# Italian Multicenter Study on Accuracy of $^{18}$F-FDG PET/CT in Assessing Bone Marrow Involvement in Pediatric Hodgkin Lymphoma

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## Abstract

**The present study investigated the utility of fluorine-18 ($^{18}$F) fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) in assessing bone marrow involvement (BMI) compared with bone marrow biopsy (BMB) in newly diagnosed pediatric Hodgkin lymphoma (HL). $^{18}$F-FDG PET/CT shows high diagnostic performance in evaluating BMI in pediatric HL. BMB should be ideally reserved for patients with doubtful $^{18}$F-FDG PET/CT BMI findings.**

**Introduction:** The present study investigated the utility of fluorine-18 ($^{18}$F) fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT) in assessing bone marrow involvement (BMI) compared with bone marrow biopsy (BMB) in newly diagnosed pediatric Hodgkin lymphoma (HL). **Patients and Methods:** A total of 224 pediatric patients with HL underwent $^{18}$F-FDG PET/CT at staging. BMB or follow-up imaging was used as the standard of reference for the evaluation of BMI. **Results:** $^{18}$F-FDG PET/CT was negative for BMI in 193 cases. Of the 193 patients, the findings for 16 were originally reported as doubtful and later interpreted as negative

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for BMI, with negative findings on follow-up imaging and BMB. At BMB, 1 of the 16 patients (6.25%) had BMI. Of the 193 patients, 192 (99.48%) had negative BMB findings. Thus, the $^{18}$F-FDG PET/CT findings were truly negative for 192 patients and falsely negative for 1 patient for BMI. **Conclusion:** $^{18}$F-FDG PET/CT showed high diagnostic performance in the evaluation of BMI in pediatric HL. Thus, BMB should be ideally reserved for patients presenting with doubtful $^{18}$F-FDG PET/CT findings for BMI.

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**Keywords:** BMI, Bone marrow biopsy, Computed tomography, Newly diagnosed pediatric HL, Positron emission tomography

## Introduction

Lymphoma is the third most common malignancy in the pediatric population (after leukemia and malignant brain tumors), comprising nearly 15% of childhood malignancies (53% Hodgkin lymphoma [HL] and 47% non-HL).[1] Classic HL accounts for > 85% of cases; in contrast, nodular lymphocyte-predominant HL is a less common subtype of HL. The 5-year survival rate has been 95% for HL.[2,3] Once a lymphoma has been diagnosed, the extent of disease must be assessed.[4,5] HL is typically staged using the Ann Arbor staging classification,[6,7] which was updated by the Cotswolds report in 1989.[8] Therapeutic options, such as chemotherapy and/or radiotherapy, depend on the disease stage at diagnosis, because the options differ for patients with localized stage versus those with advanced or disseminated disease.[9-11]

The detection of lymphomatous bone marrow involvement (BMI), which accounts for 10% of pediatric HL cases, is clinically relevant because its presence can upstage the disease to stage IV and modify the treatment plan.[11-16] In clinical or radiologic stage IA or IIA disease, the incidence of BMI has been reported to be even lower or close to 0%.[17,18] Owing to the low incidence of BMI in the early stages, the Cotswolds report has recommended restricting BMB to adult patients with stage III/IV disease or stage II disease with adverse unfavorable factors found by computed tomography (CT).[8,19]

According to the latest guidelines issued by the Italian Association Pediatric Oncology and Hematology, BMB should be preferentially performed in symptomatic patients (class B) or those with stage ≥ III. However, in Italy, BMB has been heterogeneously and commonly performed in pediatric patients with HL.

At present, BMB remains the reference standard to determine bone marrow status; however, it has poor sensitivity (50%) for 2 main reasons. First, the sample size might be small; and second, the BMI is sometimes focal.[20,21] The main advantage of BMB is the acquisition of histologic material. Moreover, a positive BMB is considered definitive proof of BMI. However, the major disadvantage of BMB is its invasiveness; it is a stressful and painful procedure, despite the use of local anesthesia.

Fluorine-18 ($^{18}$F) fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography/computed tomography (PET/CT) has become an established method for lymphoma staging. It could also potentially be a noninvasive alternative or complementary method to BMB.[22] A major advantage of $^{18}$F-FDG PET/CT is that it allows visualization of the entire bone marrow. However, the clinical value of PET/CT for the evaluation of BMI in lymphoma is still under debate and investigation. Although a large body of evidence supports the use of PET/CT for the evaluation of BMI in adults,[23] few data are available regarding the diagnostic utility of PET/CT in relation to pediatric lymphoma for assessment of BMI.[5]

The aim of the present multicenter Italian study was to define the utility of $^{18}$F-FDG PET/CT compared with BMB to identify BMI in pediatric patients with newly diagnosed HL.

## Patients and Methods

A total of 224 pediatric patients (mean age, 14 years; range, 4-18 years), with an initial diagnosis of HL, were retrospectively enrolled in the study across 10 Italian nuclear medicine departments: Padua (n = 65; 2 centers), Turin (n = 62; 2 centers), Monza (n = 37), Bari (n = 27), Genoa (n = 21), Bologna (n = 7), Ferrara (n = 3), and Catania (n = 2; Table 1).

All patients underwent physical examination, routine blood testing, contrast-enhanced CT scan of the neck, chest, and abdomen, BMB, and $^{18}$F-FDG PET/CT scan as part of the routine protocol for the initial staging. The Ann Arbor stage was determined without considering the bone marrow uptake on the $^{18}$F-FDG PET/CT study.

The inclusion criteria were (1) biopsy confirmation of HL; (2) availability of BMB and baseline $^{18}$F-FDG PET/CT results; (3) age ≤ 18 years; and (4) availability of clinical and instrumental follow-up data for ≥ 12 months. The exclusion criteria were (1) previous known and treated lymphoma; (2) the presence of other concomitant malignancy; (3) previous chemotherapy or corticosteroid therapy; and (4) an interval between $^{18}$F-FDG PET/CT and BMB > 15 days. The institutional review board granted a waiver for patient informed consent owing to the retrospective nature of this study.

**Table 1 Patient Demographic Data**

| Characteristic | n |
|---|---|
| Patients | 224 |
| Age, y | |
| Mean | 14 |
| Range | 4-18 |
| Histotype | |
| Nodular sclerosis | 155 |
| Mixed cellularity | 24 |
| Nonclassic lymphocytic predominance variant | 22 |
| Classic variant | 19 |
| Lymphocytic variant | 4 |
| Stage | |
| I | 10 |
| II | 99 |
| III | 65 |
| IV | 50 |

### $^{18}$F-FDG PET/CT Acquisition

All $^{18}$F-FDG PET/CT baseline scans were performed as whole-body scans (from the base of the skull to the mid-thigh) after a 6-hour fasting period. The patients underwent blood glucose testing before administration of $^{18}$F-FDG to ensure suitably low levels, received adequate hydration before testing, and remained recumbent and silent in a warm room to ensure fewer artifacts and to minimize $^{18}$F-FDG uptake in the muscles and brown fat activation.

The PET/CT studies were obtained using the following PET/CT devices: Gemini TF64 (Philips), Gemini GXL (Philips), Gemini TF16 (Philips), Discovery LS (GE Healthcare), and Biograph TP16 (Siemens) according to the local institutional scanning protocols. The emission data were acquired for 2 to 5 minutes for each bed position (according to the available scan system) starting 60 to 90 minutes after intravenous injection of the body weight-adapted FDG dosage recommended according to the manufacturer guidelines for each scan model. Quality control procedures were performed at regular intervals for all devices with strict adherence to local protocols, manufacturer guidelines, and European Association of Nuclear Medicine guidelines.

The low-dose CT components of the PET/CT were used for both co-localization and attenuation correction of the PET emission data. Coronal, sagittal, and transverse PET/CT projections were reconstructed using iterative methods and analyzed using the manufacturers' software.

### $^{18}$F-FDG PET/CT Interpretation

At each institution, nuclear medicine physicians independently reviewed the PET/CT images, without knowledge of the BMB results, with particular attention to the bone marrow. The $^{18}$F-FDG PET/CT findings were considered positive for BMI in the presence of isolated/multiple focal uptake in the bone marrow that could not be explained by benign findings on the underlying CT images or history (eg, fractures) and/or diffuse heterogeneous BMI with or without sites of intense focal uptake superior to the liver or spleen background (in accordance with the Deauville criteria[24]). In contrast, the $^{18}$F-FDG PET/CT findings were interpreted as negative for BMI in the presence of diffuse homogeneous BMI without sites of intense focal involvement (because diffuse intense uptake has been significantly related to the presence of anemia or inflammatory process[25-27]). In doubtful cases, a second opinion was requested of the leading center of the multicenter study, and the images were reviewed by an experienced nuclear medicine physician with 13 years' experience in pediatric PET/CT.

### BMB Protocol

A unilateral posterior iliac crest biopsy and bone marrow aspirate were performed before treatment in accordance with the Italian Association Pediatric Oncology and Hematology guidelines. The BMB specimens were evaluated by experienced hematopathologists in each hospital; the results were obtained from the individual reports and were not reviewed thereafter. The BMB material was routinely fixed in formalin and embedded in paraffin and subsequently evaluated morphologically after hematoxylin-eosin and Giemsa stains. As a rule, pan-T (at least CD3 and CD5), pan-B (at least CD19 and CD20), CD30, and CD15 stains were performed in all cases.

In cases with negative BMB findings but positive PET/CT imaging findings for BMI, the final diagnosis was established by follow-up imaging ($\leq$ 12 months), including magnetic resonance imaging with dedicated T1-weighted, T2-weighted, and fat-suppressed T2-weighted sequences, bone scan and/or CT using a bone window. For cases without follow-up imaging data available, the clinical data were retrieved and reviewed.

**Figure 1** (A-C) Diffuse Fluoro-2-deoxy-D-glucose (FDG) Bone Marrow Uptake Pattern in Skeleton Reported as Doubtful Bone Marrow Finding. Bone Marrow Biopsy (BMB) Finding Was Negative. (D-F) Focal FDG Uptake Interpreted as FDG-Avid Bone Marrow Lesion, With BMB Finding Concordant With FDG Finding

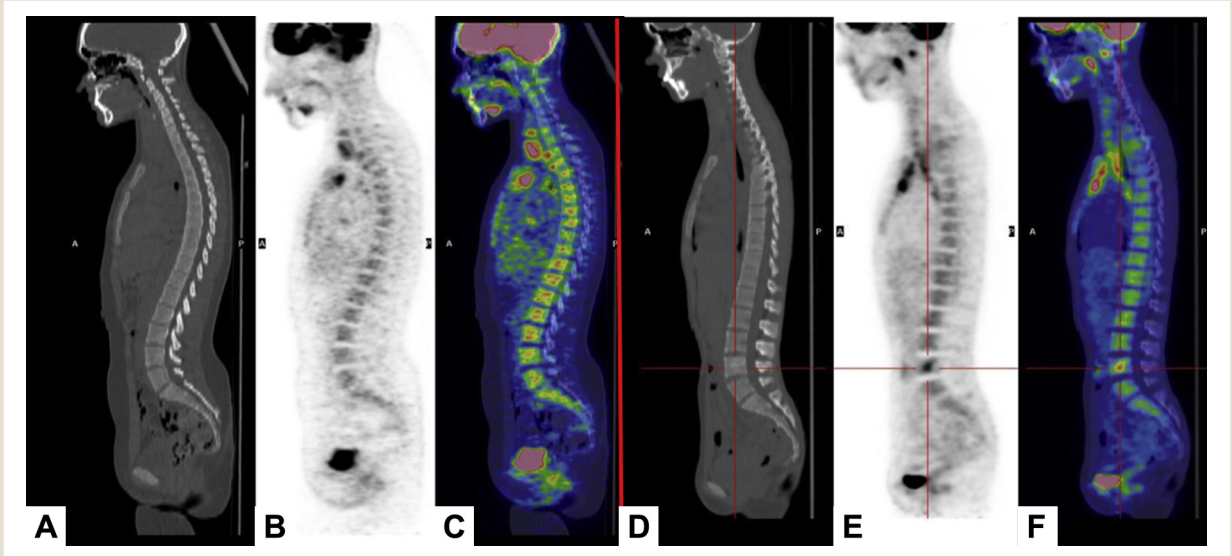

**Table 2** Agreement Between $^{18}$F-FDG PET/CT and Bone Marrow Biopsy[a]

| PET/CT Finding | BMB Finding | | Total |
|---|---|---|---|
| | Negative | Positive | |
| Negative | 192 | 1 | 193 |
| Positive | 22 | 9 | 31 |
| Total | 214 | 10 | 224 |

Abbreviations: BMB = bone marrow biopsy; CT = computed tomography; $^{18}$F = fluorine-18; FDG = fluoro-2-deoxy-D-glucose; PET = positron emission tomography.
[a]Cohen's κ agreement 0.398 ($P < .001$).

### *Statistical Analysis*

The patients were categorized according to the absence or presence of BMI evaluated by BMB and $^{18}$F-FDG PET/CT results. For the whole patient cohort, the positive and negative predictive values (PPV and NPV, respectively), sensitivity, specificity, and accuracy were calculated separately for BMB and $^{18}$F-FDG PET/CT. Agreement between the $^{18}$F-FDG PET/CT and BMB findings was assessed using Cohen's κ computation.

## Results

### *Patient Characteristics*

The data from 224 patients were analyzed. Of the 224 patients, 10 (4.4%) had stage I, 99 (44.2%) had stage II, 65 (29%) had stage III, and 50 (22.4%) had stage IV. Moreover, 155 patients (69%) had nodular sclerosis, 24 (11%) had mixed cellularity, 4 (1.7%) had lymphocytic predominance, and 19 (8.4%) had a classic and 22 (9.9%) a nonclassic lymphocytic predominance variant (Table 1).

### *Diagnostic Performance of $^{18}$F-FDG PET/CT*

The $^{18}$F-FDG PET/CT findings were reported as negative for BMI in 193 cases. Of these 193 patients, 16 showed diffuse FDG uptake in the bone marrow. Their findings, therefore, were originally reported as doubtful and were later interpreted as negative for BMI because of negative findings on follow-up imaging studies and BMB. At BMB, 1 of the 16 patients with equivocal findings had BMI (6.25%). Therefore, 192 of the 193 patients (99.48%) had negative BMB findings. Thus, the $^{18}$F-FDG PET/CT finding was truly negative for 192 patients and falsely negative in 1 patient for BMI. The $^{18}$F-FDG PET/CT finding was reported as positive for BMI in 31 patients. The BMB findings were positive in 9 of 31 patients and negative in 22 of the 31 patients. Subsequent CT, magnetic resonance imaging, and/or bone scanning confirmed the PET/CT findings in 16 of these 22 patients (Figure 1).

The remaining 6 patients were considered to have false-positive findings: 4 because of anemia (hemoglobin level < 9 g/dL) and 2 because of inflammation (erythrocyte sedimentation rate > 20 mm/h and C-reactive protein > 200 mg/L). The agreement between the PET/CT and BMB findings was considered fair; the resulting Cohen's κ for the 2 techniques was 0.4 ($P < .001$; Table 2).

The sensitivity, specificity, NPV, and PPV of $^{18}$F-FDG PET/CT for the evaluation of BMI were 96% (95% confidence interval [CI], 89%-100%), 97% (95% CI, 95%-99%), 99.5% (95% CI, 98%-100%), and 80.6% (95% CI, 65.5%-96%), respectively. In contrast, the sensitivity, specificity, NPV, and PPV of BMB were 38% (95% CI, 20%-57%), 100%, 92.5% (95% CI, 89%-96%), and 100%, respectively.

The distribution of disease stage and $^{18}$F-FDG PET/CT results are presented in Table 3. All 6 patients with false-positive PET/CT results had stage IIIA/B or IVA disease. In contrast, patients with true-positive PET/CT results had a heterogeneous disease stage (8 with stage III-IV vs. 8 with stage II; 68% vs. 32%, respectively).

Of the 16 patients with a false-positive BMB result, 8 with stage IIA/IIB disease had true-positive findings at $^{18}$F-FDG PET/CT for BMI, with a change in the treatment management. In the remaining 8 patients with stage IIIA/B (n = 5) or stage IVA/B (n = 3), no change in management was reported. In contrast, the $^{18}$F-FDG PET/CT findings were falsely positive in 6 patients with stage IIIB/IVA. All false-positive PET cases (1 with stage III and 5 with stage IV) had negative findings on follow-up imaging studies and negative BMB findings.

Only 1 patient with false-negative findings (stage IIIA) was reported for PET/CT and did not lead to an alteration in treatment planning. The patient with false-negative PET findings had positive findings on both BMP and CT imaging.

One limitation of the present study might have been that image interpretation was not centralized; however, we consistently used qualitative interpretation of imaging, evaluating the cases as positive or negative using the Deauville criteria. Also, for doubtful cases, a second opinion was requested from the leading center of the multicenter study, and the PET/CT images were reviewed by an experienced nuclear medicine physician with 13 years' experience in pediatric PET/CT.

## Discussion

The present study reports on the performance of BMB and $^{18}$F-FDG PET/CT for the identification of BMI in a series of 224 lymphoma pediatric patients. The bone marrow is an important anatomic site where lymphomatous cells can reside. The detection

**Table 3** Distribution of PET/CT Results Stratified by Clinical Stage

| PET/CT | Patients, n | Stage I | | Stage II | | Stage III | | Stage IV | |
|---|---|---|---|---|---|---|---|---|---|
| | | IA | IB | IIA | IIB | IIIA | IIIB | IVA | IVB |
| TP | 25 | 0 | 0 | 3 | 5 | 3 | 2 | 5 | 7 |
| TN | 192 | 9 | 1 | 58 | 33 | 30 | 28 | 30 | 3 |
| FP | 6 | 0 | 0 | 0 | 0 | 0 | 1 | 5 | 0 |
| FN | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Total | 224 | 10 | | 99 | | 65 | | 50 | |

Abbreviations: CT = computed tomography; FN = false-negative finding; FP = false-positive finding; PET = positron emission tomography; TN = true-negative finding; TP = true-positive finding.

**Table 4** Reported Data on $^{18}$F-FDG PET/CT and CI in Initial Staging of Disease

| Investigator | Year | Patients, n | FDG PET or PET/CT, % | | | | Conventional Imaging, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sensitivity | Specificity | NPV | PPV | Sensitivity | Specificity | NPV | PPV |
| Kabickova et al[37] | 2006 | 55 children and adolescents | 96.5 | 100 | NR | NR | 87.5 | 60 | NR | NR |
| Furth et al[38] | 2006 | 33 pediatric | 84 | 95 | 94 | 87 | 74 | 96 | 91% | 88% |
| Cheng et al[39] | 2013 | 51 pediatric (30 HL and 21 NHL) | NR | NR | NR | NR | NR | NR | NR | NR |
| London et al[40] | 2011 | 71 pediatric | 95.9 | 99.7 | NR | NR | 70.1 | 99 | NR | NR |

Abbreviations: HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

of lymphomatous BMI could be clinically relevant from several perspectives. First, identifying lymphomatous cells in the bone marrow can aid in the diagnosis of lymphoma. Second, the bone marrow assessment is a crucial part of the Ann Arbor staging system. Third, the presence of BMI can change the choice of therapy. Finally, knowing all sites of lymphomatous involvement, including bone marrow sites, allows one to monitor the effects of therapy.

BMB is an invasive procedure that allows for histologic examination of just a small bone marrow sample. In contrast, $^{18}$F-FDG PET/CT is a noninvasive method that lacks histologic material but allows for visualization of the entire marrow.[17] The distribution of $^{18}$F-FDG throughout the skeleton follows that of the red marrow,[28,29] which changes during normal aging.[30] Under normal conditions, the bone marrow will show a homogeneously low uptake of $^{18}$F-FDG, with the bone marrow appearing less intense than the liver. However, as paraphysiologic variants, increased $^{18}$F-FDG activity in the bone marrow can be observed in patients undergoing, or soon after the end of, chemotherapy (usually within 1 month), patients with hyperplasia and hematopoietic stimulation from anemia, and patients who received granulocyte colony-stimulating factor, hematopoietic growth factor, or erythropoietin.[31]

In our pediatric patient population, we found that the $^{18}$F-FDG PET/CT findings were negative for BMI in 86% of the patients. Using the reference standard of BMB, $^{18}$F-FDG PET/CT resulted in true-negative findings in 192 patients, false-negative findings in 1 patient, true-positive findings in 25 patients, and false-positive findings in 6 patients. However, the latter finding was more frequent in patients with advanced-stage disease (IIIA/B and IVA). In contrast, we found that BMB resulted in a high number of false-negative findings and, thus, had lower sensitivity than that of $^{18}$F-FDG PET/CT imaging (38% vs. 96%, respectively). Nevertheless, BMB did not result in any false-positive findings.

To date, a large amount of data have been reported on the role of $^{18}$F-FDG PET/CT in the evaluation of BMI in adult patients with HL. However, the data relative to pediatric lymphoma remain limited. In adults, $^{18}$F-FDG PET/CT has been proposed as a very sensitive method for the detection of BMI that might overcome the diagnostic yield of BMB.[32-34] Furthermore, Liden et al[35] reported that in a series of 235 adult patients, ~70% experienced procedure-related pain, with severe pain in one third of these patients. Nevertheless, at least until recently, the variation in the use or omission of BMB for patients with HL in routine clinical practice was great.[36]

In the pediatric population, some retrospective studies have demonstrated that $^{18}$F-FDG PET/CT is superior to conventional imaging modalities (ie, CT, ultrasonography, magnetic resonance imaging, bone scintigraphy) in the primary staging of lesions, for both Hodgkin and non-Hodgkin disease (Table 4).[37-40] In the initial staging of pediatric lymphoma, the $^{18}$F-FDG PET/CT findings have usually been consistent with the CT scan findings. Although its specificity is decreased when the disease is located in anatomic sites in which physiologic $^{18}$F-FDG uptake occurs,[41-43] in 9.4% to 22.6 % of the cases, $^{18}$F-FDG PET/CT could show abnormalities not displayed by other imaging methods and is useful during disease staging and treatment planning.[44,45] Overall, all studies were performed by considering all lesion sites (nodal and extranodal) without specific information about BMI. Additionally,

our study showed that $^{18}$F-FDG PET/CT was more accurate in the detection of BMI than was BMB (sensitivity, 96% vs. 38%, respectively).

Similar results were reported by Purz et al,[46] who compared the results from BMB and $^{18}$F-FDG PET/CT for the diagnosis of BMI in 175 pediatrics patients with HL greater than stage IIA. They concluded that $^{18}$F-FDG PET can safely replace BMB for routine staging in pediatric HL, especially in patients with focal BMI. Salaun et al[27] retrospectively analyzed the data from 106 pediatric and adult patients who had undergone $^{18}$F-FDG PET/CT for initial staging of HL and concluded that increased bone marrow uptake could more likely be due to inflammation than BMI and only the presence of bone foci should be interpreted as BMI on the visual $^{18}$F-FDG PET/CT evaluation. In the present study, we considered diffuse BMI with or without the presence of focal foci. The interpretation of the PET/CT scans used the Deauville criteria. These criteria are mainly used for the evaluation of the interim response to therapy[24]; however, they can also be applied at the initial staging of the disease.

In a recent study presented at the Annual Congress of the Society of Nuclear Medicine, Chen et al[47] reported that in 75 pediatric patients with diagnosed non-HL, $^{18}$F-FDG PET/CT demonstrated greater sensitivity and specificity than BMB (94% and 98% vs. 55% and 100%, respectively, for $^{18}$F-FDG PET/CT vs. BMB).

In our analysis, we found that 6 patients with stage II HL, falsely assessed by BMB, were reclassified as having stage IV after the inclusion of the $^{18}$F-FDG PET/CT findings in the diagnostic algorithm, changing both the clinical stage and the therapeutic management. In contrast, the false-positive findings from $^{18}$F-FDG PET/CT did not change either the disease stage or the therapeutic management. Furthermore, from these results, all 31 patients in our series with BMI would have been classified as having advanced-stage disease. Thus, the identification of BMI by BMB would not have altered the treatment recommendations for any of these patients. Of interest, BMB-based lymphomatous BMI has not been proved to be a major adverse predictor of outcome in patients with HL. In the cohort used in the development of the international prognostic score with advanced-stage HL, progression-free survival and overall survival for 614 patients with BMB-proven BMI (60% and 70%, respectively) were not significantly different from those for 1351 patients without BMI according to BMB (61% and 74%, respectively).[4] These findings indicate that omission of BMB would not result in a major decline in the prognostic power of the international prognostic score in patients with advanced-stage disease.[48] In early-stage disease, the incidence of BMI is extremely low, and the prognostic value of BMB in this subpopulation has, therefore, not been well documented. However, our study has shown that $^{18}$F-FDG PET/CT is superior to BMB in the identification of this subgroup of patients, changing the disease stage and patient treatment. An interest finding from our study was the modest specificity of positive BMI findings using PET/CT compared with BMB. This might reflect the highly heterogeneous environment in the bone marrow, indicating that a single-site biopsy cannot be adequate in depicting the heterogeneous characteristics of the bone marrow in pediatric HL.

However, the present study had some limitations. First, the retrospective collection of data could represent a limitation. Second, all collected cases were considered using multicenter analysis; however, the interpretation of the $^{18}$F-FDG PET/CT scans was by visual analysis rather than a semiquantitative analysis. Finally, because image-based follow-up was performed separately at each center rather than at a single center, the varied experience of the examining physicians and the different imaging protocols and facilities used might have led to different grades of reliability and accuracy of the reference standard.

## Conclusion

We have reported data on $^{18}$F-FDG PET/CT and BMB performance in the diagnosis of BMI in a series of 224 pediatric patients with HL. Our results have shown that $^{18}$F-FDG PET/CT has high diagnostic power for the evaluation of BMI involvement in HL, supporting the concept that BMB should not be systematically performed in all patients but can be reserved exclusively for patients with doubtful $^{18}$F-FDG bone marrow findings.

### *Clinical Practice Points*

- $^{18}$F-FDG PET/CT is known to have high diagnostic performance in the evaluation of BMI in adult HL.
- In our multicenter study, a similar performance for $^{18}$F-FDG PET/CT was found for pediatric HL.
- Consequently, BMB can be reserved for patients presenting with doubtful $^{18}$F-FDG PET/CT findings regarding BMI.

## Disclosure

The authors have stated that they have no conflicts of interest.

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