SUVmax (3.8 ± 0.5) before treatment in 10 patients aged < 40 years. Gawande et al. [54] reported a mean SUVmax value of 2.00 ± 0.83 for the non-invaded thymus in seven paediatric patients with lymphoma before chemotherapy. In contrast, the mean SUVmax value was 2.89 ± 0.1 for rebound thymus in 33 children and 4.74 ± 0.61 in 34 children with recurrence. They concluded that SUVmax of the thymus is a sensitive factor for differentiating normal thymus or thymic rebound from mediastinal lymphoma, as predicted by a thymus SUVmax of ≥ 3.4.

Additional data of 22 children aged 3–10 years (mean age, 6.1 years; median age, 6 years; nine children aged 3–5 years) were acquired by Gawande et al. [54] to further evaluate their finding of age-independent thymic SUVmax. A mean thymic SUVmax of 1.8 ± 0.54 (median, 1.75; range, 0.8–2.9) was achieved in their study. The SUVmax was < 3 in the present study; therefore, it was also< 3.4 from the data of 19/30 patients whose thymus was considered to be HL-free on bPET in the present study. The SUVmax of the thymus was significantly lower on iPET, at < 1.7 in 22/30 patients considered as having thymus without HL invasion. The criteria for probable HL invasion requiring a focal uptake used in the present study indicates that no thymic rebound was observed in these patients immediately after two cycles of chemotherapy. Data regarding the frequency and intensity of thymic rebound on FDG PET after two chemotherapy cycles could not be retrieved; only post-treatment data were available.

Spinal cord

FDG uptake by the spinal cord in adults without cancer has been explored for over a decade [55]. The spinal cord FDG uptake in adult patients with cancer have also been

explored [56, 57]. For instance, Amin et al. conducted a study involving 101 patients, including 25 patients with lymphoma [57].

McCarville et al. conducted a study involving 128 children [58], including 58 patients with HL, and reported that the highest FDG SUVmax values were observed at the mid-cervical and lower thoracic levels. However, patients with spinal disease were excluded from their study. The median SUVmax at Th12 was > 1.5 in the groups comprising patients aged > 10 years. Taralli et al. [59] evaluated the FDG uptake of non-pathological spinal cord in 62 children with HL. The mean SUVmax values for C1–C7, Th1–Th6, and Th7–L1 were 1.90, 1.55, and 1.80, respectively. The median SUVmax value of patients with HL was higher than those the patients with NHL or other diseases. The FDG uptake in the lower thoracic region of the cord was higher than that in the upper part of the thoracic spinal cord in these studies involving patients with cancer. Therefore, the FDG uptake by the spinal cord at the Th12 level was quantified in the present study. The SUVmax value on bPET was 1.7 in the 30 children with HL, which is consistent with the findings of the study by Taralli et al. [59].

Kiamanesh et al. [46] also referenced the pilot study as one of the 13 studies involving a total of 24,125 patients included in their systematic review of the physiologic distribution of FDG in the spinal cord. The cumulative results confirmed that the FDG uptake was highest in the lower thoracic portion of spinal cord (Th11–Th12). They concluded that on 18F-FDG PET/CT imaging, focal hypermetabolism of the spinal cord at the level of lower thoracic and lower cervical vertebrae should be considered physiological until proven otherwise. Several explanations were presented as the cause of physiological 18F-FDG uptake variations in the spinal cord:

- Hypermetabolism of the cervical enlargement in spinal cord segments C6-C8 (correspond to the C3-T2 vertebral body levels) and the lumbar enlargement in spinal cord segments L4-S1 (correspond to the T9-T12 vertebral body levels), which are responsible for supplying the neuronal activity of the upper and lower limbs.
- White matter does not accumulate 18F-FDG in comparison with the gray matter. Therefore, it can be concluded that abundant amount of gray matter in the spinal cord

enlargements at the C4-C8 and L4-S1 vertebral levels, involving in neuronal transmission for upper and lower extremities, could be responsible for the relative hyperactivity.

- Sensory stimuli (e.g. tactile or thermal) from the extremities to the spinal cord can be the reason of regional hypermetabolism.
- Inadequate clearance of 18F-FDG from the Adamkiewicz artery (largest medullary segmental artery originated from aorta around the T9 to T11 thoracic vertebrae on the left side) is another explained mechanism.
- Technical limitations like partial volume effect are another proposed mechanism that may be a cause of underestimation of SUVmax in spinal segments except for cervical and lumbar enlargements.

V.1.2. Evolution of diffuse uptake with chemotherapy

To the best of our knowledge, no previous study has investigated the evolution of diffuse and intense FDG uptake in children with HL following chemotherapy. Vera et al. [60] conducted a study involving adult patients with lymphoma, including 17 patients with HL and 33 patients with NHL and reported the findings after a median of three cycles of chemotherapy.

Consistent with the findings of the present study, the average SUVmax increased in the liver (+33%) and decreased in the spleen (−8%). However, the absolute values of the average baseline SUVmax were far greater than those observed in the present series: 2.69 for the liver ($p < 0.001$; 1.7 in our series) and 2.58 for the spleen ($p < 0.01$; 1.8 in our series). This difference could be attributed to the differences between the ages of the patients as well as the greater proportion of patients with NHL in the study by Vera et al. [60]. Diffuse uptake exhibited a more marked reduction in the spleen after two cycles of chemotherapy in the present study, in addition to that observed in the thymus and bone marrow. A reduction in the number of cases wherein these organs appeared more active than the liver was also observed. Furthermore, a significant reduction in their

SUVmax was observed. Thus, this finding cannot be attributed solely to the rise in the intensity of FDG uptake by the liver, the reference organ for visual interpretation. The reduction in the diffuse uptake in these organs may be attributed to the response of HL to therapy. The criteria set forth by De Jong et al. [31] indicated that this evolution during chemotherapy suggests that the spleen and/or the other organs are diffusely invaded by HL. At least two other underlying mechanisms have been identified. The first underlying mechanism is the reduction in the non-specific stimulation of glucose metabolism of organs without invasion by HL, since HL responds to treatment. The baseline FDG SUVmax of these organs in healthy children has not been reported owing to the radiation exposure linked with FDG PET. The values observed on bPET may be normal and not enhanced. Thus, a reduction on iPET from this normal baseline value would indicate a decline in the glucose metabolism of the organs without invasion as a consequence of chemotherapy toxicity.

A major result of the present study is the significant increase in the liver uptake of children with HL after two cycles of chemotherapy. Vera et al. [60], who reported a significant increase in average liver SUVmax in adults with HL or NHL who received treatment, could provide “no explanation” for this phenomenon.

The liver is used as a reference organ for interpreting the response exhibited by patients with HL after receiving two cycles of chemotherapy according to the Deauville criteria [61, 62] or at the end of first-line treatment [63]. Thus, a rise in the liver uptake from its baseline value may lead to an underestimation of the actual response of the HL lesions on iPET/CT. Consistent with this hypothesis, a previous study confirmed that the difference between the SUVmax on bPET and iPET was a better criterion than the visual Deauville criteria for identifying adult patients with large B cell lymphoma [64]. The study by Marko et al. [47], which evaluated the diagnostic and therapeutic management of patients with malignant uveal melanoma, mentioned our pilot study in connection with the evaluation of reaction to chemotherapy and radiotherapy and the differentiation of benign and malignant lesions.

V.1.3. Ability of diffuse FDG uptake to predict refractory or relapsing Hodgkin lymphoma

A lack of increase in the liver SUVmax of bPET and iPET was identified as a predictor of refractory HL necessitating further treatment at the end of scheduled initial therapy to achieve CR. The predictive values of this criterion were at least as good as those of the criteria based on the visual scoring of the FDG uptake by the target HL lesions (EuroNet-PHL-C1 or Deauville criteria). However, the decisions made after two cycles of OEPA for the management of the patients were based on morphologic and metabolic response. Thus, the management was adjusted when the EuroNet-PHL-C1 predicting responses were not met. The results of the metabolic approach were considered false-positive for predicting refractory HL if the patient responded to the initial treatment. True-positive values may have been achieved if refractory HL would have been observed without this adjustment of the management.

An increase of > 5% in the SUVmax of the spinal cord at Th12 after two cycles of chemotherapy was another criterion for predicting an unfavourable patient outcome.

All four patients who satisfied the two criteria exhibited an unfavourable outcome (initially refractory HL or relapse within 12 months). A significant difference was observed between this group of patients and those who matched one or no criteria in terms of RFS. However, no significant value for predicting the patient outcome could be derived from the EuroNet-PHL-C1 or Deauville criteria in this study. A possible explanation for the observed phenomena can be related to the therapy. Increase of FDG uptake by the liver on iPET after 2 cycles of chemotherapy would indicate the increase of the glucose metabolism of liver cells, to be able to handle the consequence of chemotherapy toxicity. The adequate metabolic response for toxic agents can be missing in case of lack of such an increase in FDG uptake by the liver. This can reflect a general immunological or metabolic constitutional weakness that can be connected even to the inadequate elimination of the cancer cells from the system, becoming even a possible cause for refractory HL.

Ibrahim et al. [48] compared the performance of SUVmax reduction (ΔSUVmax%) with that of Deauville score (DS) by assessing the response to chemotherapy in paediatric patients with HL who underwent ^{18}F-FDG PET/CT imaging. Fifty-two patients with the diagnosis of HL confirmed through biopsy (age 8–16 years) with baseline, interim (after the second or third round of chemotherapy), and post-therapy (upon completion of first-line chemotherapy) ^{18}F-FDG PET/CT images available were enrolled. The interim and post-therapy DS and ΔSUVmax% were compared as response predictors. This comparison revealed that DS can predict chemotherapy response better than ΔSUVmax% in paediatric patients with HL.

Isik et al. [44] cited our approach in their study comparing different methods of FDG PET/CT interpretation for predicting paediatric HL outcome; however, only the "classical" approach based on FDG uptake by HL lesions was evaluated. The baseline, interim, and post-treatment PET images of 72 children were interpreted according to the revised International Harmonization Project criteria (IHP) and Deauville criteria. The Deauville criteria for the interim FDG PET/CT, i.e., a score of 3 indicates risk of relapse, predicted relapse within 3 years with Se, Sp, NPV, and PPV of 80%, 64%, 97%, and 17%, respectively. A "conservative" interpretation considering a DS of 3 as non-indicative of relapse achieved Se, Sp, NPV, and PPV of 29%, 78%, 89%, and 17%, respectively. A direct comparison with the findings of the "conservative" Deauville criteria reported by the present study can only be indicative as only the performance of predicting relapse within one year of completing CR was considered. The Se, Sp, NPV, and PPV were 17%, 83%, 83%, and 20%, respectively. The findings of both studies were concordant. The approach used in the present study suggests that an increase of > +5% in the spinal cord uptake at Th12 on bPET and iPET was indicative of a higher risk of relapse. This cutoff value achieved Se, Sp, NPV, and PPV of 83%, 71%, 94%, and 42%, respectively, for predicting relapse within 1 year. Isik et al. [44] concluded that all methods based on FDG uptake in the HL lesions demonstrated high NPV but substantially low PPV. The Deauville criteria exhibited a superior ability to predict HL outcomes in paediatric patients using interim FDG PET/CT data. However, quantitative evaluation and visual evaluation by IHP can be used reliably only at the end of the

treatment. This result reinforces the decision to consider the Deauville criteria as the comparator to the proposed approach to derive a predictive value from interim FDG PET/CT.

V.1.4. Limitations of the pilot study

The main limitations of the pilot study include its retrospective nature and the limited number of patients with resistant disease (n = 5) and recurrence within 12 months (n = 6) or during the overall follow-up period (n = 9). Furthermore, recruiting a large number of children with HL is difficult and the current therapy is very effective (only a low number of recurrences being reported during the follow-up period).

A consequence of the retrospective nature of this study is that the delay between FDG injection and image acquisition was not strictly controlled. Only relative variations of SUVmax on bPET and iPET were effective in predicting resistance or recurrence of HL. Therefore, the delay between FDG injection and image acquisition comparing bPET and iPET in each patient being close to zero was considered important. This requirement was satisfied in the majority of cases; however, the delay was > 30 min in five patients, resulting in an increased uncertainty in the paired determination of SUVmax.

A consequence of the limited number of patients and the difference in imaging timing for some patients is that the cutoff values determined for the two elements of the RRI proposed using the ROC analysis has an uncertainty. In particular, the +5% cutoff value for the SUVmax of the spinal cord at Th12 may not differ significantly from that for 0%. Few values for the repeatability coefficient of SUVmax determination published in a different neoplasia are > 5% [65]. Therefore, a “grey zone” between at least 0 and +10% for this criterion must be considered from the preliminary data.

V.2. Discussion of the validation study on non-tumour-specific FDG uptake in children with Hodgkin lymphoma

Similarly with the pilot study but in a larger series of children with HL, we evaluated the frequency and intensity of visually diffuse FDG uptake by BAT and by the four selected organs without tumour invasion, at bPET and on iPET. Results of the pilot study related to the prevalence of FDG uptake by sites without tumour invasion in paediatric patients with HL were confirmed by the validation study.

V.2.1. Comparison with the results from the pilot study

Tables 3, 7 and 8 (validation study) were compared with Tables 2, 5 and 6 (pilot study). The validation study confirmed the following results of the pilot study involving 30 patients in a completely different cohort of 112 patients:

- The median **age** was similar (ca. 14 years), and similar to that in the published series.

- The **male-to-female ratio** (0.7 vs 1.0, p = 0.5) and the non-CR:CR ratio on iPET according to the "conservative" interpretation of the Deauville score (0.38 vs. 0.20, p = 0.2) did not exhibit significant differences.

- Some increase in the proportion of children with **BAT** activation on iPET after two cycles of treatment was observed compared with that on bPET; however, the difference did not reach the significance level in a three-fold larger cohort.

- About **overall non tumour invaded sites**, FDG uptake visually greater than that of the liver was observed in at least one site without invasion in a large proportion of

patients (72% and 77% in the validation and pilot studies, respectively). However, it declined dramatically after two cycles of treatment to 27% (validation study) and 23% (pilot study), respectively.

- In the case of **bone marrow and spleen**, a FDG uptake visually greater than that of the liver was observed in the bone marrow and spleen without invasion. The prevalence was significantly higher on bPET (approximately 40% in both studies). This uptake declined after two cycles of treatment according to the visual and quantified evaluations of FDG uptake (Figure 7).

Salaun et al. [30] evaluated 106 patients (median age = 31) with HL on bPET to evaluate diffuse bone marrow FDG uptake. The bone marrow FDG uptake was higher than the liver uptake in 58% of patients. In contrast, bone marrow FDG uptake was higher than the liver uptake in 44% of patients in the present study, and in 37% of patients in the pilot study. The lower frequency observed in our studies (in case of the validation study difference close to significance $p = 0.07$ using Fisher's test) could be attributed to this phenomenon not being considered at a whole-body level but only in the iliac crest, and we used criterion to exclude the cases where bone marrow was invaded by HL. Zwarthoed et al. [66] evaluated the pre-treatment FDG PET/CT images of 180 adult patients with HL and revealed focal lesions in the bone marrow (focal) of 38 (21%) patients, pure strong (> liver) diffuse uptake (diffuse) in 53 (29%) patients, and faint or absent (≤ liver) bone marrow uptake (negative) in 89 (48%) patients. The frequency of uptake greater than that of the liver among diffuse uptake was 37% (53/142) compared with 44% in the present study ($p = 0.3$). Bone marrow biopsy was positive for focal and diffuse PET lesions in 6/38 (16%) and 1/53 (2%) patients, respectively. Bone marrow biopsy was negative for PET bone marrow results in 5/89 (6%) patients. The 3-year PFS of patients exhibiting a pure diffuse PET bone marrow pattern was identical to that of patients without any ^{18}F-FDG uptake (83% and 82%, respectively, $p = 0.92$). In contrast, the 3-year PFS of patients with focal PET bone marrow lesions was significantly inferior to that of patients with diffuse and negative PET (67% and 83%, respectively, $p = 0.03$). This study, which was published 2 years

after our pilot study, confirms the validity of the criterion used in the pilot and validation studies that considered nodal uptake in bone marrow as evocative of HL invasion.

The splenic uptake on bPET was higher than the liver uptake in 25% of patients in the study conducted by Salaun et al. [30]. In contrast, the splenic uptake on bPET was higher than the liver uptake in 44% of patients in the validation study ($p = 0.02$) and in 45% of patients in the pilot study ($p = 0.04$). In addition to the younger age of the patients included in the present study, the higher frequency of intense spleen uptake in the present series may be attributed to diffuse HL involvement of the spleen being missed more frequently.

Salaun et al. [30] reported that diffuse spleen uptake could reflect lymphoma infiltration. Moreover, it can reflect activation and proliferation of macrophages as observed following the administration of G-CSF or granulocyte-macrophage colony-stimulating factor injection [67]. This activation may be attributed to the inflammatory context of HL.

- A significant increase in the median SUVmax of the **liver** on bPET and iPET was observed in 85% of the cases in the validation study. Analysis with visual interpretation is not possible as the liver is used as the reference organ for predicting high FDG uptake at sites without invasion. The findings observed in the children included in our study are consistent with the those of the study by Chiaravalloti et al. [68] involving 68 adults with HL; the liver SUVmax on iPET (3.13 ± 0.67) was higher than those on bPET (2.82 ± 0.64; $p < 0.0001$) and PET after six cycles of therapy (2.96 ± 0.52; $p = 0.01$). Comparison between the SUVmax of the mediastinum on bPET, iPET, and PET after six cycles of therapy revealed no significant differences ($p > 0.05$). The findings of the present study confirms that the following conclusion drawn for adults by previous studies is applicable to the paediatric population: liver FDG uptake varies across patients with HL during the treatment and the disease course; thus, it should be interpreted with caution when used to define the response to therapy of HL on iPET.

- The variation between the FDG uptake by the **spinal cord** at Th12 on bPET and iPET were paradoxical, but similar in both studies: visual interpretation revealed a significant reduction on iPET, which is in contrast with the non-significant increase in the actual SUVmax observed on bPET and iPET. This finding can be attributed to the significant increase in liver SUVmax on iPET: visual comparison with the uptake of the liver, which increased in 85% of cases, will lead to the incorrect conclusion that the number of cases with hypermetabolism of this organ decreased if the uptake of an organ remains steady (or increases slightly). The postulated (but not actual) constancy of the liver SUVmax to its bPET value was simulated and determined the number of cases with FDG uptake on iPET which would be visually considered as greater than the liver bPET uptake were determined to confirm this hypothesis. The proportion of cases of hypermetabolic spinal cord at Th12 increased to 43% (43/99) from 17% (17/99). The McNemar test revealed a near significant increase in the proportion ($p = 0.06$) compared with that of bPET in 31/99 (31%) patients (instead of a significant decrease when the iPET liver value was the reference).

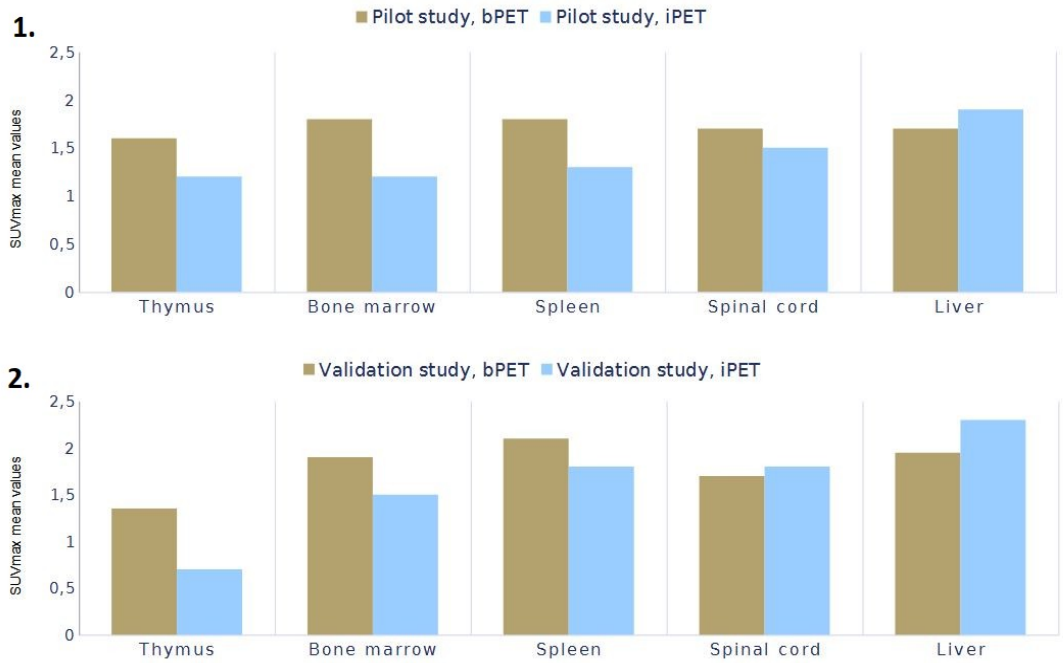

Figure 7: Comparison of FDG uptake variations of organs without tumour invasion between bPET and iPET. FDG uptake presented in SUVmax mean value, at baseline (bPET) examinations and after two cycles of treatment (iPET). **1.** Results of the quantitative analysis in the pilot study **2.** Results of the quantitative analysis in the validation study.

V.2.2. Correlation between the non-tumour-specific FDG uptakes and the metabolic activity of the Hodgkin lymphoma lesions

The correlation between the extent of HL lesions and the characteristics of glucose metabolism and glucose uptake at the sites without tumour invasion were not explored in our pilot study.

The validation study evaluated this correlation. The maximum SUVmax of all HL lesions were derived from a very limited volume of HL tissue that was likely to be the most metabolically active. The TMTV and the TLG, which integrate all visible HL tumours, were also determined. Cottereau et al. [42] reported that a high TMTV on baseline FDG PET/CT exhibited a significant association with poorer prognosis. TLG was also significantly predictive of PFS and OS in these patients, but less so than TMTV. A pilot study conducted by Tatci et al. involving 28 paediatric patients with HL [69] revealed that TMTV and several parameters derived from SUV were higher in patients with stage III–IV disease, bulky tumour, and involvement of ≥3 lymph node groups or the spleen. The TMTV in FDG bPET was validated as a major parameter for predicting inadequate response of HL in ERA performed after two cycles of induction chemotherapy. Rogasch et al. [70] conducted a study involving 50 paediatric patients with HL and revealed inadequate response in 28 children. TMTV best predicted an inadequate response among all PET parameters. The area under the ROC curve of MTV was 0.84 and 0.86 for stage I/II and stage III/IV HL, respectively. The Se, Sp, NPV, and PPV for predicting an inadequate response were 94%, 64%, 88%, and 79%, respectively, for stage I/II HL. The Se, Sp, NPV, and PPV for predicting an inadequate response were 75%, 91%, 77%, and 90%, respectively, for stage III/IV HL. The diagnostic performance of TLG was slightly worse than that of TMTV. The observation that the FDG uptake intensity in HL lesions (SUV approach) is less relevant than the anatomical distribution or volumetric extent of the lesions may be attributed to the multifocal/systemic nature of HL, in contrast to other childhood malignancies such as Ewing's sarcoma or osteosarcoma (wherein the pre-treatment maxSUVmax is a prognostic factor).

The Deauville score was also determined on iPET. Isik et al. [44] revealed that the Deauville criteria are superior to other methods in terms of predicting the outcomes in paediatric patients with HL using iPET data. The "sensitive" determination of the Deauville score on iPET yielded a statistically significant prediction of the 3-year PFS with Se, Sp, and NPV of 80%, 63%, and 97%, respectively.

A significant difference was observed between the median values of maxSUVmax, TMTV, and TLG on bPET according to the 5-grade Deauville score. ROC analysis revealed that a prevision of an inadequate response to therapy on iPET (based on the Deauville score) at an individual level could be possible from those variables on bPET (Table 10). The SUVmax of the spinal cord at Th12 can also yield a predictive value for a high Deauville score, as indicated by the findings of the pilot study. Nevertheless, the interpretation of iPET is necessary for determining the Deauville score.

The mechanism underlying this high FDG uptake by the spleen and the bone marrow at baseline observed frequently (approximately 40%) showed no evidence of HL invasion on FDG PET/CT. Furthermore, the decrease observed after two cycles of treatment, which could not be precisely elucidated, is evocative of a paraneoplastic influence of HL at the sites without tumour invasion. The close correlation of the SUVmax of the spleen and the bone marrow of the iliac crest with the variables characterising the extent and activity of HL on bPET confirm this hypothesis (Table 9). HL is characterised by the presence of multinucleated giant cells (Hodgkin/Reed–Sternberg cells; H/RS) or large mononuclear cells (e.g., lymphocytic and histiocytic cells), accounting for approximately 1% of the cells, in a background of inflammatory cells such as small lymphocytes, histiocytes, neutrophils, eosinophils, plasma cells, and fibroblasts. In addition, the close correlation of the SUVmax of the organs without invasion on bPET, including the liver and spinal cord, indicates a common cause stimulating the uptake of FDG by different organs.

Two sites responded to the therapy in a different way compared to HL tissue, spleen and bone marrow showing a decrease in FDG uptake.

The liver uptake on iPET exhibited an increase more frequently than that on bPET. This increase may jeopardise its value as a reference organ for the visual assessment of the Deauville criteria. Notably, the FDG uptake of some HL tissue that progressed may appear lesser than that of the liver, despite being more intense visually than that of the liver at baseline.

The response of the spinal cord at Th12 was somewhat intermediate between that of the liver (overall increase) and spleen and that of the bone marrow and the HL tissue (overall decrease), confirming the result of the pilot study without a clear rational for this repeated observation.

V.2.3. Aspects that could not be addressed in the validation study

The last objective of the pilot study was to determine the potential predictive value of the FDG uptake by sites without tumour invasion on bPET and iPET on the subsequent PFS at the end of the initial treatment. An encouraging result was achieved with a combination of the results of SUVmax of the liver and spinal cord at Th12. The proportion of relapse is low among children; thus, this result was based on a small number of events. This limitation of our pilot study, which was also criticised in a Letter to the Editor [49], has been acknowledged by the research team [71]. However, the results of long lasting follow-up (5 years were scheduled) of the patients of the present series could not be collected owing to logistical shortage caused by the COVID-19 pandemic.

Therefore, the end point of the validation study was the response to two cycles of treatment evaluated using DS. The variables that quantify the FDG uptake by the HL tissue exhibited a considerable advantage as DS is also based on the observation of the FDG uptake by the HL tissue. Nevertheless, as observed in the pilot study, the SUVmax of the spinal cord at Th12 added information to the TLG to delineate a CR on iPET according to the Deauville criteria.

V.3. Discussion of the “BAT on bPET” studies

In the pilot study, the FDG uptake by structures without tumour invasion as a potential determinant for predicting HL activity and prognosis was evaluated. Activation of BAT was observed on FDG PET/CT images at the time of diagnosis in two patients only

(2/30; 7%), which is consistent with the prevalence of 10% (3/31) reported by Gilsanz et al. [32]. The validation study yielded a prevalence slightly higher than that observed in the pilot study (13/112; 12%). The findings of these studies led to the evaluation of the prevalence of BAT activity and its influencing factors in a larger paediatric cohort. The results of our studies focusing on BAT activation has been accepted for publication [43, 72].

The prevalence of positive FDG uptake by BAT on PET/CT was 19% (25/135) and 23.9% (22/92) in the first (comprising only patients with HL) and secound (comprising patients with HL and sarcoma) series, respectively. These frequencies do not differ from those reported previously in paediatric patients by Yeung et al. [34] (4/26; 15% vs. 16/837; 1.9% in the adult population), Cohade et al. [35] (10/42; 23.8%), Kim et al. [73] (3/22; 13.6%), and Gilsanz et al. [32] on FDG PET/CT at diagnosis (3/31; 10%). However, Drubach et al. [38] reported a high prevalence of active BAT (76/172; 44.2%), which was significantly greater than that observed in the present study (study involving 135 patients [$p << 0.001$] and study with 92 patients [$p = 0.0013$]). Their cohort comprised 172 paediatric patients with various types of cancer, including 27% of patients with HL who underwent FDG PET/CT at the time of diagnosis or as a surveillance test. This discrepancy may be attributed to the inclusion of treated patients in the study by Drubach et al. [38]. The prevalence of active BAT in patients with HL who had received treatment was even higher in the study conducted by Gilsanz et al. [32], at 86%. This finding reinforces the hypothesis that the inclusion of patients who had received treatment in the series enhances the prevalence of BAT visualisation, rather than including only patients with pre-therapeutic FDG PET/CT images acquired at the time of diagnosis, as in the present study.

To the best of our knowledge, this study including 135 paediatric patients is the first to analyse FDG uptake by BAT in > 100 children with a homogeneous indication, HL, and

a homogeneous stage of evolution, at diagnosis, excluding the interference of the therapy.

The findings of the present study confirm that the determinants of FDG uptake by BAT differed between paediatric and adult patients. In contrast with the findings of various studies involving adult patients with HL [34, 35, 36, 37, 73, 74], the prevalence of BAT visualised on FDG PET/CT in the present study did not differ significantly between boys and girls. Furthermore, no decrease with age was observed, which is consistent with the findings of the study by Drubach et al. [38]. Thus, BAT activation increases through childhood and into adolescence, peaking around the age of 13 years in boys and girls. However, Drubach et al. [38] determined the prevalence of BAT, appearing as a hot site on FDG PET, only visually. However, they also quantified BAT activity by drawing a standard-sized region of interest in the areas with the highest FDG uptake on a coronal section within the cervical-supraclavicular BAT on CT and divided it by the FDG uptake of a region of interest in a midsection of the liver, the BAT/liver index. The value of this index peaked at 13 years. Gilsanz et al. [75] reported that the appearance and the amount of brown fat increase during puberty. The PET/CT images of patients aged 4–19.9 years who had been previously treated for paediatric malignancy but were disease-free at the time of examination were examined in their study involving 73 patients with heterogeneous diseases (patients with lymphoma and sarcoma as well). They concluded that rapid increase in brown fat observed during puberty may be attributed to the metabolic and hormonal events associated with the attainment of sexual maturity. However, similar results were not observed in the present study involving 135 patients with HL, as no significant difference in BAT visualisation according to the age class was observed (Table 11). Notably, logistic regression analysis suggested a correlation with the age of the patients in the study involving 92 patients (HL and sarcoma; age range 3–17 years). A significant correlation between the age of the patients and BAT activation in the HL subgroup ($p = 0.04$) and a near significant correlation in the whole group ($p = 0.06$) were observed.

BAT is stimulated by several factors, including exposure to cold. BAT activation was reported in adult outdoor workers in northern Finland in a previous study [76]. Histochemically, some multilocular adipose tissue, mostly around the neck arteries with increased enzyme activities of aerobic energy metabolism in the adipose tissue, have been observed in some outdoor workers. FDG PET/CT performed to detect BAT activation revealed no significant influence of outside temperature in the present study. The non-significance of this determinant in adults was initially reported by Cohade et al. [35] who noted that the incidence in the January–March period was not significantly higher in patients aged ≤18 years (35.7% vs. 17.9%, p = 0.26). Tendency of BAT activation for a colder outside temperature was observed in our study involving 135 patients (Table 11). Gilsanz et al. [32] also noted a tendency toward frequent BAT visualisation during the winter months (November, December, and January) compared with that during the rest of the year, which was not significant at the time of HL diagnosis (22% vs. 4.5%, p = 0.13). Yu Li et al. [77] could observe that local hyperthermia induce thermogenesis in human, possibly by the activation of beige adipocytes, without elevating core body temperature or catecholamine signaling (thermal source of 41°C ± 0.5°C was applied locally to the supraclavicular fat depots of each subject for 20 min) and on the other hand, Seki et al. [78] demonstrated that cold-induced BAT activation substantially decreases the blood glucose levels and impedes glycolysis-based metabolism in cancer cells in mice. Seki et al. studied also BAT activation by exposure to mild cold in healthy individuals and a patient with Hodgkin lymphoma. They performed 18F-FDG PET/CT examinations in healthy volunteers (n=6) under thermoneutral (28 °C) and cold exposure (16 °C; 2-6 hours daily for 14 days) conditions. The patient with HL was exposed to mild cold (22 °C for 7 days). The PET/CT images confirmed activation of BAT after cold exposure, and in the case of the patient with HL it was demonstrated that mild cold conditions markedly reduced glucose uptake in the tumour tissue. Quantification of FDG uptake in the BAT showed increase and in the HL lesion showed decrease, respectively, after the cold exposure. They concluded that mild cold exposure activates BAT with mitigated glucose uptake in the tumour tissue. They explained the mechanisms underlying the tumour suppression

by cold exposure with the change in the metabolism of BAT and the cancer cell. Under the thermoneutral conditions (28-30°C), cancer cells mainly acquire energy through glycolysis (Warburg effect), however the adipose tissue (both white adipose tissue (WAT) and BAT) remains metabolically dormant without significant glucose uptake and thermogenic activity. High rates of tumour cell proliferation is supported by glycolysis-generated ATP molecules and other metabolites. But under cold exposure, both WAT and BAT undergo a browning process that increases glucose uptake and thermogenesis. Owing to the elevated glucose uptake in activated BAT and WAT, glucose uptake in tumours is significantly reduced. And owing to the limited glycolysis in cancer cell, local acidosis and tumour hypoxia are reduced. The higher frequency of BAT activation observed in our studies in patients with HL exhibiting lower TMTV and TLG values may be attributed to this finding. Interestingly, 45% of the PET/CT images acquired in autumn exhibited signs of BAT activation in our study involving 92 patients; signs of BAT activation were observed in 38% of the total number of PET/CT images acquired in autumn. However, the logistic regression model revealed a significant inverse relation between the winter season and the reference autumn season for FDG uptake by BAT in the whole group ($p = 0.02$). Only a trend towards significancy was observed in the subgroup of patients with HL ($p = 0.08$), which may be attributed to the smaller sample size. The subgroup of patients with sarcoma did not exhibit a similar relation.

Thus, it was concluded that the temperature in the injection room of the Nuclear Medicine Department. may be another determinant of BAT activation. Zukotynski et al. [79] conducted a study involving 103 patients. The patients were warmed to 24°C prior to the FDG PET/CT examination. The number of patients exhibiting FDG uptake by BAT in this group was compared with that of a control group comprising 99 patients who underwent FDG PET/CT examination when the injection room temperature was 21°C. Uptake by BAT was observed in 9% of PET/CT images acquired after patient warming and 27% of PET/CT images acquired without warming ($p << 0.01$). Maintaining the room temperature at 24°C for 30 min before and 1 h after the

intravenous administration of the tracer significantly decreased FDG uptake by BAT in children. This effect was greatest in winter and summer. In our present study, the temperature in the injection room of the PET/CT centres was not recorded; thus, its effect on BAT visualisation could not be controlled.

The FDG SUVmax of three organs were compared to correlate the FDG uptake by BAT with the non-specific metabolic activation of other organs without tumour invasion in relation with the presence of HL in the study involving 135 patients, according to whether BAT was visualised as hot spots. No significant difference were observed in terms of the SUVmax values for the liver, spinal cord at Th12, and bone marrow at the iliac crest after excluding the sites with possible invasion by HL (Table 11). To the best of our knowledge, no previous study has reported this finding.

Gilsanz et al. [32] reported a lower prevalence of BAT activation in patients referred to undergo FDG PET/CT at the time of HL diagnosis compared with that observed at time points showing no evidence of disease after treatment. Gilsanz et al. concluded that this observation provides new and compelling evidence for an inverse association between the activation of BAT and the presence of viable tumour in children with lymphoma, which observation is in accordance with the results of Seki et al. [78]. However, Brendle et al. [37] reported that there is no association between BAT and the metabolic activity of lymphoma in their cohort of 235 adult patients.

The present study evaluated the potential relation between BAT and HL by characterising the metabolic activity and the volume of the lesions visible on FDG PET/CT images likely to correspond to HL itself, according to whether BAT uptake could be visualised.

The TMTV and TLG values were determined by integrating all visible HL tumours as a complement to the maximum SUVmax of all HL lesions, derived from a very limited volume of HL tissue likely to be the most metabolically active. (Figure 8)

Cottereau et al. [42] reported that TLG was significantly predictive of PFS and OS in those patients, but less so than TMTV, in 108 adult patients with peripheral T-cell

lymphoma. Tatci et al. [69] reported that TMTV and several parameters derived from SUV were higher in patients with stage III–IV disease, bulky tumour, and involvement of ≥3 lymph node groups or the spleen in their pilot study involving with 28 cases of paediatric HL. The TMTV value observed in the pre-therapeutic FDG PET/CT images were validated as a major parameter for predicting inadequate response of HL in ERA performed after two cycles of induction chemotherapy. Rogasch et al. [69], who reported an inadequate response in 28/50 children, revealed that TMTV was the best predictor for an inadequate response. The diagnostic performance of TLG was slightly poorer than that of TMTV.

The "BAT on bPET" study involving 135 patients with HL revealed a slightly significant association between the lower median values of TMTV and TLG and BAT visualisation. The subgroup of patients with HL also exhibited this near significant association regarding the TMTV and TLG values in the study involving 92 patients; however, this result could not be confirmed when combinations of several quantitative variables were tested simultaneously in logistic regression.

No statistically significant difference was observed in the subgroup of patients with sarcoma; however, a difference in the association between BAT activation and the TMTV and TLG values was found compared with that observed in the subgroup of patients with HL. BAT activation was associated with lower TMTV and TLG median or mean values in the HL subgroup, whereas BAT activation was associated with higher TMTV and TLG median or mean values in the sarcoma subgroup compared with that observed in cases without BAT activation from the corresponding subgroup; unfortunately, statistical calculations could not confirm this point. No statistically significant correlation between the TMTV and TLG values of the sarcoma mass and FDG uptake by BAT on PET/CT was observed in the present study, which results may not be sufficiently powered due to the low number of sarcoma patients. This hypothesis should be evaluated in a larger cohort of patients with sarcoma. The overall results of the present study suggest that there may be a difference between more focalised cancer tissues, such as sarcoma types, and malignancies with more dispersed tumour cells, such as Hodgkin lymphoma, in terms of BAT activation.

Pheochromocytomas and paragangliomas constitute a particular condition in relation with BAT activity, given that BAT activation, proliferation, and differentiation are mediated by norepinephrine-induced β-adrenoceptor stimulation. A previous study revealed that BAT visualisation on FDG PET/CT was associated with decreased OS and higher plasma levels of norepinephrine in patients with neuroendocrine tumours [80]. Chu et al. [81] reported that BAT metabolic volume, assessed using routine FDG PET/CT, is a predictor of tumour recurrence or mortality in adult patients with non-neuroendocrine cancer. In contrast, the findings of the present study and those of the study by Gilsanz et al. [32] suggest that BAT visualisation could be associated with non-detectable or lower HL tumour mass in paediatric patients with lymphoma.

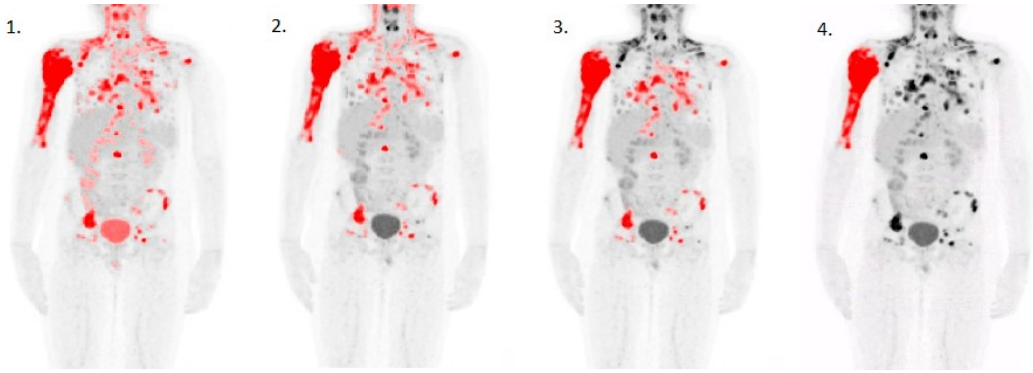

Figure 8: TMTV determination with threshold-based PET image segmentation. Delineation with a threshold of SUV >2.5 and minimum volume of 500 mm3 on PET MIP images of a patient with osteosarcoma.

1. Determination of all lesions with SUV>2.5 and minimum volume of 500 mm3 on the PET MIP image (red markings). Increased FDG uptake presented in the primary tumour (right humerus) and metastases (pulmonary, bone and lymph node). Organs with physiological FDG uptakes or FDG accumulations (i.e. in the tonsils, laryngeal muscles, urinary tract, gastrointestinal tract) also visualised. The investigator has to select manually if the segmented lesions showing SUV>2.5 belong to the tumour tissue **2.** PET image showing high FDG uptake of the primary tumour, metastases and BAT (red markings). Other, physiological FDG uptakes/accumulations are already excluded manually from the visualisation. **3.** PET image with increased FDG uptake of the primary tumour with metastases (red markings). FDG uptake of BAT excluded manually. **4.** PET image with high FDG uptake of the primary tumour tissue (red marking) [43].

VI. Conclusions

Our pilot study and validation study aimed to evaluate the frequency and intensity of visually diffuse FDG uptake by BAT and four selected organs without tumour invasion on baseline and interim PET/CT images of children with Hodgkin lymphoma.

The findings of the pilot and validation studies indicated that FDG uptake visually greater than that of the liver in at least one site without tumour invasion is observed in a large proportion of patients (72% and 77% in the validation and pilot studies, respectively) that decreases dramatically after two cycles of treatment (27% and 23% in the validation and pilot studies, respectively).

A significant increase in the FDG uptake of the liver between bPET and iPET confirms the conclusion of other studies in adults. Thus, the observation that liver FDG uptake varies across patients with HL during the course of treatment and disease should be considered carefully while defining the response to therapy as a reference organ in the interim PET in HL.

The prevalence of FDG uptake visually greater than that of the liver being observed in the bone marrow and spleen without tumour invasion was significantly higher on bPET (approximately 40% in both studies). However, visual and quantified evaluations of FDG uptake revealed that this prevalence decreased after completing two cycles of treatment. The presence of homogenous lymphoma infiltration (none of the cases had histologically-confirmed results) could not be excluded in the case of the diffuse spleen uptake. Notably, it reflects the activation and proliferation of macrophages that activation is probably in the inflammatory context of HL. The high FDG uptake at baseline by the spleen and the bone marrow not characteristic to HL invasion on FDG PET/CT images that decreased after two cycles of treatment is evocative of a paraneoplastic influence of HL on the sites without tumour invasion. This hypothesis is confirmed by the close correlation of the SUVmax values of the spleen and the bone

marrow of the iliac crest with the variables characterising the extent and activity of HL on bPET (TMTV and TLG).

The variation in the uptake of FDG uptake by the spinal cord at Th12 between bPET and iPET indicates a significant reduction on iPET at visual interpretation. This is in contrast with the non-significant increase observed in the actual FDG uptake between bPET and iPET. Visual comparison of the uptake of the liver that increased (in 85% of cases) can lead to the incorrect conclusion that the number of cases with hypermetabolism of the spinal cord decreased.

An increase in the proportion of children with BAT activation on iPET was observed after two cycles of treatment compared with that on bPET; however, this difference did not reach the significance level in the three-fold larger cohort. The findings of the additional "BAT on bPET" studies confirmed the findings of previously published studies, derived from heterogeneous conditions, that the epidemiology of BAT activation varies between paediatric patients and adults. No significant differences were observed between boys and girls in the present study in terms of BAT visualisation. BAT activation was not linked with the metabolic activation of the liver, bone marrow, or spinal cord, which may be observed in paediatric patients owing to the presence of the HL. Nevertheless, the findings of the present study suggest that BAT visualisation could be associated with a lower HL tumour mass. These studies also emphasised the importance of influencing factors, such as the temperature in injection rooms in PET/CT laboratories, in terms of the connection between the season or outside temperature and BAT activation. Furthermore, the findings of the present studies also indicated that a correlation may be observed between BAT visualisation and age in paediatric patients with HL.

Other objective was to evaluate the relation between FDG uptake by the four organs without tumour invasion (SUVmax) and that by the HL lesions (maxSUVmax, TMTV, and TLG) prior to treatment on bPET.

A significant positive correlation between the maxSUVmax of HL and the SUVmax of the sites without tumour invasion was observed before treatment. Strong correlations

were also observed between the FDG uptake (SUVmax) of the four sites without tumour invasion on bPET and iPET. The greatest correlation coefficients were observed between the bone marrow and spleen on bPET and iPET, and between the liver and spleen on bPET that reduced on iPET. Prevision at an individual level of an inadequate response to therapy could be possible either on iPET (based on DS) or using variables on bPET such as HL maxSUVmax, TMTV, and TLG.

The last objective was to evaluate the correlation of the FDG uptake by BAT and the four organs without tumour invasion with the remaining metabolic activity of HL after treatment. Two unfavourable criteria, namely, lack of increase in the FDG uptake of the liver and increase of >5% in the FDG uptake of the spinal cord at Th12, were derived from the evolution of diffuse uptake by organs between the FDG PET/CT acquisitions performed at the time of diagnosis (baseline) and after two cycles of treatment (interim) in the pilot study. Patients who satisfied these criteria seemed to be at high risk of developing refractory Hodgkin lymphoma and/or early relapse. The results of the validation study indicated that patients whose iPET is likely to correspond to an inadequate response can be delineated based on the FDG uptake by the lymphoma lesions on bPET (best with TLG, significant with TMTV, and borderline with maxSUVmax) and the FDG uptake of the spinal cord at Th12 or of the spleen without tumour invasion on iPET after two cycles of chemotherapy.
Multivariate analysis for the prediction of “complete metabolic response” according to the “conservative” interpretation of Deauville Score (DS of ≤3 was considered non-indicative for relapse) revealed that TLG on bPET and variation in the spinal cord uptake on Th12 (between bPET and iPET) were significant contributors. Multivariate analysis for the prediction of “complete metabolic response” according to the “sensitive” interpretation of DS (DS of ≥3 as indicative for relapse) identified TLG on bPET as the single significant contributor.

VII. Summary

The detection of non-tumour-specific FDG uptake by structures that are not invaded by malignant tissue on the PET/CT images has been reported for a long time, and is considered as a potential pitfall. This thesis aimed to elucidate the possible importance of FDG uptake by focusing on paediatric patients with onco-haematological diseases. Diffuse and intense FDG uptake could provide additional information that reflects the metabolic status of the patient, thereby aiding treatment management, which is a major objective in this specific patient population.

A pilot study and a validation study were conducted to analyse the frequency and intensity of diffuse FDG uptake by selected organs (thymus, bone marrow, liver, spleen, and spinal cord) and the prevalence of BAT activation on bPET and iPET. Studies focusing on BAT activation were also presented. We aimed to evaluate the correlation between FDG uptake of these non-tumour-specific sites, the metabolic response of the tumour tissue, and evolution of the disease with treatment.

Diffuse and intense FDG uptake is frequently observed at sites without tumour invasion in children with HL prior to treatment. However, the prevalence of this observation is frequently reduced after two cycles of chemotherapy. In contrast, the FDG uptake by the normal liver tissue is frequently enhanced. Inadequate response may be connected to the lack of increase in the liver FDG uptake after two cycles of chemotherapy, FDG uptake by the lymphoma on baseline PET, and FDG uptake of the spinal cord or spleen without tumour invasion on iPET.

It could be a further perspective to continue the evaluation of the value of the non-tumour-specific FDG uptake in the prediction of PFS by reaching a longer clinical follow-up in a larger patient group. Comparing the behaviour of such non-tumour-specific FDG uptake among different types of paediatric onco-haematological populations is another objective that arose in this thesis.

VIII. References

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IX. Bibliography of the candidate's publication

Publications connected to the thesis:

1. Jorgov L, Montravers F, Balogova S, Ragu C, Pacquement H, Leblanc T, Abbou S, Ducou-Lepointe H, Landman-Parker J, Talbot JN. Paediatric and adolescent Hodgkin lymphoma: information derived from diffuse organ uptake of 18 F-fluorodeoxyglucose on pretreatment and on interim PET/CT. Eur J Nucl Med Mol Imaging. 2016;43(7):1220-1230. DOI: 10.1007/s00259-015-3280-6

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3. Jorgov L, Cottereau AS, Balogova S, Montravers F, Talbot JN, FDG Uptake by brown adipose tissue in paediatric and adolescent Hodgkin lymphoma, visualised on PET/CT performed at diagnosis**.** In: Jekunen Antti ed. The evolution of radionanotargeting towards clinical precision oncology. Bentham books. 2022; 317-326. DOI: 10.2174/9781681088655122010030

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Publications beyond the topic of the thesis:

1. Györke T, Carr R, Cerci J Jokinen, Meneghetti C, Redondo F, Celli M, Gorospe Ch, Auewarakul Ch U, Jorgov L, Paez D, Fanti S. Combined visual and semi-quantitative evaluation improves outcome prediction by early mid-treatment 18 F-fluoro-deoxiglucose positron emission tomography in diffuse large B-cell lymphoma. J Nucl Med. 2020;61(7):999-1005. DOI: 10.2967/jnumed.119.231621

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