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Original Article

^{18}F-FDG PET/CT imaging features of lipomatous tumors

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Abstract: The objective was to evaluate the ^{18}F-FDG PET/CT characteristics of lipomatous tumors, and examine features helpful in differentiating benign from malignant tumor subtypes. Patients undergoing ^{18}F-FDG PET/CT from 01/2005 to 03/2018 with subsequent pathologically confirmed liposarcoma, lipoma, or hibernoma were retrospectively reviewed with IRB approval. A variety of imaging features, including metabolic activity and tumor morphology were noted. 67 tumors were included: 13 lipomas, five hibernomas, 16 atypical lipomatous tumors, 16 dedifferentiated liposarcomas, 15 myxoid liposarcomas, and two pleomorphic liposarcomas. There were 42 males and 23 females, mean age 58.8 ± 13.6 years. Mean SUVmax of lipomas measured 0.8 ± 0.2, atypical lipomatous tumors 2.3 ± 1.2, myxoid liposarcomas 3.0 ± 1.0, hibernomas 11.9 ± 8.4, pleomorphic liposarcomas 13.5 ± 2.9, and dedifferentiated liposarcomas 16.3 ± 11.4. There was no significant difference in metabolism between benign and malignant subtypes (SUVmax 3.9 ± 6.5 versus 7.6 ± 9.2, P = 0.13). There was a significant difference in metabolism between low- and high-grade liposarcoma (SUVmax 2.5 ± 1.2 versus 12.8 ± 10.8, P = 0.0001). 10/13 lipomas, 2/5 hibernomas, and 2/16 atypical lipomatous tumors had no internal soft tissue content. There are overlapping ^{18}FDG PET/CT features of benign and malignant lipomatous tumors. While liposarcoma grade correlates with SUVmax, malignant lesions (myxoid liposarcomas and atypical lipomatous tumors) may present with low FDG uptake and benign lesions (hibernomas) may demonstrate high metabolic activity. In some instances, a combination of metabolic and morphologic characteristics may narrow the differential diagnosis, or even be diagnostic.

Keywords: PET/CT, liposarcoma, atypical lipomatous tumor, lipoma

Introduction

Lipomatous tumors comprise a wide variety of benign and malignant lesions, some with overlapping imaging features. Because biologic behavior and treatment approach vary with tumor type, accurate differentiation is important. To date, most research has focused on magnetic resonance imaging (MRI) features of lipomatous tumors [1-19], particularly in evaluating imaging characteristics useful in differentiating lipomas from low-grade malignant atypical lipomatous tumors (ALTs). Imaging features that favor a diagnosis of ALT over lipoma include lesion size >10 cm, thick irregular septa (>2 mm), areas of non-adipose tissue or nodules (especially >1 cm), and fat content less than 75% [7, 12, 18]. Despite these imaging criteria, distinguishing these two tumors on MRI remains problematic [11, 15], as lipomas can contain areas of non-lipomatous signal due to fat necrosis [5] or cystic degeneration, and ALTs may present as completely fatty masses with no or only thin septa [20].

In general, liposarcomas demonstrate increasing heterogeneity and enhancing nonlipomatous components with increasing grade, and some exhibit imaging features that allow differentiation from other liposarcoma subtypes. For example, the myxoid component of myxoid liposarcomas (ML) characteristically demonstrates T1 signal less than skeletal muscle, T2 signal approaching fluid intensity, and lacy or linear and amorphous enhancement [10, 16]. Dedifferentiated liposarcomas (DDL) often manifest a bimorphic appearance, including one component with imaging features of ALT and a dedifferentiated component with imaging features that reflect the type of dedifferentiation, which may be osteosarcoma, chondrosarcoma, or undifferentiated pleomorphic sarcoma, among others [4, 19]. Among benign variants, hibernomas may show prominent intratumoral vessels, which can be a distinguishing feature [3, 17]. Computed tomography (CT) can also play a role in evaluating lipomatous tumors, because as one might expect, features such as thickened septa, nonlipomatous internal components,

and vessels may also be depicted by CT [7, 10, 21].

There has been considerably less literature regarding the FDG PET features of lipomatous tumors. Not only can FDG PET provide a noninvasive evaluation of tumor metabolism and thus biology, but lipomatous tumors are frequent incidental findings on oncologic PET, and therefore, knowledge regarding their imaging features and how to approach them is important. Prior PET studies have demonstrated a correlation between SUVmax and liposarcoma grade [22, 23]. However, these were performed with two-dimensional PET without CT attenuation correction, and therefore lacked any morphologic information that may be gained by the availability of CT images. Our goal was therefore to evaluate the ^{18}F-FDG PET/CT characteristics of a range of lipomatous tumors, and examine features helpful in differentiating benign from malignant lipomatous tumor subtypes.

Materials and methods

Institutional review board approval was obtained for this study, which was in compliance with the Health Insurance Portability and Accountability Act. Our institutional FDG PET/CT database was searched for patients with pathologically proven liposarcoma, lipoma or hibernoma between January 2005 and March 2018. Patients that had treatment (surgery, radiation therapy, chemotherapy) prior to PET imaging were excluded. All PET/CTs were analyzed by a board-certified radiologist with 5 years' experience in MSK MRI and PET/CT, and a musculoskeletal imaging fellow, both unblinded to the pathologic diagnosis. MIM software (MIM Software Inc., Cleveland, OH, USA) was used for PET/CT analysis. Anatomic location, relationship to the superficial muscular fascia, three-dimensional size, presence of intralesional fat and/or soft tissue component, and presence of calcification were noted and recorded. Several semi-quantitative features including SUVmax and CT attenuation were recorded. SUVmax was determined by creating a volume of interest incorporating the gross neoplasm volume. CT attenuation was determined by placing the largest 2D ROI possible within the confines of the lesion on any plane (axial, coronal, or sagittal).

PET/CT technique

PET/CTs (Discovery RX, 690, or 710; GE Healthcare, Waukesha, WI, USA) were performed according to the standard clinical protocol. PET/CT machines were regularly cross-calibrated against a dose-calibrated phantom standard to ensure consistency and reproducibility and activity recovery coefficients monitored for stability per institutional quality assurance protocol and American College of Radiology (ACR) accreditation guidelines. Weight, height, and blood glucose levels were recorded for all patients. All patients had a blood glucose level of less than 200 mg/dl and were injected with 10-15 mCi of 18F-FDG, with an incubation period of 60-70 min. The amount of injected radioactivity was routinely measured by means of quantifying the radioactivity within the syringe before and after injection or with an automated injection system (Medrad® Intego PET infusion system, Bayer Healthcare, Whippany, NJ, USA). Patients were imaged covering at least from orbits to midthighs, with coverage adjusted depending on clinical indication (3D OSEM without TOF, two iterations, Gaussian post-filter smoothing with a full width at half maximum of 7 mm, 128×128 matrix, 3-5 min per bed position depending on BMI). Low-dose helical CT images were obtained for attenuation correction and anatomic localization. CT images were acquired with a tube voltage of 140 kVp. Tube current was set using automatic exposure control range between 10 mA and 180 mA. With a tube rotation time set at 0.5 seconds, maximum tube current was 90 mAs. CT slice thickness was 5 mm, and CT slice interval of 3.27 mm was set to match that of the PET system. Detector pitch was 1.

Statistical considerations

Statistical analysis was performed using JMP software (JMP Pro, version 11.2.1, SAS Institute Inc). Continuous variables are expressed as mean ± SD. Categorical variables are presented with absolute and relative frequencies. *P* values for between-group comparisons of continuous data were calculated from Kruskal-Wallis one-way analysis of variance (ANOVA). For categorical variables, *p* values were computed from contingency tables using Fisher's exact test. Statistical significance was established for *p* values of less than 0.05.

Table 1. Summary of the mean metabolic activity (SUVmax) of the lipomatous tumor subtypes

Tumor Type	Mean SUVmax
Lipoma	0.8 ± 0.2
ALT	2.3 ± 1.2
ML	3.0 ± 1.0
Hibernoma	11.9 ± 8.4
PL	13.5 ± 2.9
DDL	16.3 ± 11.4

Results

Sixty-seven tumors in sixty-five patients (one patient had synchronous hibernomas and another synchronous lipomas) were identified including 13 lipomas, five hibernomas, 16 ALTs, 16 DDLs, 15 MLs (nine grade 1 tumors and six grade 2 or 3 tumors), and two pleomorphic liposarcomas (PLs). One of the hibernoma patients [24] and several of the myxoid liposarcoma patients [25] have been previously reported. There were 42 males and 23 females. The overall mean patient age was 58.8 ± 13.6 years. Mean age for patients with each tumor type were as follows: lipoma, 62.1 ± 10.9; hibernoma, 59.8 ± 14.6; ALT, 62.8 ± 8.8; DDL, 61.6 ± 11.0; ML, 48.3 ± 18.6; and PL, 60.5 ± 6.4. Patients with ML had a lower mean age (48.3 ± 18.6 years) compared with ALT (62.8 ± 8.8 years; P = 0.006), lipoma (62.1 ± 10.9 years; P = 0.007), and DDL (61.6 ± 11.0 years; P = 0.006). Otherwise, there were no significant differences in between-group age comparisons. Forty-one tumors were located in the torso, 21 in the lower extremities, three in the upper extremities, and two in the head and neck.

Metabolic activity

Average SUVmax values of the different tumor subtypes (**Table 1**) were as follows: lipoma, 0.8 ± 0.3 (range 0.5-1.3); hibernoma, 11.9 ± 8.4 (range 3.3-24.3); ALT, 2.3 ± 1.2 (range 0.8-3.9); DDL, 16.3 ± 11.4 (range 3.4-39.6); ML, 3.0 ± 1.0 (range 1.1-5.2); and PL, 13.5 ± 2.9 (range 11.4-15.5). There was no statistically significant difference between the mean SUVmax values of lipoma and ALT (P = 0.52), lipoma and ML (P = 0.35), or between ALT and ML (P = 0.75). Similarly, there was no statistically difference between the mean SUVmax values of hibernoma and DDL (P = 0.16), hibernoma and PL (P = 0.76), or between DDL and PL (P = 0.53). Between-group comparison of mean SUVmax values was otherwise significantly different: DDL and lipoma (P<0.001), ALT (P<0.001), and ML (P<0.001); PL and lipoma (P<0.01), ALT (P = 0.02), and ML (P = 0.03); and hibernoma and lipoma (P = 0.001), ALT (P = 0.003), and ML (P = 0.007). As such, the lesions generally clustered into those with low metabolic activity (comprising lipoma, ALT, and ML), and those with high metabolic activity (hibernoma, DDL, and PL). There was a statistically significant difference between the mean SUVmax values of the "low metabolic activity" and "high metabolic activity" groups (2.1 ± 1.3 vs. 15.1 ± 10.2, respectively; P≤0.0001). Conversely, when considering benign lipomatous tumors (lipoma and hibernoma) and malignant lipomatous tumors (ALT, ML, DDL and PL) there was no statistically significant difference in the metabolic activities of the two groups (SUVmax 3.9 ± 6.5 vs. 7.6 ± 9.2, respectively, P- = 0.13). If hibernomas were excluded from this analysis, there was a statistically significant difference (P = 0.01) between lipomas (SUVmax 0.8 ± 0.2) and liposarcomas including ALT, DDL, ML, and PL subtypes (SUVmax 7.5 ± 9.2). There was also a significant difference between the mean metabolic activities of the 24 low grade (ALT and grade 1 ML) and 24 high grade (DDL, PL, and grade 2 or 3 ML) malignant lipomatous tumors (SUVmax 2.5 ± 1.2 and 12.8 ± 10.8, respectively, P = 0.0001).

Morphologic features

Average CT attenuation of the tumor subtypes were as follows: lipoma, -87.0 ± 17.1 HU; hibernoma, -60.9 ± 21.0 HU; ALT, -49.3 ± 37.9 HU; DDL, 26.7 ± 12.6 HU; ML, 14.0 ± 10.5 HU; and PL, 25.2 ± 12.9 HU. As such, lesions clustered into those with positive (DDL, ML and PL) and negative (ALT, hibernoma, lipoma) average CT attenuation. There was no significant difference between the average CT attenuation of DDL and ML (P = 0.122), DDL and PL (P = 0.92), or between ML and PL (P = 0.51). Similarly, no significant difference was seen between the CT attenuation of hibernoma and ALT (P = 0.31). Otherwise, between group CT attenuation was different for the remaining tumors: lipoma and DDL (P<0.0001), PL (P<0.0001), ML (P< 0.0001), ALT (P<0.0001), hibernoma (P<0.03);

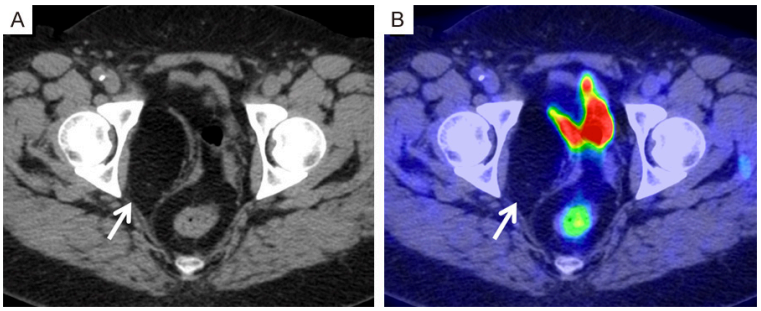

Figure 1. 54-year-old female with a pelvic lipoma presenting with abdominal pain and right sciatica. Axial CT (A) and fused PET/CT (B) images demonstrate a purely fatty mass in the right hemipelvis with no significant FDG activity (arrows).

hibernoma and ALT (P<0.0001), PL (P = 0.0001), ML (P<0.0001); ALT and DDL (P< 0.0001), PL (P<0.0001), ML (P<0.0001).

77% (10/13) of lipomas, 40% (2/5) of hibernomas, and 13% (2/16) of ALTs presented as purely lipomatous lesions with no macroscopic internal soft-tissue content. There was a significant difference in the depth of tumor location between lipomas and the other tumor subtypes. 77% (10/13) lipomas were located abo ve the superficial muscular fascia while 87% (47/54) of the remaining tumors were deep to the superficial fascia (P<0.0001). The mean volume of the different tumor subtypes were as follows: lipoma, 274.0 ± 346.4 cm^3; hibernoma, 108.5 ± 177.74 cm^3; ALT, 1616.2 ± 1749.44 cm^3; DDL, 2337.5 ± 3165.64 cm^3; ML, 1373.7 ± 1240.94 cm^3; and PL, 1258.1 ± 1685.54 cm^3. With a mean volume of 2337.5 cm^3, DDLs were significantly larger than hibernomas (109 cm^3, P = 0.026) and lipomas (274 cm^3, P = 0.005). Otherwise, there were no significant volume differences between the subgroups. Calcifications were present in 13% (2/16) ALTs, 31% (5/16) DDLs, and 20% (3/15) MLs. The presence of calcifications in DDL compared to the other subgroups trended strongly towards significance (P = 0.051).

Discussion

This study demonstrates that there is overlapping metabolic activity of benign and malignant lipomatous tumors on FDG PET/CT. We also found a correlation between liposarcoma tumor grade and degree of metabolic activity; higher grade tumors tended to have greater FDG uptake. Finally, we found that the morphologic information afforded by CT images obtained for attenuation correction and anatomic localization can provide helpful information, such as demonstrating areas of internal nonlipomatous tissue or calcification. In some cases, the combination of PET and CT information can be diagnostic.

We observed a wide range of metabolic activities for lipomatous tumors, with SUVmax as low as 0.5 in benign lipoma and as high as 39.6 in DDL. However, there was substantial overlap in metabolic activity between benign and malignant tumor subtypes. For example, there was similar low metabolic activity observed for lipoma (**Figure 1**), ALT (**Figure 2**), and ML (**Figure 3**) and similar high metabolic activity observed in hibernoma (**Figure 4**), DDL (**Figure 5**), and PL (**Figure 6**). This was a result of the intense activity observed in benign hibernomas (SUVmax 11.9 ± 8.4) (**Figure 4**) and the low-grade activity observed in MLs (SUVmax 3.0 ± 1.0) (**Figure 3**) and ALT (SUVmax 2.3 ± 1.2) (**Figure 2**). In a retrospective evaluation of 32 benign lipomas and 25 liposarcomas (10 well-differentiated, 10 myxoid, and five other types), Suzuki et al. demonstrated that FDG PET could be used to distinguish between benign and malignant lipomatous tumors (P<0.0001) [23]. Notably, their cohort did not include any hibernomas, which are characteristically hypermetabolic. When hibernomas were excluded from the metabolic analysis in the current study, there was a significant difference in FDG activity between lipomas and the various liposarcoma tumor subtypes, similar to results published by Suzuki and colleagues.

Hibernoma is a benign tumor comprised of brown fat, and several case reports and small series have demonstrated increased uptake within these tumors [9, 13, 24, 26-31]. Early reports stated that the FDG activity in hibernomas is greater than that usually seen in liposarcomas, and this can therefore be a reliable differentiator [30, 31]. However, subsequent studies showed that FDG activity in hibernomas may actually be lower and overlap with liposarcoma [28, 29, 31], although fluctuating FDG

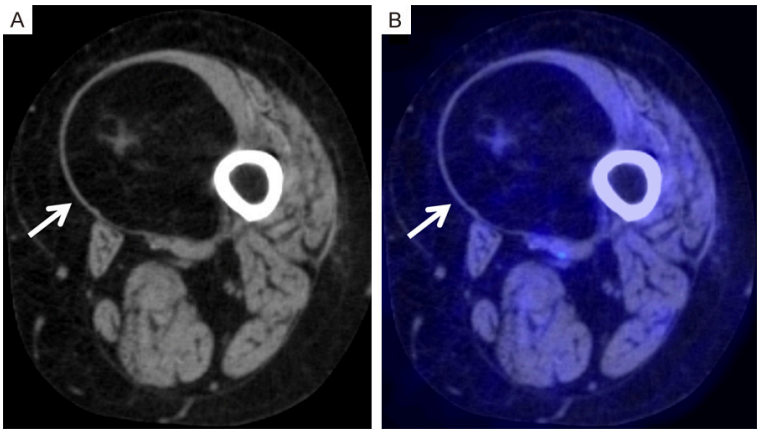

Figure 2. 64-year-old female with incidental ALT found on melanoma staging PET/CT. Axial CT (A) and fused PET/CT (B) images demonstrate a predominantly lipomatous mass in the distal left vastus medialis (arrows) with small areas of internal soft tissue attenuation and minimal FDG activity (SUVmax = 1.2).

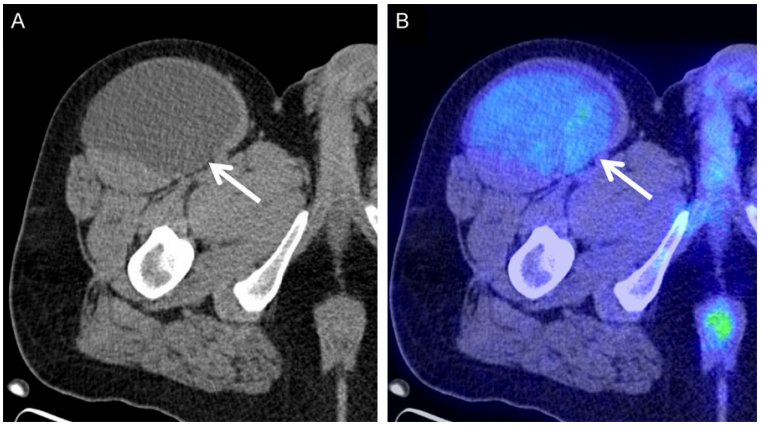

Figure 3. 37-year-old male with grade I myxoid liposarcoma. Axial CT (A) and fused PET/CT images (B) demonstrate an ovoid mass (arrows) involving the right sartorius muscle with homogeneous low-grade FDG activity (SUVmax 2.8).

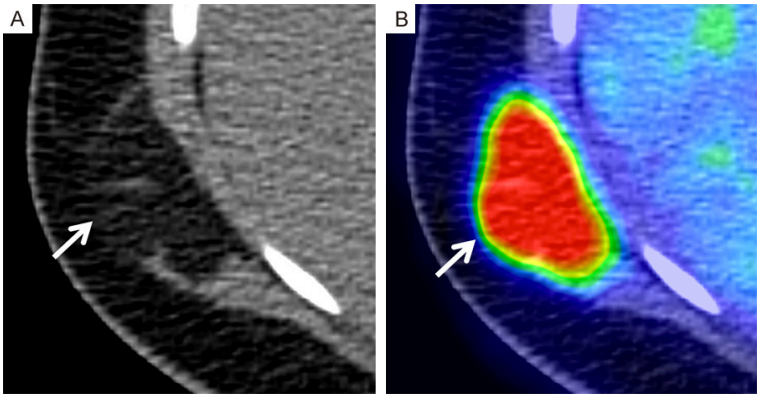

Figure 4. 41-year-old female with hibernoma incidentally discovered on melanoma staging PET/CT. Axial CT (A) and fused PET/CT (B) images demonstrate an intensely FDG avid (SUVmax = 14.4) predominantly lipomatous mass involving the right latissimus dorsi muscle (arrows).

activity in hibernomas over serial exams may be an important clue to delineate from liposarcoma [29]. To our knowledge, the five hibernoma patients in our cohort represent the largest number of hibernomas evaluated by PET/CT to date in a single study. We confirm that intense FDG activity may be present within these lesions (SUVmax 24.3), but also found that hibernoma FDG activity may be quite modest (SUVmax 3.3), similar to ML and ALT. Therefore, on the basis of metabolic activity alone, it is not possible to differentiate hibernoma from liposarcoma, especially as we found quite hypermetabolic DDL (SUVmax range 3.4-39.6) and PL (SUVmax range 11.4-15.5) cases in our cohort.

We identified a correlation between the metabolic activity and liposarcoma tumor grade, supporting data in earlier studies [22, 23]. The cohort analyzed by Suzuki et al. included 25 liposarcomas of varied biological grades. The authors reported four different biological grades of tumor based on the metabolic activity (benign tumors, well-differentiated liposarcomas, myxoid type, and other types) [23]. Brenner et al. retrospectively reviewed 54 patients with liposarcomas and demonstrated that SUVmax values could be used to differentiate between FNCLCC grade I, II and III lesions ($P = 0.005$) [22]. The authors further showed that SUVmax >3.6 had 75% accuracy for predicting tumor relapse. Patients with SUVmax >3.6 also had significantly shorter disease-free survival of 21 months compared to 44 months in patients with SUVmax ≤3.6, whereas tumor grade and subtype were

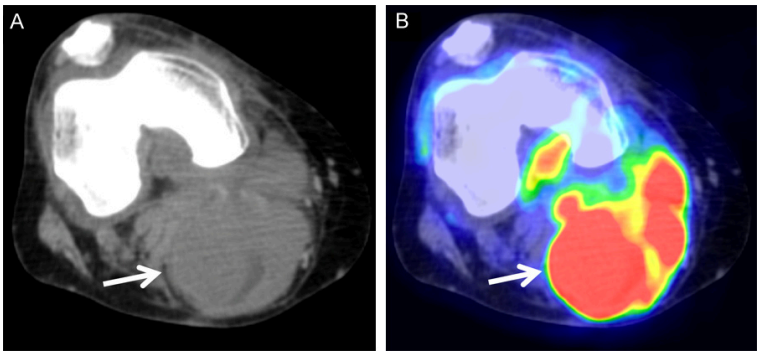

Figure 5. 53-year-old male with a right popliteal fossa dedifferentiated liposarcoma. Axial CT (A) and fused PET/CT (B) images demonstrate a mass (arrows) with predominant soft tissue attenuation and marked FDG activity (SUVmax 39.6).

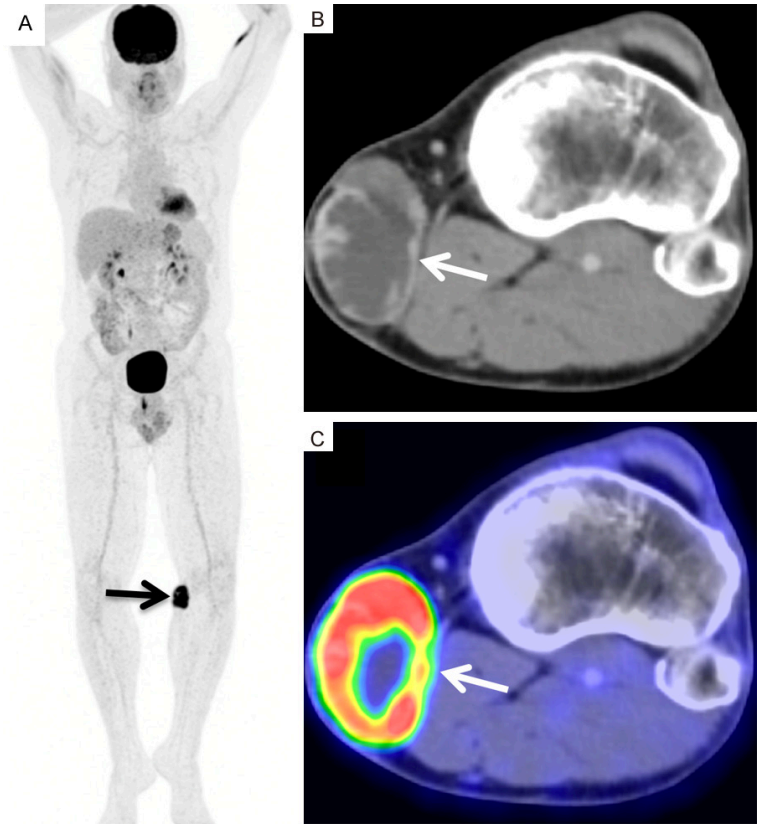

Figure 6. 57-year-old male with pleomorphic liposarcoma. PET MIP (A), axial contrast-enhanced CT (B) and axial fused PET/CT (C) images demonstrate an intensely FDG avid (SUVmax 15.5) centrally necrotic left lower extremity pleomorphic liposarcoma (arrows), without evidence of metastatic disease.

not predictive of disease-free survival. Results presented in our current study are in keeping with data presented in earlier reports, namely that greater FDG uptake is seen in higher grade tumors. Of note, the current study differs from the work of Suzuki et al. and Brenner et al. because the exams were performed on a three-dimensional PET system with CT attenuation correction versus two-dimensional PET without CT attenuation correction for the earlier studies.

The morphologic information provided by CT in the modern PET/CT era can be helpful in lipomatous tumor evaluation in a number of ways. If a purely fatty lesion with intense metabolic activity (SUVmax >10) is encountered on oncologic PET/CT, this combination of PET and CT imaging features is pathognomonic for hibernoma, which may obviate the need for biopsy (**Figure 7**). Any other fat-containing mass with that degree of FDG uptake should be a liposarcoma, and these will invariably contain areas of internal soft tissue attenuation. Interestingly, we found that hibernomas, lipomas, and ALTs may all present as masses without visible internal soft tissue content (**Figure 8**), and that hibernomas and ALTs have similar morphologic features and average attenuation on CT. The differing average metabolic activity of hibernomas compared to lipomas and ALTs is helpful in distinguishing these lesions, although it should be acknowledged that less FDG-avid hibernomas may appear similar to ALTs on PET/CT.

If a fat-containing lesion has significant internal soft tissue content on CT (>25% based on previous studies), it should be regarded as suspicious for liposarcoma irrespective of FDG activity, since both ALT and ML may present with low metabolic activity. In other words, low FDG activity should not be mistaken for a sign of benignity. Several prior studies have focused on MRI as a noninvasive means to differentiate lipomas from

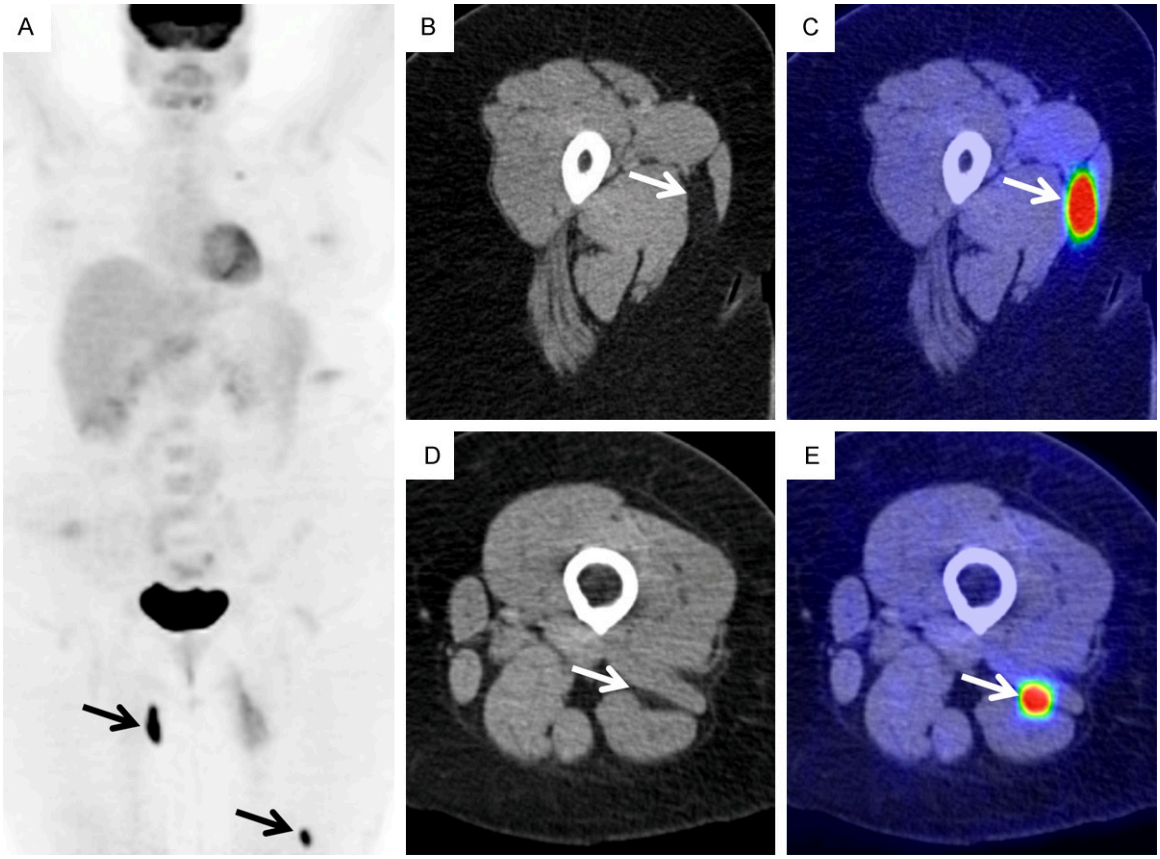

Figure 7. 57-year-old female with synchronous bilateral lower extremity hibernomas. PET MIP (A), axial CT (B, D) and fused PET/CT (C, E) images demonstrate purely fatty lesions with marked FDG uptake in the right thigh (SUVmax 24.3) and left thigh (SUVmax 12.3) (arrows). Subsequent CT-guided biopsy biopsy confirmed hibernomas at both sites.

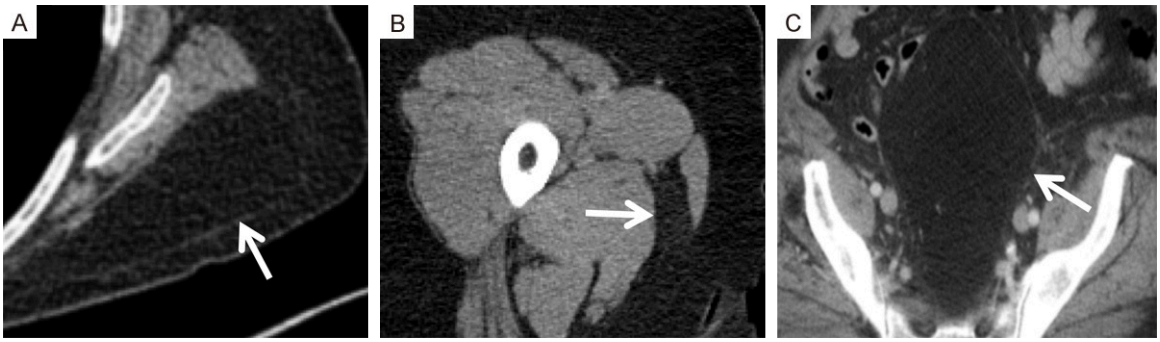

Figure 8. Purely lipomatous lesions. Axial CT images of a lipoma (A), hibernoma (B), and ALT (C) demonstrate lipomatous tumors consisting entirely of fat.

ALTs [7, 12, 15, 18, 20], and some have noted that ALTs may present as purely fatty masses [20], similar to the cases in the present study. We did not find average SUVmax to be a helpful discriminator between lipomas and ALTs (P = 0.52), which is similar to the work by Suzuki and colleagues, who also reported no statistical difference in the metabolic activity of the two lesion types (P = 0.13) [23]. Since lipomas and ALTs can both have similar low grade metabolic activity and morphologic features on PET/CT, in a purely fatty mass with higher risk features for ALT such as a deep location, >10 cm in size, or age >60 years, MRI may be warranted .

Limitations of this study include its retrospective nature and sampling bias. There was an unequal number of tumors identified for each tumor subtype, with some groups being relatively small such that there may have been inadequate power to detect differences between subgroups. Finally, the inclusion criteria might have excluded a significant cohort of lipomatous tumors which may have undergone prior surgery, radiation or chemotherapy, or those without a pathologic diagnosis.

There are overlapping ^{18}FDG PET/CT features of benign and malignant lipomatous tumors. While liposarcoma grade correlates with SUVmax, malignant lesions (myxoid liposarcomas and atypical lipomatous tumors) may present with low FDG uptake and benign lesions (hibernomas) may demonstrate high metabolic activity. In some instances a combination of metabolic and morphologic characteristics may narrow the differential diagnosis, or even be diagnostic.

Disclosure of conflict of interest

None.

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