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Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography for Osteochondromas Utilizing a Triple-Time Point Protocol

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Abstract

Purpose: The purpose of this study was to assess solitary osteochondroma and hereditary multiple osteochondral exostoses (HMOCE) utilizing FDG PET and a triple time point protocol. **Methods:** Seven patients were consented and recruited for PET evaluation of presumed benign osteochondroma. Following injection of 15 mCi of FDG, the lesion(s) of interest was imaged with PET-CT at 45 minutes post injection, whole body at 50 minutes post, and lesion of interest at 95 minutes post injection. A maximum standardized uptake value (SUV_{max}) was obtained for the lesion(s) of interest at each time point, and an SUV_{Δ} was calculated for each lesion of interest from the first time point to the third time point. **Results:** 16 lesions from 7 patients were included in the study. Mean SUV_{max} for all 3 time points was 1.04 with a standard deviation of 0.50 (range 0.3 - 2.2). The mean SUV was 0.096 with a range of 0 - 0.4. Among the 3 patients with histologically confirmed osteochondromas, mean SUV_{max} was 0.67, with standard deviation of 0.23 and range of 0.3 to 1.0. The mean $SUV_{\Delta 13}$ was 0.081 (range 0 - 0.4), mean $SUV_{\Delta 12}$ was 0.10 (0 - 0.3), and mean $SUV_{\Delta 23}$ was 0.11 (range 0 - 0.4) ($p = 0.74$). **Conclusion:** Benign lesions were found to not have progressively increasing uptake on multiple time point FDG PET. Until chondrosarcomas are evaluated using triple time point ^{18}FDG PET, its applicability in the evaluation of osteochondroma versus malignant change remains uncertain.

Keywords: Positron Emission Tomography, Osteochondroma, Chondrosarcoma, Fluorine-18 Fluorodeoxyglucose

1. Introduction

Osteochondromas are the most common benign cartilagenous tumors, typically presenting during the second decade and often diagnosed as incidental radiological findings [1]. Lesions may be solitary or multiple as in hereditary multiple osteochondral exostoses (HMOCE), which is an autosomal dominant disorder characterized by two or more exostoses. The primary concern for patients with osteochondromas or HMOCE is the risk of malignant transformation, with described rates of less than 1% and 5% to 25% respectively [2-4]. Asymptomatic lesions require observation and can be closely monitored for signs of malignant change.

The key to surveillance is early detection of malignant transformation; however this is a daunting task especially in HMOCE, where multiple lesions limits conventional imaging modalities and continued growth beyond skeletal maturity may occur [5,6]. While several imaging modalities including radiographs, ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) are used for initial evaluation, F18 fluoro-2-deoxy-glucose (^{18}FDG) positron emission tomography (PET) can provide additional physiologic information. ^{18}FDG shares an intracellular transport mechanism with glucose, resulting in increased uptake in metabolically active cells [7].

As a result, ^{18}FDG PET has become increasingly re-

lied upon for diagnosis and staging of numerous neoplastic processes including lung, breast, and colon cancer [7]. Several studies have also evaluated the diagnostic value of PET in a variety of musculoskeletal lesions [3,5,8-10], and have reportedly distinguished benign from malignant musculoskeletal lesions with a sensitivity of 90.9% to 91.7% and specificity of 100% in trials involving 29 and 45 patients respectively [11,12]. The diagnostic criteria of these studies are largely based upon standardized uptake values (SUV) obtained at a single time point of 60 minutes following injection of ^{18}FDG, despite ^{18}FDG's half-life of approximately 110 minutes. Additional studies have evaluated the use of dual time point ^{18}FDG PET, noting additional diagnostic accuracy compared to standard single time point ^{18}FDG PET scanning [13,14]. The purpose of this study is to assess and describe the inherent characteristics of ^{18}FDG PET utilizing triple time points in solitary osteochondroma and HMOCE. We hypothesize that the addition of a third time point will result in better characterization of osteochondromas based on the half-life of ^{18}FDG.

2. Methods

Approval was obtained from the Institutional Review Board prior to beginning of the study. From 2008 to 2010, all patients with suspected or diagnosed osteochondroma or chondrosarcoma, including patients with recurrence, were eligible for participation in the trial. Pregnant and/or lactating women, infants and children under 12 years of age and those subjects who would not be able to tolerate the exam were excluded from the study. In addition, diabetic patients were also excluded to prevent interference with quantitation of FDG metabolism. Patients participating in the study were scheduled for an FDG PET-CT scan utilizing a triple time point protocol.

Following history, physical exam, and conventional imaging studies such as plain radiographs, MRI or CT, patients underwent a triple time point FDG PET-CT scan. Before undergoing FDG PET-CT study, patients were instructed to fast for 4 hours prior to the scan and blood sugar levels were checked to ensure fasting levels of <160 mg/dL. Intravenous access was obtained and 15 mCi of FDG was injected intravenously in standard fashion. Low dose CT scans were performed using 120 kV and 50 - 100 mAs for adults and 20 - 30 mAs for children. Field-Of-View (FOV) was 600 mm, with 5 mm slices acquired in increments of 5. Collimation was separate on all scanners. Pitch and rotation were 0.813 and 0.5, respectively. Imaging matrix was 512 × 512. After injection, three PET-CT scans were obtained. The first scan was a regional scan that started approximately 45 minutes (T_1) post injection and proceeded for 5 minutes over the tumor(s) of interest. The second scan was a whole body scan (top of head to toes) and started approximately 50 minutes (T_2) post injection and proceeded for approximately 30 minutes. The third scan was a regional scan that started approximately 95 minutes (T_3) post injection and proceeded for 5 minutes over the tumor(s) of interest. All images were acquired using a Philips GEMINI TF PET-CT system (Netherlands) and reconstructed utilizing an iterative reconstruction algorithm with low-dose CT attenuation correction. Images were analyzed on a Philips workstation in the transaxial, coronal and sagittal planes. A maximum standardized uptake value (SUV_{max}) was obtained for the tumor(s) of interest within the field of view at each time point ($SUV_{max}T_1$, $SUV_{max}T_2$, $SUV_{max}T_3$) using the equation below.

SUV = tissue activity (mCi/mg)/[injected FDG dose (mCi)/body weight (kg)]

Additionally, SUV deltas ($SUV_{\Delta 12} = SUV_{max}T_1 - SUV_{max}T_2$, $SUV_{\Delta 13} = SUV_{max}T_1 - SUV_{max}T_3$, $SUV_{\Delta 23} = SUV_{max}T_2 - SUV_{max}T_3$) were calculated for the tumor(s) of interest. A SUV_{max} was measured for all other tumors seen in the whole body scan at T_2.

When possible, diagnosis was confirmed histologically. In the majority of cases osteochondromas exhibit normal-appearing medullary bone and marrow fat/elements surrounded peripherally, by a variable thickened cartilagious cap. The chondrocytes in the cartilage may be solitary or clustered and may undergo enchondral ossification resembling the epiphyseal growth plate.

The mean, range and standard deviation of the SUV_{max} and SUV measurements were calculated for both osteochondromas and HMOCE lesions, and compared using Wilcoxon rank sum test, and Kruskal-Wallis test.

3. Results

Seven patients with a total of 16 discrete lesions were enrolled in the study, of which 3 patients had solitary osteochondromas and 4 patients had HMOCE (**Table 1**, **Figure 1**). The mean SUV_{max} from all 3 time points was 1.04 with a standard deviation of 0.50 and range of 0.3 - 2.2 (**Table 2**). The mean $SUV_{\Delta 13}$. was 0.081 with a range of 0 - 0.4, the mean $SUV_{\Delta 12}$ was 0.10 with a range of 0 - 0.3, and the mean $SUV_{\Delta 23}$. was 0.11 with a range of 0 - 0.4 ($p = 0.74$). Among patients with HMOCE, 3 patients had 3 lesions and 1 patient had 4 lesions for a total of 13 lesions in the study. There was no difference in mean SUV_{max} among patients with solitary lesions (0.96 ± 0.12) compared to patients with HMOCE (1.06 ± 0.55) ($p = 0.68$). The mean SUV_{Δ} among patient with solitary lesions and HMOCE was 0.022 and 0.11 respec-

Table 1. Patient demographic characteristics.

Age: yrs	35.1 ± 9.8
Total: n	7
Male: n (%)	4 (57%)
HMOCE: n (%)	4 (57%)
Solitary Osteochondroma: n (%)	3 (43%)

HMOCE = hereditary multiple osteochondral exostoses.

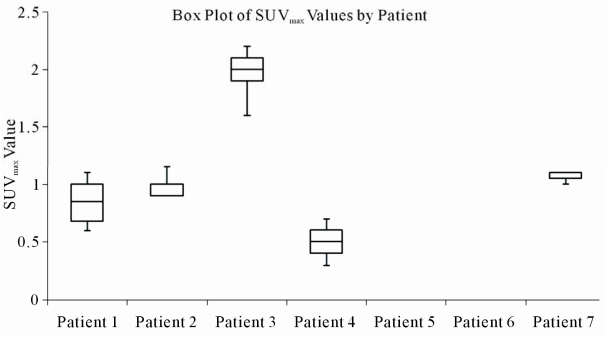


Figure 1. Box plot of SUV_{max} values by patient.

tively (p = 0.02).

Tumors were histologically confirmed to be benign in 3 patients who underwent surgical resection secondary to pain (**Figures 2** and **3**). The mean SUV_{max} among patients with confirmed benign lesions was 0.67, with standard deviation of 0.23 and range of 0.3 to 1.0.

Of note, patient 3 had an SUV ≥ 2 with a range of 1.6 to 2.2, and there is no histopathological correlation. However, the patient remained clinically stable during 2-years follow-up.

4. Discussion

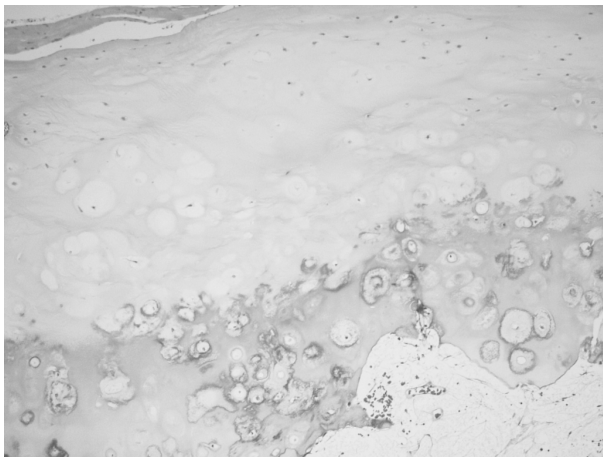
While advanced or large malignancies are readily identified using conventional radiographic methods, the early detection of malignant transformation of osteochondromas remains a clinical dilemma. Although historically a cartilage cap of >1 cm was thought to indicate malignant potential, large benign caps have been described particularly in patients with HMOCE whose lesions may continue to grow beyond skeletal maturity. Bone scans are nonspecific and their ability to distinguish malignant from benign entities is poor. Previous studies have evaluated the diagnostic utility of positron emission tomography in musculoskeletal lesions, as well as in lung, breast, and colon cancer [3,5,7-10]. These studies suggested malignant transformation with maximal standardized uptake values greater than 2.0 or 3.0, while more recent studies noted improved diagnostic accuracy utilizing dual time point PET scans compared to single time point scanning [13,14].

Aoki *et al.*, investigated the results of PET scan between benign cartilaginous tumors and chondrosarcoma and found that the average SUV_{max} for the chondrosarcoma group to be 2.23 ± 0.80, with a range from 1.3 to 3.3 [8]. Based on these findings, a SUV of 1.3 was suggested as a possible cutoff for differentiating benign from malignant cartilaginous tumors. Similarly, Feldman *et al.* [11] found that an average SUV_{max} of 2.0 differentiated between benign and malignant lesions with a sen-

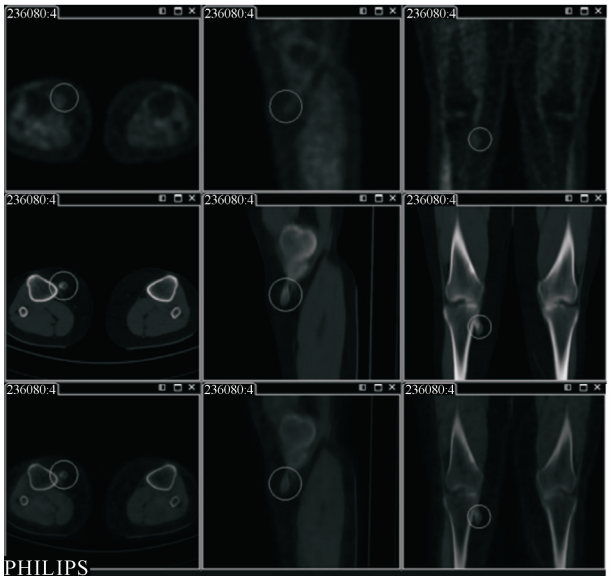
Table 2. SUV_{max} values by timepoint & SUV.

	Time	Lesion 1	Lesion 2	Lesion 3	Lesion 4
Patient 1	T_1	1	0.6	1.1	0.8
	T_2	0.9	0.6	1	0.8
	T_3	0.9	0.6	1	0.7
	$SUV_{\Delta 13}$	0.1	0	0.1	0.1
Patient 2	T_1	1	0.9	1.2	
	T_2	0.9	1	1	
	T_3	1	0.9	1.2	
	$SUV_{\Delta 13}$	0	0	0	
Patient 3	T_1	2.1	1.9	1.8	
	T_2	2.1	2.2	1.6	
	T_3	2	1.9	2	
	$SUV_{\Delta 13}$	0.1	0	0.2	
Patient 4*	T_1	0.6	0.7	0.5	
	T_2	0.7	0.5	0.4	
	T_3	0.5	0.3	0.4	
	$SUV_{\Delta 13}$	0.1	0.4	0.1	
Patient 5*	T_1	0.8			
	T_2	0.8			
	T_3	0.8			
	$SUV_{\Delta 13}$	0			
Patient 6*	T_1	1			
	T_2	1			
	T_3	1			
	$SUV_{\Delta 13}$	0			
Patient 7	T_1	1			
	T_2	1.1			
	T_3	1.1			
	$SUV_{\Delta 13}$	0.1			

*Tumors were histologically confirmed to be benign. Only the $SUV_{\Delta 13}$ is listed for each lesion due to the non-significant difference between the $SUV_{\Delta 13}$ values.

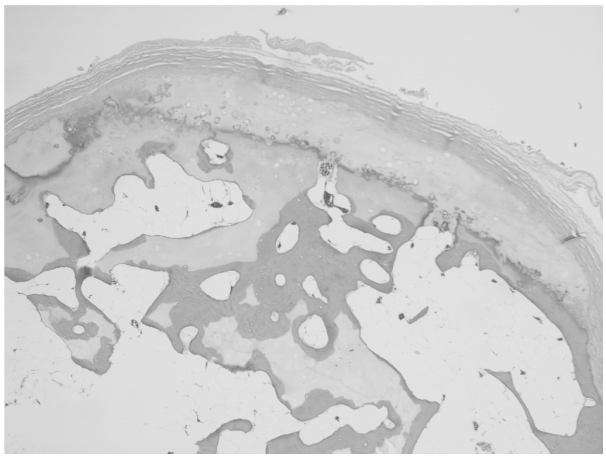


(a)

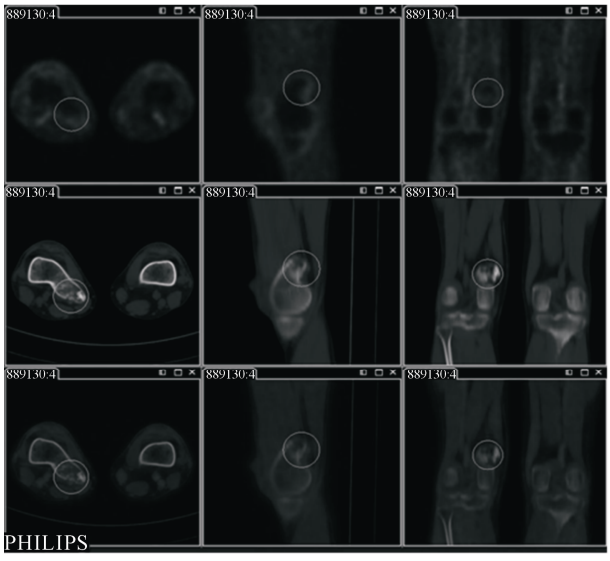


(b)

Figure 2. 19-year-old female with solitary right medial tibia osteochondroma that was surgically resected due to pain. (a) Osteochondroma on hematoxylin and eosin stain (20×) demonstrating calcification of the cartilage cap, before going enchondral ossification; (b) PET (first row), CT (second row) and fused (third row) displayed in the transanxial, sagittal and coronal planes showing the right medial tibia osteochondroma (circle) at T_2 where SUV_{max} = 0.8.



(a)



(b)

Figure 3. 25-year-old man with single right medial femur osteochondroma that was surgically resected due to pain. (a) Osteochondroma on hematoxylin and eosin stain (10×) with hyaline cartilage cap covered by fibrous perichondrium. The superficial cancellous bone of the stalk is undergoing enchondral ossification; (b) PET (first row), CT (second row) and fused (third row) displayed in the transanxial, sagittal and coronal planes showing the right medial femur osteochondroma (circle) at T_2 where SUV_{max} = 1.0.

sitivity of 91.7% and a specificity of 100%. Additionally, all aggressive lesions had a SUV_{max} > 2.0. More recent literature investigated the mean maximal standard uptake values in benign cartilaginous tumors, grade-1 chondrosarcomas, and high-grade chondrosarcomas [10]. Their results did not show a significant difference between benign cartilage tumors (1.147 ± 0.751), and grade-1 chondrosarcomas (0.898 ± 0.908), but did show a significant difference between low-grade (benign and grade-1 chondrosarcoma) and high-grade chondrosarcomas (6.903 ± 5.581). These results demonstrate the difficulty and radiological limitations in determining malignant transformation of benign cartilaginous tumors from low-grade chondrosarcomas.

The current study demonstrates concordant results with those previously published in regards to maximum standardized uptake values in benign osteochondromas. The previous cutoff of 2.0 is supported in our study when examining the SUV_{max} in those with confirmed histologic benign lesions, with a range from 0.3 to 1.1 (mean 0.67 ±

0.24). Furthermore, our study demonstrates that benign lesions do not have progressively increasing uptake on multiple time point FDG PET unlike metabolically active malignant lesions as shown in the prior studies. Thus, for benign osteochondromas, the addition of a triple time point did not provide additional clinical utility.

The use of imaging modalities such as ultrasound, CT or MRI to differentiate benign osteochondromas from secondary chondrosarcomas is well described in the literature [15-18]. Cartilage cap thickness is commonly used as a marker of malignant transformation as malignant transformation typically occurs with cartilage cap thicknesses greater than 1 - 3 cm [15]. In a study of 101 patients, 34 of which had secondary chondrosarcomas, Bernard *et al.* [19] suggested a 2 cm cutoff based on their described imaging technique to distinguish benign osteochondromas from secondary chondrosarcomas. The sensitivity and specificity of a 2 cm cutoff was 100% and 98% for MRI and 100% and 95% for CT, which are encouraging results and which arguably may support this method of evaluation as the current standard of care [19].

Limitations of our study include a small sample size as well as a lack of malignant tumors for comparison and characterization. Even though maximum standardized uptake values utilizing triple time points were similar in histologically confirmed benign lesions, we were unable to make a similar conclusion for low or high-grade chondrosarcomas, which are inherently more metabolically active. In addition, the natural history of osteochondromas and their malignant transformation rate is quite rare, making it difficult to evaluate the use of PET scan to differentiate benign osteochondroma from chondrosarcoma at a single institution.

In conclusion, our preliminary study demonstrated that maximum standardized uptake values utilizing triple time point FDG PET for histology confirmed osteochondromas showed no difference to previously published values utilizing single or dual time point protocols. The clinical utility of triple time point protocol based on the half-life of FDG in chondrosarcomas, which are inherently more metabolically active, remains unknown. A multi-institutional study would provide increased numbers and the ability to detect the rare transformation of osteochondromas to chondrosarcomas. This may ultimately enable investigators to determine reliable and relevant SUV cutoff points allowing for the distinction of benign osteochondromas from low-grade chondrosarcomas.

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