The role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the evaluation of pediatric Hodgkin's lymphoma and non-Hodgkin's lymphoma

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Abstract

Pediatric lymphomas (PL) are the third most common malignancy and account for 10% to 15% of all cancers in the pediatric age group. Accurate classification and staging are important for appropriate prognosis and treatment of pediatric Hodgkin's lymphoma (PHL) and non-Hodgkin's lymphomas (PNHL) and impact patient prognosis significantly. The role of fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and ^{18}F-FDG PET/computed tomography (^{18}F-FDG PET/CT) in diagnosis, staging, localization of tumor radiotherapy, evaluation of treatment response and detection of recurrent tumors of PHL and PNHL is reviewed in this paper. The results of published ^{18}F-FDG PET and ^{18}F-FDG PET/CT studies in pediatric patients with HL and NHL were promising for initial diagnosis, for the localization of tumors, for radiation treatment and for early assessment of treatment response. However, as the sample size of these original articles was often small and a unified study design standard is lacking, more data are needed to better specify the role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the management of PHL and PNHL. *In conclusion*, the ^{18}F-FDG PET and ^{18}F-FDG PET/CT appear superior to other imaging methods such as X-rays, CT, MRI and ultrasound, other nuclear medicine methods and bone marrow biopsy for the evaluation of pediatric lymphomas.

Introduction

Pediatric lymphomas, including pediatric Hodgkin's lymphoma (PHL) and pediatric non-Hodgkin's lymphomas (PNHL), constitute 10% to 15% of all childhood cancers (representing 2%-3% of all malignancies) in children and adolescents younger than 20 years old, and are the third most common group of cancers following leukemia and malignant brain tumors in children [1]. The incidence of PHL and PNHL increases with age, accounting for 3% of cancers in children younger than 5 years of age and for 24% of cancers in adolescents aged 15 to 19 years. With a timely diagnosis and appropriate treatment, the reported overall 5 years survival for HL and NHL in patients younger than 20 years is 91% and 70%-76%, respectively [2]. To improve the survival rate and obtain a more favorable prognosis, a diagnostic method that can accurately classify and stage PHL and PNHL is needed.

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging is one of the most advanced multi-mode techniques available. The biodistribution of ^{18}F-FDG can be detected by PET and PET/CT with high sensitivity. Numerous original publications have investigated the value of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the evaluation of PHL and PNHL. This review describes briefly the classification and incidence of PHL and PNHL, compares ^{18}F-FDG PET and ^{18}F-FDG PET/CT with other diagnostic techniques for PHL and PNHL and evaluates the role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the evaluation of PHL and PNHL.

Classification and incidence of pediatric lymphomas

PHL is more frequent in adolescents while PNHL is more frequent in children younger than 10 years [1]. PHL and PNHL may not be limited to a single organ system and often appear systemically. Classic PHL involves contiguous nodal groups at presentation. In contrast to that, PNHL is more commonly extranodular.

Pediatric Hodgkin's lymphoma

PHL represents approximately 40% of all PL [3, 4]. Male incidence is slightly greater under the age of 15 (male/female ratio: 1.3 to 1) and significantly greater under the age of 5 (male/female ratio: 5.3 to 1) [1]. Carl Sternberg (in 1898) and Dorothy Reed (in 1902) described the histologic characteristics and cellular abnormalities of the neoplastic cells seen in HL. The Reed-Sternberg (RS) cell, a giant multinucleated lymphocyte with eosinophilic nucleoli, is considered as the hallmark of HL [2].

Classification of HL is based on morphology, immunohistochemistry and clinical manifestations. The World Health Organization (WHO) classification separates the less common nodular lymphocyte predominant (LP) form of HL from the relatively common classical PHL form. According to this classification, subtypes of classical HL are: a) nodular sclerosis (NS), b) lymphocyte rich (LR) (previously LP), c) mixed cellularity (MC) and d) lymphocyte depletion (LD) subtype. The Rye pathological classification distinguishes four subtypes, among which: a) NS (in adolescents) and b) MC (in pre-pubertal children) are the most frequent subtypes. The RS cells are abundant in the NS subtype, less frequent in the MC and LD subtypes and rare in the LR subtype, thus the diagnosis of the LR subtype of HL requires the evaluation of multiple tissue sections [5].

Pediatric non-Hodgkin's lymphomas and comparison to adult NHL

PNHL represents 60% of pediatric lymphomas; its incidence peaks between the ages of 5 and 9 years [6]. There is a marked male incidence in PNHL, 70% of them occur in male children [1], in all age groups. Contrary to the many subtypes of NHL in adults, there are only four major subtypes of NHL in the pediatric population. The WHO divides PNHL into four major histologic subtypes: a) Burkitt lymphoma (BL) 40% of the cases, b) diffuse large B-cell lymphoma (DL-BCL) 20% of the cases, c) anaplastic large cell lymphoma (ALCL) 10% of cases and d) lymphoblastic lymphoma (LBL) 30% of the cases [2].

Pediatric NHL differs from adult NHL with respect to biology, disease type, staging system, treatment and outcome. Nearly equal proportions of PNHL are B-cell and T-cell lymphomas; in contrast, the majority of NHL in adults are of B-cell origin. Nearly all PNHL are high-grade tumors that are usually diffuse in nature, while adult NHL are more commonly of low or intermediate grade [7]. About 90% of PNHL disease subtypes observed in children and adolescents are either mature B-cell NHL, lymphoblastic lymphoma or anaplastic large cell lymphomas. The other 10% are subtypes commonly observed in adults [8].

The Murphy staging system is used most widely for PNHL while the Ann Arbor staging system and the International Prognostic Index are usually used for adult NHL. The Murphy staging system differs from the Ann Arbor system primarily with respect to the classification of abdominal, intrathoracic and paraspinal/epidural disease [9]. Minimal disease can be detected in the peripheral blood of the vast majority of PNHL patients at diagnosis [10, 11].

Therapeutic approaches differ for children and adults having similar histologic classifications. In children NHL is considered a disseminated disease, despite having localized sites of involvement. Therefore, in children complete surgical resection and local radiotherapy are rarely used while central nervous system (CNS) prophylaxis is necessary.

The outcome for PNHL is generally better than that of adult NHL. Older children also tend to have worse outcomes when treated on the aggressive pediatric regimens [12].

Comparison of diagnostic methods for PHL and PNHL

Appropriate treatment of PHL and PNHL is dependent on timely, accurate classification and initial staging. This evaluation of PL should begin with an observation of signs and symptoms, which vary. The most common symptom of PL is one or more enlarged lymph nodes in the neck, axilla or groin, which are usually painless. Other frequent signs and symptoms include unexplained fever, night sweats, itchy skin, fatigue, loss of appetite, weight loss, coughing, difficulty in breathing, frequent viral infections and abdominal swelling. Large lymphomas in the chest or the abdomen can be asymptomatic. Physical examination, although limited by the location of the disease, contributes to peripheral lymph node staging.

The physician's choice of auxiliary examination should be guided by the findings of a thorough history and physical examination. The imaging modalities of ultrasonography (US), plain film radiography (X-rays), computed tomography (CT), and magnetic resonance imaging (MRI) that are often used to evaluate the size criteria for nodal involvement have several limitations. Specifically, normal-sized lymph nodes harboring micrometastases can be missed and lymphatic enlargement due to other causes cannot be differentiated by the above-mentioned imaging modalities [13].

Sensitivity and specificity of CT for nodal disease has been reported to be 87.5% and 85.6%, respectively [14]. Evaluation by CT of nodal size was considered to be the standard anatomical imaging technique for staging of pediatric lymphomas [15]. However, strict CT size criteria are not distinct in pediatric patients because the nodal size range of benign reactive lymph node hyperplasia overlaps with that of malignant lymphadenopathy [16]. Moreover, CT performs rather poorly in detecting splenic and liver involvement by PHD [17].

A safer alternative and the procedure of choice to assess bone marrow and central nervous system infiltration is MRI, but it is not convenient for routine imaging of the entire bone marrow. This limitation is most evident in post-treatment cases, where MRI is unable to differentiate residual tumor from fibrosis or to detect early recurrence [18]. Fluorine-18-fluorodeoxyglucose is a glucose analogue that can provide unique information about glucose metabolism of normal and abnormal tissues in a whole-body imaging of PET/CT and thus, can compensate for the shortcomings of MRI.

Optimal management of PL requires accurate detection of bone marrow (BM) involvement, a sign of advanced disease that portends worse prognosis. For decades, BM biopsy (BMB) has been performed to assess BM infiltration and is considered the "gold standard" in the initial staging of lymphoma. However, BMB is invasive and stressful, especially in pediatric patients who may require general anesthesia. Moreover, BMB can only evaluate a sample of the

entire BM (most commonly in the region of the anterior or posterior iliac crests), while lymphomatous involvement of the BM is occasionally focal and can be missed at selected biopsy sites [19]. It has also been reported [20] that eight malignant lymphoma patients had bone scintigraphy lesions not detected by BMB. This limited assessment of BMB can lead to false-negative findings and adversely affect clinical management.

The use of nuclear medicine scans, such as a gallium-67 (^{67}Ga) scintigraphy and bone scanning (BS) is warranted to detect skeletal involvement with metabolically active lymphomas.

Gallium-67-citrate scintigraphy is very useful for baseline functional imaging of high-grade lymphomas and for evaluation of treatment response [21] but has several limitations: First, its sensitivity and specificity are affected by the type and site of disease involvement, therefore intermediate and low-grade lymphomas are more difficult to evaluate than the more aggressive ones (Fig. 1). Second, ^{67}Ga-citrate scintigraphy is less accurate in assessing infradiaphragmatic involvement due to the physiological uptake of ^{67}Ga in the abdomen (liver, spleen, and kidneys initially, then bowel). Furthermore, adequate clearance of background activity requires a substantial interval between injection of gallium and imaging (at least 3 days) [22].

Other researchers (1995) [23] showed that ^{67}Ga scintigraphy was more reliable than bone scanning for evaluating the therapeutic response in patients with bone lymphoma. It has also been reported [24] that bone scanning was unnecessary in the initial staging of children with malignant lymphomas. Bone scans were less frequently used in patients with lymphoma because ^{67}Ga scintigraphy can better detect most lymphomas and their metastases. Currently, bone scanning is particularly recommended for patients with bone pain, elevated alkaline phosphatase or extensive disease [25].

The most valuable imaging modality available for the evaluation of PHL and PNHL is ^{18}F-FDG PET/CT. In contrast to CT and MRI, the diagnostic criteria of ^{18}F-FDG PET/CT for malignant tumors are based on both the anatomical location and the metabolic activity of tumor cells. In addition, ^{18}F-FDG PET/CT can be employed as a whole-body imaging method to search for lesions. Thus, ^{18}F-FDG PET/CT is obviously superior to CT and MRI. ^{18}F-FDG can accumulate in cells regardless of their location within the body and assess malignancy in osseous structures and in BM, thus challenging the traditional role of ^{67}Ga scintigraphy and bone scanning for staging and follow-up of children and adolescents with lymphomas [26].

The role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in initial staging of PHL and PNHL

After lymphoma has been diagnosed and classified histopathologically, physicians have to evaluate accurately the initial clinical stage based on the distribution of enlarged lymph nodes and the extent of extranodal involvement. Accurate initial clinical staging is important. Advanced stages require an aggressive therapeutic regimen, while over-treatment increases the risk of long-term side effects.

Scanning with ^{18}F-FDG PET and PET/CT can detect insidious lesions with high sensitivity, leading to more accurate initial staging of PL as compared to CT or MRI. Other researchers [27] reported that ^{18}F-FDG PET up-staged four of 22 pediatric patients with PHL and others [28] that changed the stage of the disease in four of seven cases having PHL or PNHL. Other researchers [29] reported that ^{18}F-FDG PET modified both the stage and the treatment approach in 10.5% of the pediatric patients and others [30] using ^{18}F-FDG PET found that the stages of PHL or PNHL differed from those diagnosed by CT in six of 25 patients. In a study of patients with 39 PHD and 2 NHL Burkett's lymphoma, it has been reported [18] that by using ^{18}F-FDG PET/CT the initial staging results in 11 of 41 patients were not the same with those of CT, MRI, and US. In these 11 cases, five patients were upstaged and six were downstaged. Similar results were reported recently by others [31, 32], who found much better staging results by ^{18}F-FDG PET/CT than by CT, BMB, MRI, ^{67}Ga-citrate scan and bone scan in 53 PHL patients and by diagnostic contrast-enhanced CT in 30 PHL patients.

Compared with CT and MRI, ^{18}F-FDG PET/CT imaging is more sensitive for the detection of extranodal lesions. Other authors [33] using ^{18}F-FDG PET/CT in 76 PHL pediatric patients concluded that ^{18}F-FDG PET/CT could effectively detect extranodal lesions, especially within the liver, the spleen and the BM. Others [34] assessed the diagnostic utility of CT, ^{18}F-FDG PET and ^{18}F-FDG PET/CT for initial staging of PHL. They found that the accuracy of CT or MRI, of ^{18}F-FDG PET and of ^{18}F-FDG PET/CT was 86%, 89% and 97%, respectively for lymph node regions above the diaphragm and 94%, 94% and 98%, respectively for lymph node regions below the diaphragm. For extranodal regions, the accuracy was 96%, 96% and 100%, respectively.

Scanning with ^{18}F-FDG PET/CT was especially valuable for the detection of unexpected extranodal sites of PL. In a study of 24 PHL and 7 PNHL patients, other authors [35] studied ^{18}F-FDG PET/CT and diagnostic CT (DCT) and on an analy-
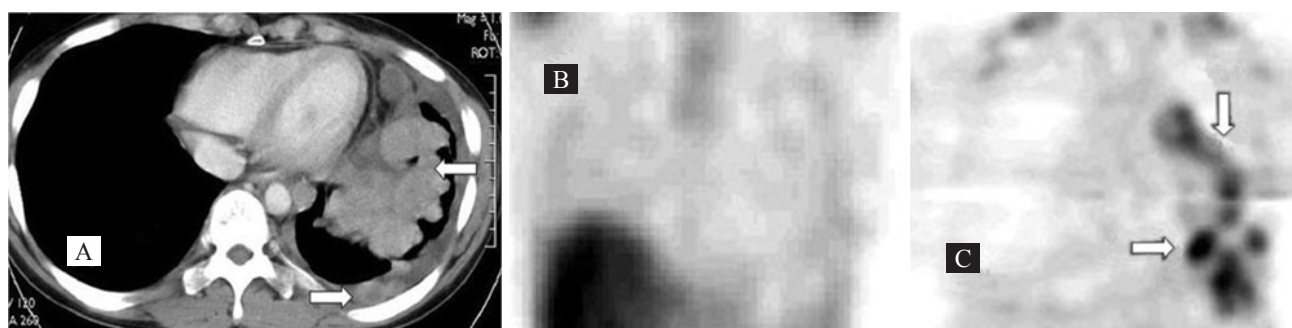
Figure 1. Left panel (A): chest CT; middle panel (B): coronal gallium SPET; right panel (C): coronal ^{18}F-FDG PET. There are extensive abnormalities in the chest CT scan which are shown to be metabolically active by PET imaging. But these foci don't accumulate gallium [22].

sis of 164 lesions, 38 sites were detected by ^{18}F-FDG PET/CT but not by DCT. The 38 lesions missed by DCT were located in normal-sized lymph nodes (n=11), bone marrow (n=8), spleen (n=6), thymus (n=5), liver (n=3), bone (n=3), pancreas (n=1) and ascending colon (n=1). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ^{18}F-FDG PET/CT were 99%, 100%, 100% and 86%, respectively; and the corresponding values of DCT were 80%, 23%, 92% and 7%, respectively.

Scanning with ^{18}F-FDG PET/CT is a more sensitive and specific method than BMB and BS for the detection of BM involvement in PL (Fig. 2). In 175 pediatric patients with newly diagnosed classical HL, staged more than IIA, ^{18}F-FDG PET detected BM involvement in 45 patients, while BMB was positive in only 7 patients. The sensitivity of BMB for the detection of BM involvement in pediatric lymphoma was 4%, while for ^{18}F-FDG PET/CT was 100%, respectively [36].

It has been reported [37] that among 13 PNHL patients with BM involvement, tested by ^{18}F-FDG PET/CT found BM involvement in 12 patients, while BMB revealed BM involvement in 7 patients. BMB also demonstrated 1 false-negative result. The sensitivity for BM involvement in PL was 92% and 54%, respectively, for ^{18}F-FDG PET/CT and BMB. The BM involvement can be well detected by a whole-body PET/CT imaging. As expected, ^{18}F-FDG PET/CT guidance can improve the sensitivity of BMB. The authors reported that BMB

Figure 3. A 9 years old boy with Burkitt lymphoma stage IV. (A) A PET study was performed at baseline. The 3D-projection image showed massive nodal, hepatic, splenic, renal and medullary involvement. (B) After two cycles of chemotherapy, the 3D-projection PET image was already negative. The child is in complete remission [29].

was positive in 86% of patients with positive ^{18}F-FDG PET/CT findings at the biopsy sites.

Other researchers [25] reported that ^{18}F-FDG PET/CT indicated bone involvement not otherwise evident on bone scan in 4 out of 18 PHL patients. Bone scan also showed abnormal uptake in a benign lesion (non-ossifying fibroma patient), indicating a false positive result.
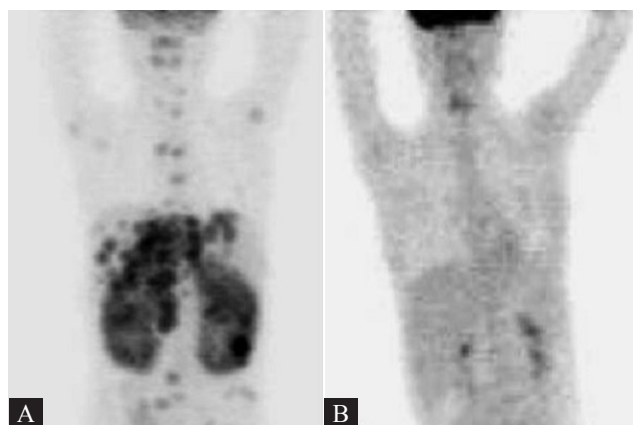
The role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in radiotherapy of PHL

Disease sites found on ^{18}F-FDG PET/CT can show that the involved-field of radiation treatment (IFRT) should be enlarged to cover the greater extent of the tumor. Treatment of all sites of the initial disease improves control of the disease. In 53 PHL patients studied by others [31], the IFRT changed in 9 patients, with at least 1 discordant site between ^{18}F-FDG PET/CT and CT. In 8 patients, the IFRT became more extensive while in one patient it became less extensive. The most common change in IFRT was the inclusion of the spleen in four cases. Another study also demonstrated that 10 of 30 patients had a change in the IFRT as a result of ^{18}F-FDG PET/CT examination. The IFRT became larger in 7 of the 10 patients [38].
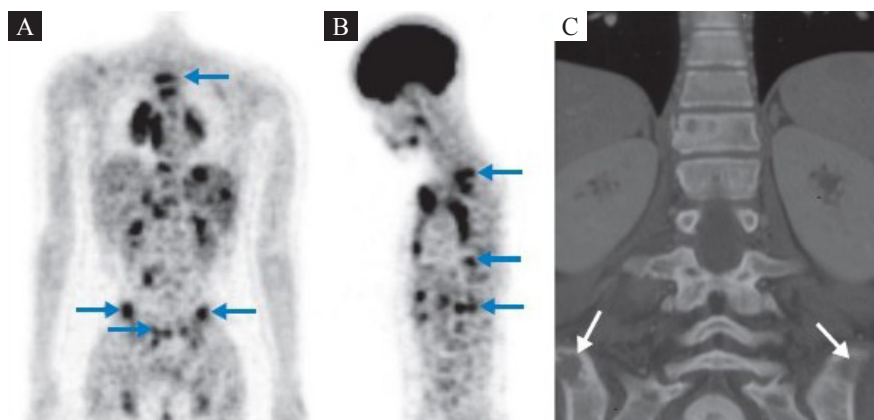
Other authors [32] adjusted the IFRT volumes in 21 of 30 PHL patients on the basis of initial ^{18}F-FDG PET/CT findings, so that 32 sites were added and 15 sites were excluded from IFRT. The most commonly added sites were the contralateral neck, the para-aortic nodes and the spleen. The most commonly excluded sites were the pleura, pericardial and lung nodules. Other researchers [39] performed a study in 20 children with HL. They concluded that the addition of ^{18}F-FDG PET/CT to the treatment plan lowered interobserver variability in determining the extent of nodal involvement and significantly increased the consistency of tumor volume definition.

The role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the evaluation of treatment response of PHL and PNHL

[18]FDG PET/CT can reveal the post-treatment tumor growth and proliferation, providing a basis to early judge the clinical curative effect (Fig. 3). It has been reported [29] that in evaluating treatment response specificity of ^{18}F-FDG PET was 94% as compared to a specificity of 54% for physical examination,

Figure 2. A 13 years old girl with a negative BMB. (A and B) PET shows focal enhanced ^{18}F-FDG uptake (arrows) in multiple areas of the thoracic spine, sternum, and pelvic bones. (C) CT scan shows corresponding lytic lesions (arrows) in both iliac crests [36].

chest X-rays, CT, MRI, US and bone scan. Other researchers [35], compared ^{18}F-FDG PET/CT and CT for monitoring response to treatment in 31 PL patients. CT demonstrated 76 residual masses in 22 patients, while ^{18}F-FDG PET/CT detected 11 masses in 4 patients. The 65 ^{18}F-FDG PET/CT negative masses were false positive findings of the CT scans. Thus, the positive predicted value (PPV) of ^{18}F-FDG PET/CT for residual masses was 100% and that of CT only 14% [35].

Other researchers [18] compared ^{18}F-FDG PET/CT and CT, MRI, and US in a group of 51 PL patients (45 PHD, 6 PNHL), to evaluate early response to treatment after two to three courses of chemotherapy. Findings were discordant in 17 of the 51 cases. The ^{18}F-FDG PET/CT findings were true-negative in 15 patients (all were false-positive on CT) and true-positive and false-positive in one patient, respectively. The sensitivity, specificity, accuracy, PPV and NPV of the ^{18}F-FDG PET/CT scan for the evaluation of treatment response after two to three courses of chemotherapy were 100%, 97.7%, 98%, 85.7% and 100%, respectively, as compared to 83%, 66.6%, 68.6%, 25% and 96.7% for CT combined with MRI. In another group of 42 PL patients (29 PHD, 13 PNHL), evaluated for treatment response 4-8 weeks after end of therapy, the above authors reported that the sensitivity, specificity, accuracy, PPV and NPV of ^{18}F-FDG PET/CT were 100%, 90.9%, 92.8%, 75% and 100%, respectively, and the corresponding values of CT combined with MRI were 55.5%, 57.5%, 57.1%, 26.3% and 82.6% [18].

It has also been reported [34] that the sensitivity and NPV of PET-negative patients at either early or late treatment response in 40 and in 29 PHL children was significantly higher compared to the proportion of CT and MRI negative patients. Sensitivity and NPV of ^{18}F-FDG PET for early and late therapy response assessment were both 100%. Specificity of early and late response of PET and of CT combined with MRI were 68% vs 3% and 78% vs 11%, respectively. Specificity of early treatment response assessment by ^{18}F-FDG PET was increased to 97% by quantitative analysis of SUVmax reduction using a cutoff value of 58% .
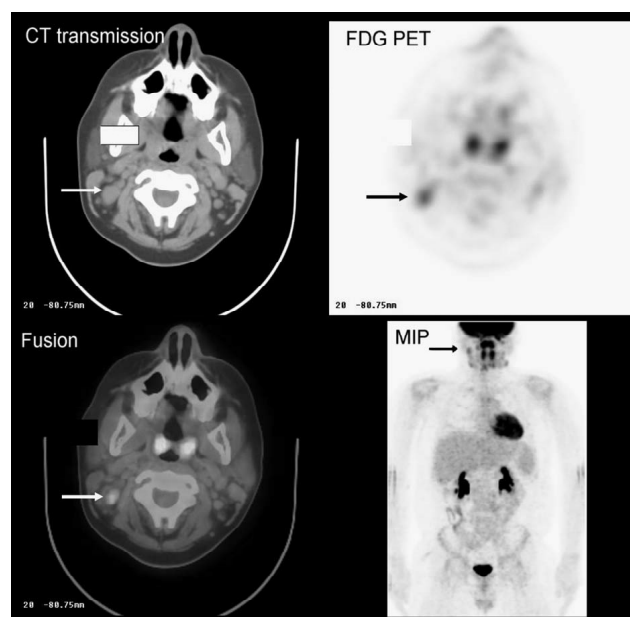
Figure 4. False positive PET/CT scan, MIP image with moderate ^{18}F-FDG uptake in a cervical lymph node (arrow) in a 12 years old boy with HL during routine follow-up. Biopsy of this node was negative for recurrence [41].

The role of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the detection of recurrence after treatment of PHL and PNHL

Residual abnormalities occur in 30%-60% of PL patients after chemotherapy. However, only a maximum of 10%-20% residual masses are reported to be positive for PL on biopsy and only 18% will eventually relapse [40]. Morphologic image methods such as CT, MRI, or US cannot differentiate between necrotic tumor tissue, inflammatory process or persistent malignant disease, while ^{18}F-FDG PET and ^{18}F-FDG PET/CT can identify the nature of the residual mass. Other authors [29] indicated the ability of ^{18}F-FDG PET to detect recurrence after chemotherapy. After studying 38 PHL and 21 PNHL by ^{18}F-FDG PET in a systematic long-term follow-up, 56 of the 59 studies were negative compared with 39 negative of physical examination, chest X-rays, CT, MRI, US and bone scan. ^{18}F-FDG PET scan was considered to be false positive in 3/59 studies due to muscle activity, asymmetrical thymus and atrial myocardial uptake. The authors reported that the specificity of ^{18}F-FDG PET for monitoring recurrence was 95% and that of the X-rays, CT, MRI and bone scan was 66% in this follow-up study of all 59 PL patients.

It has been reported [22] that in 26 PL ^{18}F-FDG PET provided incremental, clinically important information in 21% of 14 PHL cases and 33% of the 12 PNHL cases and was especially useful in differentiating scar tissue from recurrent masses or residual disease at the end of treatment. Other authors [18] in 18 PL patients (6 PHL,12 PNHL) reported 100% sensitivity, specificity, accuracy, PPV and NPV for ^{18}F-FDG PET/CT, while the corresponding values of CT, MRI, and US were 100%, 38.4%, 72.2%, 50% and 100%, respectively.

Other researchers [41] retrospectively reviewed the ^{18}F-FDG PET/CT and diagnostic CT images performed during follow-up after completion of treatment by chemotherapy (28 patients), chemotherapy and radiation (10 patients), and hematopoietic stem cell transplantation (3 patients) in a total of 41 PL (24 PHL and 17 PNHL). They found that ^{18}F-FDG PET/CT was 95% sensitive, with a PPV of 53% and CT was 79% sensitive, with a PPV of 52%. The authors concluded that a negative ^{18}F-FDG PET/CT scan strongly suggests absence of recurrence; however due to low PPV, a positive ^{18}F-FDG PET/CT and diagnostic CT scans should be interpreted with caution in PHL or PNHL during routine follow-up after completion of treatment. Figure 4 shows an example of false positive PET/CT scan. Similarly, in another study [42], 23 consecutive PHL patients were evaluated with ^{18}F-FDG PET scan either at diagnosis, during treatment or after completion of chemotherapy or chemotherapy and radiation. Both sensitivity and NPV of ^{18}F-FDG PET were 100%, but with a poor specificity (57.1%) and PPV (18.2%) and concluded that ^{18}F-FDG PET is a sensitive but not specific method for evaluating post-treatment PHL patients and that treatment decisions based solely on ^{18}F-FDG PET scan results were inadvisable.

Conclusion, remarks and future prospects

Scanning with ^{18}F-FDG PET and ^{18}F-FDG PET/CT are useful techniques in the evaluation of PL greatly contributing to the diagnosis of initial staging of PL. These methods are also valuable for the localization of tumors for IFRT and for early

assessment of treatment response and also highly specific to allow for accurate characterization of residual masses, which are common in PL patients. Scanning by ^{18}F-FDG PET and ^{18}F-FDG PET/CT is also more useful than CT, MRI and US or other nuclear medicine methods, such as ^{67}Ga scintigraphy, bone scanning and BMB, for the evaluation of pediatric patients with HL or NHL.

However, ^{18}F-FDG PET and ^{18}F-FDG PET/CT have several limitations. First, they may be falsely positive in high ^{18}F-FDG-uptake sites such as nonspecific pulmonary inflammation, treatment-induced areas and lymphoid reactive hyperplasia. Second, various body areas including brain, tonsils, tongue, vocal cords, brown fat, heart and urinary system demonstrate increased metabolic activity thereby obscuring involved small lymph nodes around these areas [32]. Furthermore, ^{18}F-FDG PET/CT imparts a substantial dose of ionizing radiation, which is further increased by repeating imaging for treatment response assessment and follow-up. Radiation exposure increases the risk of malignancy and radiation induced malignancy is more likely in pediatrics. The most radiosensitive organ in pediatrics receiving a mean dose in Gy from PET/CT whole body scans is thyroid gland (0.1-0.6Gy), breasts (0.3-0.7Gy), bone marrow (0.3Gy), brain (1.5Gy) and skin (4.3-6.1Gy) [43, 44]. A dose limit of 30mSv should not be exceeded and can only be approached if there is a benefit to the pediatric patient [45].

The original articles that were cited in this evaluation of PL are mostly retrospective analyses from specific centers. Sample size was often small and a unified study design standard is lacking. Although the results of published ^{18}F-FDG PET and ^{18}F-FDG PET/CT studies are better than those of conventional imaging, like X-rays, CT, MRI, US, bone scan, ^{67}Ga-citrate scan and BMB, prospective studies of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in a larger number of pediatric lymphoma patients are warranted.

Bibliography

1. Percy CL, Smith MA, Linet M et al. Lymphomas and reticuloendothelial neoplasms. In: Ries LA, Smith MA, Gurney JG et al. Eds. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995*. Bethesda, Md. National Cancer Institute, SEER Program, 1999: 35-50.
2. Abramson SJ, Price AP. Imaging of pediatric lymphomas. *Radiol Clin North Am* 2008; 46(2): 313-38.
3. Oberlin O. Hodgkin's disease. In: Voûte PA, Kalifa C, Barrett A, Eds. *Cancer in children. Clinical management*. 4th edn. New York: Oxford University 1998; 137-53.
4. Lanzkowski P. Hodgkin's disease. In: Lanzkowski P, Ed. *Manual of pediatric hematology and oncology*. 3rd edn. San Diego: Academic. 1999: 413-43.
5. Hudson MM, Donaldson SS. Hodgkin's disease. *Pediatr Clin North Am* 1997; 44: 891-906.
6. Büyükpamukçu M. Non-Hodgkin's lymphomas. In: Voûte PA, Kalifa C, Barrett A, Eds. *Cancer in children. Clinical management*. 4th edn. New York: Oxford University 1998; 119-36.
7. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. *N Engl J Med* 1996; 334: 1238-48.
8. Gross TG, Termuhlen AM. Pediatric non-Hodgkin lymphoma. *Curr Hematol Malig Rep* 2008; 3(3): 167-73.
9. Murphy SB, Fairclough DL, Hutchison RE et al. Non-Hodgkin's lymphomas of childhood: an analysis of the histology, staging, and response to treatment of 338 cases at a single institution. *J Clin Oncol* 1989; 7: 186-93.
10. Sabesan V, Cairo MS, Lones MA et al. Assessment of minimal residual disease in childhood non-Hodgkin lymphoma by polymerase chain reaction using patient-specific primers. *J Pediatr Hematol Oncol* 2003; 25: 109-13.
11. Campana D, Coustan-Smith E, Sandlund JT et al. A novel approach for staging and minimal residual disease detection in patients with T-cell lymphoblastic lymphoma: a Children's Oncology Group study. *Ann Oncol* 2005; 16(Suppl 5): 62.
12. Burkhardt B, Zimmermann M, Oschlies I et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. *Br J Haematol* 2005; 131: 39-49.
13. Weihrauch MR, Re D, Bischoff S et al. Whole-body positron emission tomography using ^{18}F-fluorodeoxyglucose for initial staging of patients with Hodgkin's disease. *Ann Hematol* 2002; 81: 20-5.
14. la Fougére C, Hundt W, Bröckel N et al. Value of PET/CT versus PET and CT performed as separate investigations in patients with Hodgkin's disease and non-Hodgkin's lymphoma . *Eur J Nucl Med Mol Imaging* 2006; 33(12): 1417-25.
15. Vinnicombe SJ, Reznek RH. Computerised tomography in the staging of Hodgkin's disease and non-Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging* 2003; 30 (Suppl1): S42-S55.
16. Kumral A, Olgun N, Uysal KM et al. Assessment of peripheral lymphadenopathies: experience at a pediatric hematology-oncology department in Turkey. *Pediatr Hematol Oncol* 2002; 19(4): 211-8.
17. Munker R, Stengel A, Stabler A et al. Diagnostic accuracy of ultrasound and computed tomography in the staging of Hodgkin's disease. Verification by laparotomy in 100 cases. *Cancer* 1995; 76: 1460-6.
18. Riad R, Omar W, Kotb M et al. Role of PET/CT in malignant pediatric lymphoma. *Eur J Nucl Med Mol Imaging* 2010; 37: 319-29.
19. Carr R, Barrington SF, Madan B et al. Detection of lymphoma in bone marrow by whole-body positron emission tomography. *Blood* 1998; 91: 3340-6.
20. Esmaili J, Safaee SR, Sharifian R et al. The relation of bone marrow scintigraphy and unilateral bone marrow biopsy in malignant lymphoma. *Hell J Nucl Med* 2005; 8(2): 125-8.
21. Bar-Shalom R, Mor M, Yefremov N et al. The value of Ga-67 scintigraphy and F-18 fluorodeoxyglucose positron emission tomography in staging and monitoring the response of lymphoma to treatment. *Semin Nucl Med* 2001; 31(3): 177-90.
22. Mody RJ, Bui C, Hutchinson RJ et al. Comparison of [18]F Flurodeoxyglucose PET with Ga-67 scintigraphy and conventional imaging modalities in pediatric lymphoma. *Leuk Lymphoma* 2007; 48(4): 699-707.
23. Moon TY, Kim EE, Kim YC et al. Comparison of nuclear bone and gallium scans in the therapeutic evaluation of bone lymphoma. *Clin Nuc Med* 1995; 20: 721-4.
24. Mouratidis B, Gilday DL, Ash JM. Comparison of bone and ^{67}Ga scintigraphy in the initial diagnosis of bone involvement in children with malignant lymphoma. *Nucl Med Commun* 1994; 15: 144-7.

25. Shulkin BL, Goodin GS, McCarville MB et al. Bone and [¹⁸F]fluorodeoxyglucose positron-emission tomography/computed tomography scanning for the assessment of osseous involvement in Hodgkin lymphoma in children and young adults. *Leuk Lymphoma* 2009; 50(11): 1794-802.

26. Bar-Sever Z, Keidar Z, Ben Barak A et al. The incremental value of ¹⁸F-FDG PET/CT in paediatric malignancies. *Eur J Nucl Med Mol Imaging* 2007; 34: 630-7.

27. Weihrauch MR, Re D, Bischoff S et al. Whole body positron emission tomography using ¹⁸F-flurodeoxyglucose for initial staging of patients with Hodgkin's disease. *Ann Hematol* 2002; 81: 20-5.

28. Montravers F, McNamara D, Landman-Parket J et al. ¹⁸F-FDG in childhood lymphoma: clinical utility and impact on management. *Eur J Nucl Med Mol Imaging* 2002; 29: 1155-65.

29. Depas G, De Barsy C, Jerusalem G et al. ¹⁸F-FDG PET in children with lymphomas. *Eur J Nucl Med Mol Imaging* 2005; 32(1): 31-8.

30. Hermann S, Wormanns D, Pixberg M et al. Staging in childhood lymphoma: differences between FDG-PET and CT. *Nuklearmedizin* 2005; 44(1): 1-7.

31. Paulino AC, Margolin J, Dreyer Z et al. Impact of PET-CT on involved field radiotherapy design for pediatric Hodgkin lymphoma. *Pediatr Blood Cancer* 2012; 58(6): 860-4.

32. Robertson VL, Anderson CS, Keller FG et al. Role of FDG-PET in the definition of involved-field radiation therapy and management for pediatric Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2011; 80(2): 324-32.

33. Bashir H, Maaz AU, Saadullah M et al. FDG-PET/CT of extranodal involvement in pediatric Hodgkin lymphoma. *Cancer Imaging* 2011; 11: S177-8.

34. Furth C, Denecke T, Steffen I et al. Correlative imaging strategies implementing CT, MRI, and PET for staging of childhood Hodgkin disease. *J Pediatr Hematol Oncol* 2006; 28(8): 501-12.

35. Miller E, Metser U, Avrahami G et al. Role of ¹⁸F-FDG PET/CT in staging and follow-up of lymphoma in pediatric and young adult patients. *J Comput Assist Tomogr* 2006; 30(4): 689-94.

36. Purz S, Mauz-Korholz C, Korholz D et al. [¹⁸F]Fluorodeoxyglucose positron emission tomography for detection of bone marrow involvement in children and adolescents with Hodgkin's lymphoma. *J Clin Oncol* 2011; 29(26): 3523-8.

37. Cheng G, Chen W, Chamroonrat W et al. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. *Eur J Nucl Med Mol Imaging* 2011; 38(8): 1469-76.

38. Hutchings M, Loft A, Hansen M et al. Clinical impact of FDG-PET/CT in the planning of radiotherapy for early-stage Hodgkin lymphoma. *Eur J Haematol* 2007; 78: 206-12.

39. Metwally H, Courbon F, David I et al. Coregistration of prechemotherapy PET-CT for planning pediatric Hodgkin's disease radiotherapy significantly diminishes interobserver variability of clinical target volume definition. *Int J Radiat Oncol Biol Phys* 2011; 80(3): 793-9.

40. Burton C, Ell P, Linch D. The role of PET imaging in lymphoma. *Br J Haematol* 2004; 126(6): 772-84.

41. Rhodes MM, Delbeke D, Whitlock JA et al. Utility of FDG-PET/CT in follow-up of children treated for Hodgkin and non-Hodgkin lymphoma. *J Pediatr Hematol Oncol* 2006; 28(5): 300-6.

42. Meany HJ, Gidvani VK, Minniti CP. Utility of PET scans to predict disease relapse in pediatric patients with Hodgkin lymphoma. *Pediatr Blood Cancer* 2007; 48(4): 399-402.

43. Brenner D, Elliston C, Hall E et al. Estimated risks of radiation-induced fatal cancer from pediatric CT. *Am J Roentgenol* 2001; 176(2): 289-96.

44. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. *Pediatr Radiol* 2006; 36(suppl 2): 121-5.

45. Grammaticos P, Fountos G. The physician should benefit, not harm the patient. *Hell J Nucl Med* 2006; 9(2):82-4.