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Comparison of ^{18}F -FDG-PET-CT and bone scintigraphy for evaluation of osseous metastases in newly diagnosed and recurrent osteosarcoma

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Abstract

Background—Bone scintigraphy (BS) is used to detect osseous metastases in osteosarcoma. ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F -FDG-PET-CT) is being increasingly used for staging. We compared the sensitivity, specificity, and diagnostic accuracy of ^{18}F -FDG-PET-CT and BS for detecting osseous metastases in osteosarcoma.

Methods—We retrospectively reviewed 39 patients with osteosarcoma who had paired PET-CT and BS at diagnosis and/or first recurrence from 2003–2012. Imaging studies were reviewed by 2 pediatric imaging specialists who were blinded to results of the opposing modality and reference standard. Reviewers categorized lesions as benign, malignant or indeterminate. Reference standard for lesion histology was biopsy or clinical follow-up. Diagnostic performance of PET-CT, BS, and combined modalities were determined.

Results—There were 40 examinations from 39 patients and 65 distant lesions evaluated. Median age was 12 years (range 5–19 years). Four patients had 15 osseous metastases at diagnosis (2 biopsied, 13 clinically), and two had 5 osseous metastases at recurrence (1 biopsied, 4 clinically). For distant sites, sensitivity, specificity and diagnostic accuracy were 79%, 89% and 86% for PET-CT, 32%, 96%, and 77% for BS, and 95%, 85%, and 88% for PET-CT/BS combined. Sensitivity of PET-CT was superior to BS ($p=0.035$); combined imaging modalities were superior to BS ($p<0.001$) but not better than PET-CT alone ($p=0.25$). Specificity for BS approached significance

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Conflicts of Interest

The authors declare that they have no relevant conflicts of interest.

compared to combined imaging ($p=0.063$). Examination-based analysis yielded similar results between individual and combined imaging modalities.

Conclusion— ^{18}F -FDG-PET-CT demonstrated superior sensitivity over BS for detecting osseous metastases, supporting the use of ^{18}F -FDG-PET-CT for staging of osteosarcoma.

Keywords

osteosarcoma; FDG-PET; bone scan; metastatic; diagnostic

Introduction

Osteosarcoma is the most common primary pediatric bone malignancy, with an incidence of approximately 4.8 per million per year that peaks in adolescence.[1] The presence of metastatic disease is the single most important prognostic factor, with lesions primarily arising in the lung parenchyma and bone. The 10 year overall survival for localized osteosarcoma is approximately 70% compared to 25% for patients with metastatic disease. [1–3] Comprehensive imaging is necessary at the time of diagnosis and relapse in order to fully evaluate the extent of disease to ensure appropriate staging, risk stratification and subsequent risk-directed therapy.

Currently, bone scintigraphy is routinely used to detect osseous metastases in osteosarcoma and chest computed tomography (CT) is obtained to evaluate for pulmonary lesions. The use of ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F -FDG-PET-CT) to assess tumor extent in pediatric sarcomas has recently increased.[4–8] In addition to identification of distant metastatic sites, ^{18}F -FDG-PET-CT can be combined with diagnostic chest CT to identify pulmonary lesions in a single imaging study. Few studies have evaluated the performance of ^{18}F -FDG-PET-CT in comparison to standard imaging modalities, including MRI and bone scintigraphy, to identify osseous metastases.[9–12] We therefore compared the sensitivity, specificity, and diagnostic accuracy of ^{18}F -FDG-PET-CT and bone scintigraphy for detection of osseous metastases in osteosarcoma in an effort to determine if ^{18}F -FDG-PET-CT can effectively replace bone scintigraphy as the primary diagnostic staging evaluation for skeletal metastases in pediatric patients with osteosarcoma.

Methods

Patients

A retrospective review was conducted on pediatric patients diagnosed with high grade osteosarcoma at a single center tertiary pediatric oncology center between 2003 and 2012, who underwent paired ^{18}F -FDG-PET-CT and bone scintigraphy at diagnosis and/or first recurrence. A paired imaging set was defined by a maximum time interval of 1 month between ^{18}F -FDG-PET-CT and bone scintigraphy at the time of diagnosis or recurrence. Institutional Review Board approval was obtained prior to collection of data and analysis.

Image Acquisition and Analysis

Before July 13, 2011 PET-CTs at our institution were performed on a Discovery LightSpeed PET-CT scanner (GE Healthcare, Milwaukee, WI). After July 12, 2011 patients were

scanned on a GE 690 Discovery LS PET-CT scanner. Images were obtained from the skull vertex to the toes. For examinations performed on the Discovery LightSpeed scanner the CT component of the examination was performed with milliamperes/second (mAs) adjusted for body weight (maximum 90 mAs), 120 kilovoltage peak (kVp), 5 mm slice thickness and without intravenous (IV) or oral contrast material. For examinations performed on the GE 690 scanner the CT parameters were optimized to minimize radiation exposure; the kVp ranged from 80 to 120 and the mAs from 10 to 35, depending on body weight. Images were reconstructed at 3.75 mm to match the PET slice thickness. Subjects were instructed to fast for 4 hours before receiving an injection of 0.15 mCi/kg ^{18}F -FDG (55 MBq/kg, maximum 12 mCi) approximately 60 minutes before PET imaging. Emission images were acquired in 2D mode for 5 minutes per bed position. Images were reconstructed in axial, coronal, and sagittal planes and reviewed at a Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden). Images obtained on the GE 690 scanner were acquired in 3D mode from 3 to 5 minutes per bed position for the upper body, and 2 to 3 minutes per bed position for the lower extremities.

Bone scintigraphy was obtained two hours after the IV injection of 12 mCi/m² (maximum, 20 mCi) of $^{99\text{m}}\text{Tc}$ methylene diphosphonate (MDP), with a dual headed Siemens Multispec 2 (Chicago, IL), GE Infinia Hawkeye (Milwaukee, WI), or Siemens Ecam Duet gamma camera (Hoffman Estates, IL). Whole body planar images in the anterior-posterior projection were obtained allowing one minute of signal acquisition per 12 cm. body length. Additionally, images of 500,000 counts were obtained of the ribs in the anterior-posterior and both oblique projections and the skull in anterior-posterior and lateral projections. Additional images of areas of interest were obtained at the discretion of the interpreting physician. Bone scan images were reviewed at either a Hermes workstation or an Intelrad Medical Systems (Montreal, Quebec, Canada) Picture Archive and Communication workstation.

^{18}F -FDG-PET-CT and bone scintigraphy studies were independently reviewed by one pediatric radiologist (MBM) with 16 years of nuclear medicine experience and one nuclear medicine physician (BLS) with 31 years of experience. Each reviewer interpreted half of the bone scans and half of the PET-CT scans. The reviewers were aware of the patient's primary diagnosis but were blinded to the initial imaging reports, the presence or absence of metastatic lesions and the other reviewer's interpretation of the opposing modality. For both modalities reviewers scored each lesion on a 5 point scale based on the degree of radiotracer uptake and corresponding CT appearance (where applicable). Interpretation of areas with increased FDG or Tc99m activity was subjective and left to the discretion of the reviewer based on years of experience reading pediatric nuclear studies. We attempted to standardize the interpretations by using the following scoring system: 1 = increased uptake definitely due to normal physiologic or benign process, 2 = increased uptake probably due to a normal physiologic or benign process, 3 = indeterminate whether increased uptake is benign or malignant, 4 = increased uptake probably due to a malignant process and 5 = increased uptake definitely due to a malignant process.[13]

Clinical

The reference standard for the benign or malignant nature of each lesion was determined from biopsy histopathology reports, when available, or clinical follow-up; criteria for malignancy based on clinical follow-up was defined as persistent or increasing evidence of metastatic disease on subsequent imaging studies, and/or development of associated clinical symptoms including pain and swelling. Clinical reference standards were determined by chart review of clinician documentation and follow up imaging reports. Additionally, demographic data including date of birth, date of diagnosis, ethnicity, sex, location of primary tumor, presence of osseous metastatic disease, location of biopsies and histopathology results at time of diagnosis and/or recurrence were extracted from review of medical records.

Statistical Analysis

Statistical analyses were conducted using SAS v9.3 (SAS Institute Inc., Cary, NC). Sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value were determined for ^{18}F -FDG-PET-CT, bone scintigraphy, and combined imaging modalities. Both examination-based (defined as presence/absence of any osseous metastases on an imaging examination) and lesion-based analyses were performed; lesion-based analysis was conducted for all lesions combined (primary and distant sites) and for distant (non-primary) sites only. Comparisons of sensitivity and specificity between imaging modalities were conducted using Fisher exact test, exact Chi Square test, and McNemar's test where appropriate. For purposes of statistical analysis, lesions scored as 1 or 2 were considered benign and those scored as 4 or 5, malignant. The worst case scenario was imputed; by considering a score of 3 (indeterminate) to be false positive in the absence of clinical or pathological diagnosis of disease, and false negative when disease was confirmed by histopathology or clinical follow-up.[13]

Results

Patient demographics

Table 1 outlines patient demographics and clinical characteristics of 39 patients who met study inclusion criteria. The median age of patients was 12 years (range 5–19 years) and 51% were female. The most frequent primary tumor location was the femur in 22 (56%) patients. Overall, 4 of the 39 patients (10.2%) were found to have osseous metastases (n=15) at the time of diagnosis. Of patients who developed recurrence, only 1 (2.6%) was identified to have osseous metastatic lesions (n=5) at the time of recurrence; only one of the 4 patients with osseous metastases at diagnosis had paired PET and bone scintigraphy studies for review at the time of relapse.

Imaging analysis

There were a total of 40 paired examinations reviewed from the 39 patients and 105 bone lesions were evaluated. Forty lesions were identified as the location of the primary tumor (including one patient with development of local recurrence adjacent to the surgical bed), and 65 lesions were at distant sites. All primary lesions demonstrated uptake on both PET-

CT and bone scintigraphy. Of the 65 distant lesions that were evaluated, 19 were confirmed as metastatic disease by histopathology or clinical follow-up, yielding an overall total of 59 malignant lesions (primary and distant) identified on imaging, and 46 non-malignant sites. Two metastatic sites were confirmed by biopsy at the time of diagnosis, while the other metastatic sites were followed by imaging and clinical symptoms. Indeterminate lesions (a score of 3) were identified in 12 of the 105 total bone lesions, with only a single primary lesion classified as indeterminate on bone scintigraphy. The remaining 11 indeterminate lesions were detected on distant sites (PET-CT: n=5, bone scintigraphy: n= 6).

The average time between imaging studies was 14 days, with a median and mode of 7 days. Bone scintigraphy preceded PET-CT in 35 of the 40 paired exams (88%). PET-CT was completed before the initiation of chemotherapy in 37 of the 40 (92.5%) paired exams. In the one relapsed case, the patient received chemotherapy for 18 months prior to the repeat scan evaluations at the time of recurrence, with the most recent chemotherapy administered 27 days prior to PET-CT. The remaining two events, chemotherapy began 3 and 8 days prior to obtaining PET-CT.

Results of lesion-based analyses are shown in Table 2. When evaluating all sites combined (primary and distant), sensitivity, specificity and diagnostic accuracy were 93%, 89% and 91% respectively for PET-CT, 75%, 95%, and 84% for bone scintigraphy, and 98%, 85%, and 92% for PET-CT and bone scintigraphy combined. For all sites, both PET-CT and combined imaging modalities were demonstrated to have superior sensitivity to bone scintigraphy alone ($p=0.013$ and $p<0.001$, respectively). When only distant sites were considered, sensitivity, specificity and diagnostic accuracy were 79%, 89% and 86% for PET-CT, 32%, 96% and 77% for bone scintigraphy, and 95%, 85% and 88% for combined modalities. PET-CT showed significantly better sensitivity for metastatic lesions than bone scintigraphy ($p=0.035$). Sensitivity for combined imaging with PET-CT and bone scintigraphy was superior to bone scan ($p<0.001$) but was not statistically greater than PET-CT alone ($p=0.25$). Specificity for bone scintigraphy was borderline significant when compared to combined imaging ($p=0.063$) but was similar to specificity for PET-CT.

An examination-based analysis was also conducted to determine the absolute sensitivity of PET-CT and bone scintigraphy to detect the presence or absence of bony metastatic disease (Table 3). Sensitivity, specificity, and diagnostic accuracy for PET-CT were 100%, 91.4%, and 92.5% respectively, and 60%, 100%, and 95% for bone scintigraphy. The sensitivity, specificity, and diagnostic accuracy for combined imaging modalities were equivalent to those for PET-CT alone. None of the examination-based analyses comparing sensitivity, specificity and accuracy for imaging modalities reached statistical significance.

Sensitivity for bone scintigraphy for the identification of distant lesions was noted to be strikingly low (32%), with 13 false negatives reported. We reviewed the imaging characteristics of these 13 lesional sites. Nine (69%) were in the area of the growth plate, and were obscured by physiologic activity around the physis (Figure 1). Of the remaining four false negative results, 3 were rib lesions and one was located in the distal tibia (Figure 2). There were four false negative lesions on PET-CT analysis. On *post hoc* review, three of the four lesions were located in the pelvis and lumbar spine and were clearly visualized on

the repeat assessment. The fourth false negative lesion was located on the 11th rib near the costovertebral junction, and was reported as an indeterminate lesion on both PET-CT and bone scintigraphy. Subsequent imaging studies more clearly demonstrated a true metastatic lesion at this location.

Discussion

Consistent with prior reports we found that all primary osteosarcomas demonstrated increased radiotracer uptake on both ¹⁸F-FDG PET-CT and ^{99m}Tc MDP bone scintigraphy. [8, 14] We also found that, in our cohort, ¹⁸F-FDG-PET-CT was superior to bone scintigraphy for the identification of osseous metastases when evaluated on a lesional basis. Sensitivity for combined imaging modalities was not statistically different than ¹⁸F-FDG-PET-CT alone. When considering overall staging by examination, ¹⁸F-FDG-PET-CT did not demonstrate a significant sensitivity advantage when compared to bone scintigraphy. However, bone scintigraphy added no additional value to PET scan, as the sensitivity of combined imaging modalities was equivalent to ¹⁸F-FDG-PET-CT alone. Based on these results, our findings suggest that bone scintigraphy does not routinely provide additional useful diagnostic information beyond what is observed by ¹⁸F-FDG-PET-CT, and that PET-CT based imaging in combination with diagnostic CT of the chest is sufficient for standard diagnostic evaluations for osteosarcoma.

Previous studies have provided variable results for comparisons of PET imaging and bone scintigraphy for detection of bone metastases in osteosarcoma patients. An early study by Franzius and colleagues showed an inferior sensitivity for PET alone compared to bone scan.[15] However, in that study only a limited number of skeletal metastases (5 lesions) were observed in osteosarcoma patients. A subsequent larger, prospective study of pediatric patients with bone and soft-tissue sarcomas found that PET alone and conventional imaging (including bone scintigraphy) were equivalent in their detection of 31 osseous metastases in 12 osteosarcoma patients.[8]

The sensitivity of bone scintigraphy for detection of skeletal metastases has been reported to be lower than PET-CT in other studies,[9] and was markedly inferior in our analysis. A substantial number of osseous metastases in our study were observed within the growth plate region which resulted in several false negative interpretations. Intense physiologic uptake within the physis on bone scintigraphy is commonly observed in pediatric patients,[16] and may create difficulties in correctly diagnosing the presence of metastatic disease. As has been previously noted, planar imaging techniques used in bone scintigraphy and limitations of spatial resolution may further affect the ability to readily detect disease.[9, 15] The addition of single photon emission computed tomography-computed tomography (SPECT-CT) to bone scintigraphy may improve the sensitivity of this imaging technique but also adds to the patient's radiation exposure, an issue of considerable concern in the pediatric population. Whole body SPECT-CT imaging was not available at our institution during the early period of our study.

In our study, the repeat evaluation of the false negative ¹⁸F-FDG-PET-CT lesions was completed in an effort to determine a possible pattern or explanation for the false negative

results. It became evident that three of the four lesions were present on the PET-CT but were not initially recognized (type II error). This change increased PET-CT sensitivity to 98% for all sites and 95% for distant sites, with equivalent values for combined PET-CT and bone scintigraphy. This further supports the use of PET-CT alone as bone scintigraphy was less sensitive and added no additional value when combined with PET-CT.

There are no reports, such as ours, that specifically address the value of hybrid PET-CT in detecting bone metastases for osteosarcoma staging. We found that PET-CT was superior to bone scintigraphy in detecting bone metastases, and that a combination of bone scintigraphy and PET-CT did not have improved sensitivity over PET-CT alone. PET-CT offers the important benefit of a direct correlation between lesional metabolic activity and CT imaging features that can improve lesion characterization. For example, benign lesions such as non-ossifying fibromas can appear intensely FDG avid but have CT features that are nearly pathognomonic.[17] In contrast, metastatic lesions from osteosarcoma typically cause bone destruction and often contain calcification, features that are readily apparent on CT imaging. Furthermore, hybrid PET-CT provides the advantage of pairing whole-body imaging with diagnostic quality CT of the chest to assess for pulmonary nodules, which comprise the greatest percentage of metastases.[2] PET-CT imaging at diagnosis and prior to surgical resection provides an opportunity to measure therapeutic response and potential association with outcome,[18, 19] and can be utilized to identify distant skeletal metastatic disease at recurrence.[4, 18] Other novel whole-body imaging modalities including ^{18}F -sodium fluoride (^{18}F -NaF) PET imaging,[20] whole body magnetic resonance imaging (MRI),[21] and hybrid PET-MRI[22] are being evaluated for detection of distant metastases in adult and pediatric cancers, and may be worthy of inclusion in future prospective studies for comparison with ^{18}F -FDG-PET-CT and bone scintigraphy.

The strengths of our study include the use of paired examinations for patients with high grade osteosarcoma only at the specific time points of diagnosis or recurrence of disease; the inclusion of serial imaging studies for individual patients may potentially augment results via observations of the same metastatic lesions over time. Our study is also unique in its exclusive focus on osteosarcoma; several prior analyses have included both osteosarcoma and Ewing sarcoma in analysis and have frequently demonstrated disparate results between these two histologic entities.[6, 8, 15, 23] Furthermore, ^{18}F -FDG-PET-CT was obtained prior to chemotherapy initiation in 37 of the 40 (93%) paired exams, limiting the possibility of a confounding treatment induced inflammatory response at the site of disease resulting in increased ^{18}F -FDG-PET-CT uptake. This study is limited by its retrospective design of patients from a single institution; the total number of paired studies may have prevented sufficient power to detect a difference between imaging modalities at the examination level. Furthermore, the majority of metastatic lesions were not confirmed by histopathology, but were confirmed subsequently by serial imaging studies and by clinical features such as pain and swelling that were indicative of an underlying malignant process. As commented above, a type II error likely occurred in the review of some imaging examinations; while review of all imaging by both reviewers with a measure of inter-rater reliability and concordance would have strengthened results, our *post hoc* analysis suggests that our findings would be similar to those reported herein. Lastly, over the nine year period of this retrospective review, ^{18}F -FDG-PET-CT scans were obtained from two different scanners. It is possible

that differences between our results and prior studies are due to slight differences in scanners used at different institutions. However, there have been no major advances made in nuclear bone scanning or PET-CT scanning during our study period that would be expected to result in significant differences.

In conclusion, our findings indicate that ^{18}F -FDG-PET-CT is more sensitive than bone scintigraphy for the diagnosis of osseous metastases in pediatric patients with osteosarcoma. Presently, the Children's Oncology Group Bone Tumor Committee recommends, but does not require, the use of FDG-PET imaging for the evaluation of primary and metastatic sites in osteosarcoma, and PET-CT is only obtained on prospective collaborative trials as an optional examination at the discretion of the treating physician.[24] Based on our findings and the utility of PET-CT imaging to identify soft tissue and pulmonary metastases, we believe that ^{18}F -FDG-PET-CT may be able to replace bone scintigraphy as a standard imaging evaluation (along with computed tomography of the chest) for staging of newly diagnosed and recurrent osteosarcoma.

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Abbreviation List

BS	Bone scintigraphy
FDG	Fluorodeoxyglucose
PET	Positron emission tomography
CT	Computed tomography
MRI	Magnetic resonance imaging
mA	Milliampere
kVp	Kilovoltage peak
IV	intravenous
mCi	milliCurie
kg	kilogram
MBq	megabecquerel
MDP	Methylene diphosphonate
cm	centimeter

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Figure 1.

(A) ^{18}F FDG-PET-CT of a 9 year old female with primary osteosarcoma of the right distal femur (curved arrow). Image demonstrates metastatic osseous lesion in the left proximal tibia at the site of the growth plate (straight arrow). (B) Bone scintigraphy of the same patients at the time of diagnosis. The metastasis in the left tibial growth plate was not detected. (C) The metastatic lesion (arrow) is confirmed by T1 weighted magnetic resonance imaging.

Figure 2.

(A) ^{18}F FDG-PET-CT of an 18 year old female with primary osteosarcoma of the right femur presenting with recurrent disease. Image demonstrates both local recurrence (curved arrow), along with a new metastatic osseous lesion in the left tibia (straight arrow). (B) Bone scintigraphy of the same patient at the time of disease recurrence does not clearly identify the presence of osseous metastasis in the left tibia.

Table I

Clinical and diagnostic characteristics of patients with newly diagnosed or recurrent osteosarcoma with paired ^{18}F -FDG-PET-CT and bone scintigraphy examinations.

Number of patients	39
Male	19
Female	20
Age at diagnosis (range)	12 years (5–19 years)
Location of primary tumor	
Femur	22
Tibia	9
Humerus	5
Fibula	1
Radius	1
Mandible	1
Osseous metastases at diagnosis (Clinical)	
No	35
Yes	4
Number of lesions evaluated	105
Primary	40 *
Distant	65
Number of confirmed metastatic sites	20
At initial diagnosis (n=4 patients)	15
Histopathology	2
Clinical follow-up	13
At time of relapse (n=1 patient)	5
Histopathology	–
Clinical follow-up	5

* 39 primary tumors; one local recurrence at the site of the primary tumor identified

Table II

Lesion-based analysis of PET-CT, BS and combined modalities in detecting disease.

	TP	FP	FN	TN	Sen (%)	Spec (%)	DA (%)	PPV (%)	NPV (%)
All sites (n= 105)									
PET	55	5	4	41	93.2 (p=0.013)	89.1	91.4	91.7	91.1
BS	44	2	15	44	74.6	95.7	83.8	95.7	74.6
PET+BS	58	7	1	39	98.3 (p<0.001)	84.8	92.4	89.2	97.5
Distant only (n= 65)									
PET	15	5	4	41	78.9 (p=0.035)	89.1	86.2	75	91.1
BS	6	2	13	44	31.6	95.7	76.9	75	77.2
PET+BS	18	7	1	39	94.7 (p<0.001)	84.8	87.7	72	97.5

Abbreviations: TP = true positive; FP = false positive; FN = false negative; TN = true negative; Sen = sensitivity; Spec = specificity; DA = diagnostic accuracy; PPV = positive predictive value; NPV = negative predictive value; PET = positron emission tomography; BS = bone scintigraphy.

Examination-based analysis of PET-CT, BS and combined modalities in detecting osseous metastases. (n=40 exams)

Table III

	TP	FP	FN	TN	Sen (%)	Spec (%)	DA (%)	PPV (%)	NPV (%)
PET	5	3	0	32	100	91.4	92.5	62.5	100
BS	3	0	2	35	60	100	95	100	94.6
PET+BS	5	3	0	32	100	91.4	92.5	62.5	100

Abbreviations: TP = true positive; FP = false positive; FN = false negative; TN = true negative; Sen = sensitivity; Spec = specificity; DA = diagnostic accuracy; PPV = positive predictive value; NPV = negative predictive value; PET = positron emission tomography; BS = bone scintigraphy.