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ARTICLE

Clinical applications of molecular imaging in sarcoma evaluation

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Abstract

A wide range of molecular imaging techniques are available that can provide complementary information to conventional, anatomical imaging for the evaluation of known or suspected bone and soft tissue sarcomas. In particular, positron emission tomography (PET), particularly in the form of hybrid PET/CT technology, offers many potential advantages over current imaging approaches by delineating not only the extent of disease but also the biological heterogeneity that can exist both between and within sarcomas. This review discusses the clinical situations where nuclear medicine techniques can aid in the management of patients with sarcoma. These include biopsy guidance, whole body staging, therapeutic response assessment and evaluation of residual mass lesions after treatment.

Keywords: *PET; FDG; ^{201}Tl; biopsy guidance; grading; therapy monitoring.*

Introduction

Sarcomas represent a disparate group of malignancies with highly variable natural history and a correspondingly diverse range of potential therapeutic strategies. The choice of treatment is largely driven by prognostic factors but is also dependent on local expertise, philosophies and the particular clinical circumstances of individual patients. Important considerations include the type, grade, extent and location of tumour. Curative treatment approaches almost always include surgery but a combination of surgery with adjuvant radiotherapy[1] or systemic chemotherapy[2,3] is now an integral component of the multidisciplinary care of many sarcoma patients.

There is a wide range of nuclear medicine techniques that can be used to characterise biological characteristics of bone and soft tissue sarcomas[4]. These include traditional nuclear medicine techniques like bone and gallium scanning as well as newer cancer imaging approaches, like the combination of thallium-201 and technetium-99m (V) DMSA scanning for evaluating chondroid matrix tumours[5]. Positron emission tomography (PET) is an exciting technology for cancer evaluation, combining relatively high spatial resolution with high lesion contrast and the ability to assay biological processes throughout the body. New hybrid PET/CT devices provide further enhancement of the potential of this modality by allowing accurate co-registration of functional and anatomical information, improving the localising ability of PET[6].

The clinical situations where molecular imaging techniques can provide complementary information to that available from conventional techniques extend from the diagnostic process, through staging to therapeutic

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monitoring and surveillance. The best test or combination of tests will be defined by local cost, availability, and expertise with a given modality, in addition to patient specific circumstances. In our sarcoma group, molecular imaging techniques have played an important role in management of patients for over a decade. While single photon techniques continue to play an important role, PET scanning is becoming the preferred imaging technique in many situations. Of more than 17 000 scans performed in our PET facility since late 1996, more than 900 (5%) have been for evaluation of sarcoma. Since installing our PET/CT scanner in late 2001, 472/6996 (7%) scans have been for this indication. In this review, the clinical applications of molecular imaging techniques in sarcoma evaluation are discussed.

Biopsy guidance

Histopathological classification is a vital step in the management of suspected sarcomas. Tumour grade determined from biopsy has significant prognostic and management implications. However, in lesions with significant tissue heterogeneity, there is the possibility of sampling error. For example, areas of secondary fibrosis may lead to an erroneous diagnosis of a benign lesion whereas immature osteoid in response to an unrecognised fracture may lead to misdiagnosis of a high-grade sarcoma. Similarly, extensive necrosis may lead to non-diagnostic biopsy results. Due to the risks associated with seeding of the biopsy, the need to repeat non-diagnostic biopsy may have adverse consequences for patients[7]. All these issues can make histopathological grading a difficult process[8]. Even with an adequate biopsy, histopathological grading is still recognised as having significant limitations[9].

By identifying the most metabolically active portion of a tumour mass, nuclear medicine techniques can guide biopsy to a site most likely to contain tumour tissue of the highest grade present. This can be particularly important in soft tissue sarcomas since the primary lesion is often treated with neoadjuvant radiotherapy and/or chemotherapy prior to surgery. As a result, the resection specimen often contains partially or completely necrotic tumour and is not useful for accurate diagnosis and grading. For many years our group has used ^{201}Tl to guide biopsy of soft-tissue sarcomas. More recently, we have used PET/CT to plan and perform difficult biopsies (Fig. 1). Based on excision specimen pathology, FDG PET scan findings have been shown to correlate with a number of histopathological parameters that are known to be of prognostic significance[10]. More accurate biopsy guidance by metabolic imaging should help to improve pre-treatment characterisation of suspected musculoskeletal sarcomas.

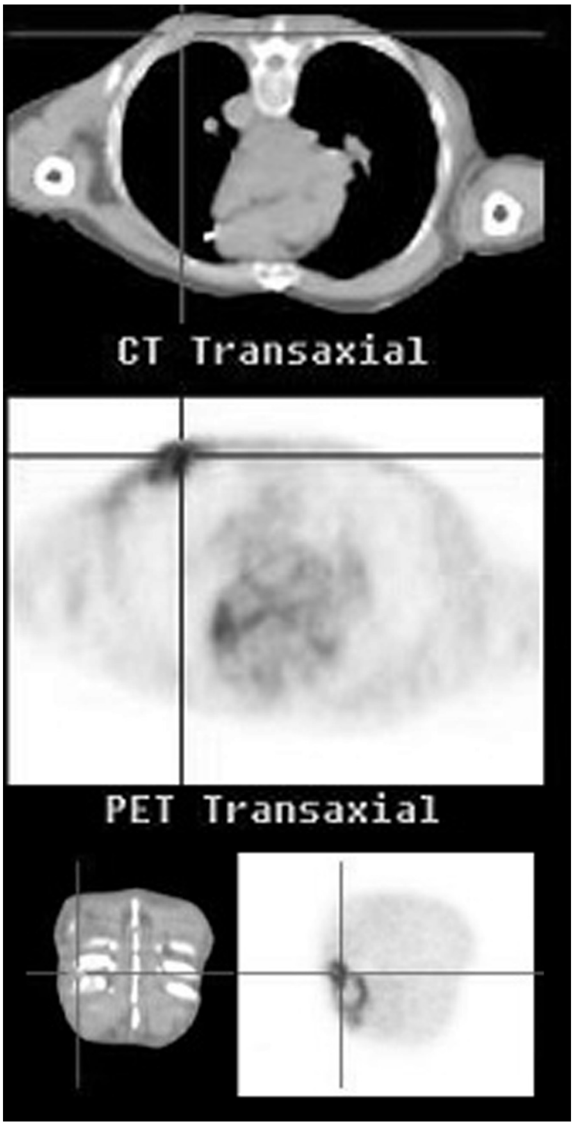

Figure 1 **A progressively enlarging soft tissue mass had been noticed by this patient. MRI suggested a soft tissue sarcoma but initial biopsy yielded no useful diagnostic tissue. Repeat biopsy was planned using PET/CT with the patient positioned prone. The site of high metabolic activity was identified on PET (middle panel) and its CT co-ordinates (upper panel) were used to guide the biopsy. The lower panel demonstrates the coronal projection of this lesion and emphasizes the heterogeneity of metabolic characteristics within the mass, explaining the initial negative biopsy.**

Sarcoma detection and grading

^{201}Tl has been used to evaluate the malignancy of various musculoskeletal mass lesions prior to biopsy. An early study in apparently primary bone tumours demonstrated that high uptake was a better predictor of aggressive lesions than bone or ^{67}Ga scanning[11]. In a recent report of our own experience in 92 consecutive chondroid matrix tumours, ^{201}Tl uptake was observed in all grade III tumours, 58% of grade II tumours but in no grade I chondrosarcomas and had a positive predictive value of 88% for malignancy[5]. Furthermore, development of metastatic disease was limited to patients with high ^{201}Tl uptake. Unfortunately, single-photon techniques do not lend themselves to other than qualitative assessment and therefore are generally only used to dichotomise scan appearances into positive and negative groups.

As a semi-quantitative or quantitative technique PET can potentially provide more objective evaluation of metabolic processes that are influenced by tumour grade and therefore might provide prognostic information. The first use of FDG PET for this purpose was reported for brain tumours[12] where FDG-avidity both correlated with tumour grade and provided prognostic stratification. An early study evaluating FDG PET in musculoskeletal tumours also suggested that this approach might have promise for grading purposes[13]. In 25 sarcomas there was a high correlation ($\rho = 0.83$) between a semi-quantitative measure of FDG retention (the standardised uptake value or SUV) and NCI grade. A subsequent smaller study[14] found similar concordance between sarcoma grade and SUV with a cut-off of 1.6 stratifying high and low-grade tumours. A larger series involving 202 patients demonstrated that using a tumour-to-background ratio (TBR) cut-off of 3.0, the sensitivity for detection of malignancy was 93%, the specificity 67% and the overall accuracy 82%[15]. The same group had earlier reported that all lesions, with the exception of pseudotumoral myositis ossificans, that had a TBR of >3.0 were malignant[16]. Our own experience also suggests that myositis ossificans can mimic high-grade sarcoma in its FDG PET imaging features and can also be difficult to characterise on MRI. A recent meta-analysis of the use of FDG PET for grading mixed soft tissue tumours revealed a significant difference in the SUV of benign vs. malignant lesions and between low-grade and high-grade sarcomas[17]. Although the SUV obtained from a delayed FDG PET scan appears to correlate reasonably well with histopathological grade, this has not been demonstrated in all studies. For example, one study comparing dynamic acquisition with quantitative glucose metabolism assessment and delayed SUV demonstrated a good correlation between the former and histopathological grade but not with the latter[18].

Nevertheless, there are limitations to this approach. For example, one series evaluating the SUV of 52 primary bone lesions demonstrated several chondroblastomas and inflammatory lesions that had FDG uptake as high as those of osteosarcomas despite demonstrating that in all patients combined, there was a significantly higher FDG-avidity in benign than malignant lesions[19]. Furthermore, sarcomas containing a significant amount of acellular matrix material can have dilution of the FDG signal and therefore, PET may provide an underestimate of the biological aggressive of such sarcomas. Myxoid liposarcomas and chondrosarcomas are good examples of sarcomas that can have relatively low FDG uptake. Direct imaging of acellular matrix using [^{99m}Tc(V)]DMSA for chondroid lesions[5,20] and [^{99m}Tc(V)]pertechnetate for myxoid soft tissue lesions[21] can improve the sensitivity for detection and characterisation of these types of sarcoma. Nevertheless, a recent study demonstrated that there is a significant correlation between the grade of chondrosarcoma and the SUV[22]. Furthermore, patients with recurrence or metastatic disease after primary treatment had significantly higher SUV than those without. The combination of pre-treatment SUV and histopathological grade provided the most powerful prediction of relapse. Using an SUV of 4 and tumour grade of III, the positive and negative predictive values for relapse were 90% and 95%, respectively. Therefore, a positive FDG PET in such cases is likely to have a good positive predictive value and the intensity of uptake may also have prognostic implications.

The prognostic value of PET may be even more important than its ability to define histopathological grade. In 209 patients with a variety of tumours treated with neoadjuvant chemotherapy or resection[23], multivariate Cox regression analysis demonstrated that the maximum SUV recorded in the tumour was a statistically significant predictor of survival after adjusting for standard clinical prognostic factors, including grade. Preliminary experience with the PET cellular proliferation agent, FLT, suggests that it may be a very useful technique for grading soft tissue sarcomas with uptake characteristics correlating with known indicators of tumour aggressiveness[24].

Tumour staging

Bone scanning is a useful technique to stage primary bone and soft tissue sarcomas since it allows whole body screening for sites of metastatic bone disease as well as assessing the extent of local bony involvement. In osteosarcoma, soft tissue metastases may also be evident by virtue of malignant osteoid formation. Thallium-201 can also be used to stage sarcomas. Evaluation of the abdominal region is, however, compromised by the presence of normal uptake in abdominal organs and the intestines. The relatively poor spatial resolution of ^{201}Tl imaging is also likely to limit the sensitivity of this technique for the detection of lung metastases. A comparison of bone scanning and ^{201}Tl chloride scanning demonstrated slightly higher specificity and overall accuracy of ^{201}Tl than delayed bone uptake images for staging osteosarcoma[25].

FDG PET has the significant advantage over ^{201}Tl of lower intra-abdominal background activity and higher spatial resolution. This generally leads to higher contrast and therefore, higher lesion sensitivity. Since lung metastasis is relatively common in sarcoma, sensitive detection of lung metastases is vital for accurate staging.

Due to the high contrast between air and soft tissue on CT scanning, it is possible to detect metastatic disease as small as 1–2 mm using this technique. Partial volume effects due to respiratory motion during acquisition of the PET scan and the lower spatial resolution of PET offset the benefits of relatively high metabolic contrast. Accordingly, CT has been shown to be more sensitive than FDG PET for the detection of small lung metastases[26]. However, because lung nodules are relatively common in the general population, false positive results are not uncommon on CT. For lesions of sufficient size to allow visualisation on PET (8–10 mm), absence of any uptake significantly decreases the likelihood of a metastatic basis, particularly if the primary tumour has or had high radiotracer avidity (Fig. 2).

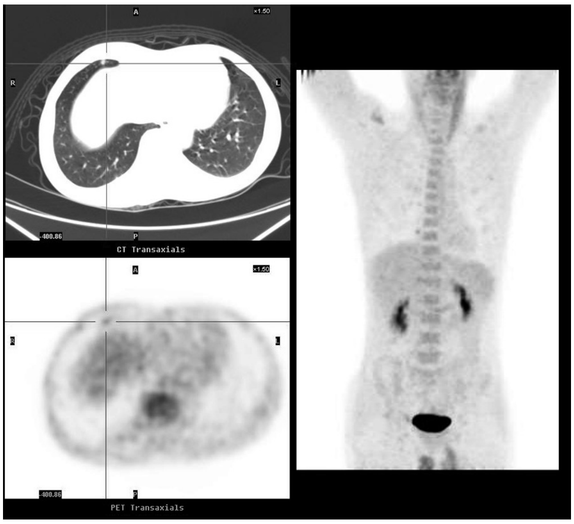

Figure 2 **Despite relatively small basal nodules on CT, definite FDG uptake very significantly increases the likelihood of a malignant basis since both lesion size and respiratory movement would tend to decrease apparent compared to actual counts in this region.**

Therapeutic monitoring

The importance of therapeutic response assessment in sarcoma is best exemplified by osteosarcoma. The percent tumour necrosis found histologically following chemotherapy has been shown to be a powerful predictor of outcome in osteosarcoma. Prognosis is substantially better if the percentage tumour necrosis is $>$90%[27]. Unfortunately, the degree of necrosis has primarily been evaluated from the resection specimen and this provides no opportunity for a change in therapy in poor responders. Biopsy after commencing therapy poses its own difficulties with the risk of sampling error and theoretical concerns related to seeding the biopsy tract from repeated biopsy. Therefore a robust method for assessing therapeutic response non-invasively would be worthwhile. Conventional non-invasive imaging techniques have significant limitations although contrast-enhanced MRI is widely used for this purpose[28]. Because uptake of a range of radiotracers into malignant tumours reflects the metabolic and proliferative activity of the cells within them, and the number of viable cells surviving after treatment, these radiotracers can be potentially used to monitor the response of sarcomas to therapy in a manner independent of structural changes. In the case of primary bone tumours, where remodelling of bone and the normal structural integrity of bone may limit the ability to detect disease regression, functional imaging is likely to play a particularly important role.

The most widely used single photon agent for this application has been ^{201}Tl but PET using [^{18}F]FDG or [^{11}C]methionine is being used increasingly. Preliminary results[11] encouraged further evaluation of the role of ^{201}Tl in assessing response of osteosarcoma to chemotherapy. There is evidence that the reduction of ^{201}Tl uptake in osteosarcoma correlates well with the percentage of tumour necrosis[29]. Similar results were obtained by a more recent study of 30 patients with osteosarcoma treated with chemotherapy[30,31]. Although its role in other sarcomas types is less clear, ^{201}Tl uptake has been shown to correlate with therapeutic response in soft tissue sarcomas including rhabdomyosarcoma[32]. ^{67}Ga scanning and ^{99m}Tc MDP bone scanning were found to be less accurate in assessing therapeutic response in this series. A reduction in ^{201}Tl following radiotherapy of soft-tissue sarcomas has also been shown to be predictive of therapeutic response[33]. A range of radiotracers can detect impairment of cellular viability preceding cell death. For example, ^{99m}Tc MIBI is reduced in pre-necrotic cells with impaired mitochondrial function. Preliminary studies using ^{99m}Tc MIBI for therapeutic monitoring of osteosarcoma demonstrated a correlation between the reduction in radiotracer uptake and histologic response but the variation was too large in their small sample to allow prediction of individual patient outcome[34]. Although changes in [^{18}F]FDG, ^{201}Tl and ^{99m}Tc MIBI uptake all appear to some degree reflect therapeutic response, the cellular processes which they trace clearly differ and they may each provide differing information regarding the effect of chemotherapy on cellular metabolism and viability[35]. A study comparing PET with [^{18}F]FDG and ^{99m}Tc MIBI SPECT demonstrated both higher sensitivity and specificity for PET (98% vs. 82% and 90% vs. 80%, respectively)[36]. The visual grade for confirmed recurrent tumours was also higher for PET than ^{99m}Tc MIBI (2.1 vs. 1.6). Interestingly, 4 of 9 patients with [^{18}F]FDG but not ^{99m}Tc MIBI uptake failed to respond to multi-drug therapy. These data may reflect the ability of ^{99m}Tc MIBI to demonstrate p-glycoprotein expression and to thereby predict for multi-drug resistance.

There are substantial data on the accuracy of PET for therapeutic monitoring in a range of malignancies. Decreased uptake of [^{18}F]FDG[37,38] or [^{11}C]methionine[39] was shown to be an accurate marker of therapeutic response more than a decade ago. As with single-photon techniques, the ability of FDG PET to evaluate therapeutic response of osteosarcoma to chemotherapy has been an important focus of validation studies. In a series of 27 patients with osteosarcoma treated with chemotherapy, University of Ulm researchers found that a decrease in the ratio of pre-therapy to post-therapy tumour-to-background (TBR) activity was highly correlated with the degree of tumour necrosis[40]. Other studies have also suggested the utility of FDG PET in assessing therapeutic response to chemotherapy using FDG PET[41,42]. With increasing availability of PET and particularly, combined PET/CT scanners that allow simultaneous evaluation of both morphological and metabolic characteristics, it is considered that PET will increasingly supplant standard nuclear medicine techniques in the evaluation of therapeutic response assessment (Figs. 3 and 4).

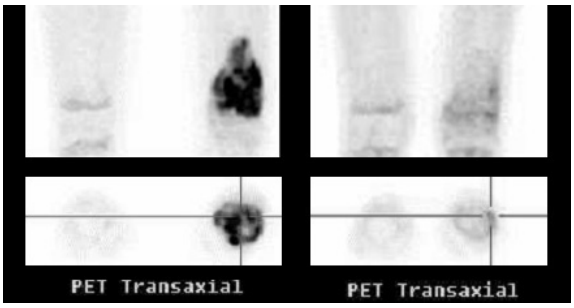

Figure 3 **Baseline (left) and post-chemotherapy (right) FDG PET scans demonstrate loss of metabolic abnormality in a left distal femoral osteosarcoma. Normal FDG in the epiphyseal growth plates is apparent. Despite lack of change on CT, MRI or bone scan; the PET findings correctly predicted an excellent pathological response (>97% necrosis).**

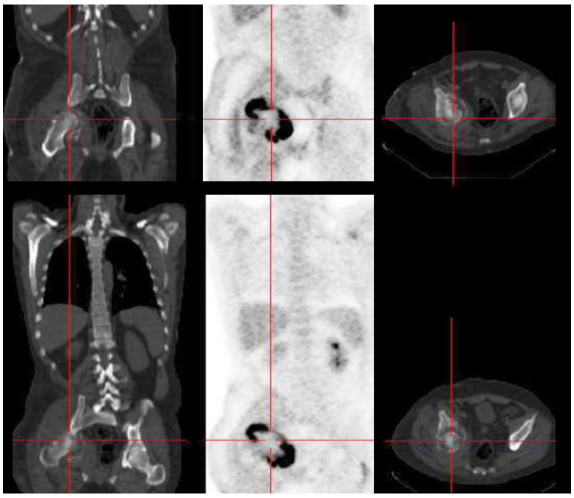

Figure 4 **An extensive Ewing's sarcoma of the right acetabulum is demonstrated on CT and FDG PET before (above) and after (below) chemotherapy. No metabolic response was seen. This finding suggests a poor prognosis and led to a change in chemotherapy.**

Differentiation of scar from residual or recurrent tumour

Following surgery, radiotherapy and, less often, chemotherapy there may be scarring in the region of the primary tumour that may distort normal anatomical relations. Furthermore, scar tissue may co-exist with residual sarcoma. While sarcoma will generally demonstrate contrast enhancement on CT or MRI scanning, this can be seen also with organising scar tissue. Low metabolic activity and cellularity is seen in chronic scar tissue whereas most malignant tumours have high cellularity and metabolic activity (Fig. 5).

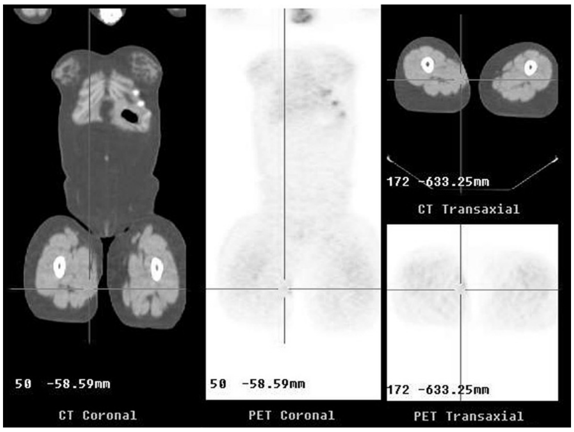

Figure 5 **Residual soft tissue thickening and a palpable mass following radiotherapy and resection of a high-grade soft tissue sarcoma. No FDG uptake was apparent at the site of concern and the patient was managed conservatively. There was no evidence of local or distant progression over a 2-year interval.**

^{201}Tl imaging has been evaluated for detection of suspected residual or recurrent bone and soft tissue sarcomas at the Memorial Sloan Kettering Institute[43]. The overall accuracy of ^{201}Tl scintigraphy was 97% vs. 83% for conventional approaches. Most importantly, ^{201}Tl was true negative in 7/8 patients without recurrence and equivocal in the remaining patient, while conventional imaging was false positive in 4/8 cases. [^{18}F]FDG and [^{11}C]methionine PET appear to have similar sensitivity for recurrent sarcoma[44]. As with primary evaluation, the ability to more accurately localise the site of recurrence with PET/CT may aid biopsy for confirmation purposes and targeting of salvage therapies if the recurrence is loco-regionally confined. Since PET is much less influenced by metal artefacts than CT or MRI, PET may be the best technique for surveillance for local recurrence in patients with limb-sparing surgery. The ability to simultaneously assess for both soft tissue and skeletal sites of relapse is also a practical advantage (Fig. 6).

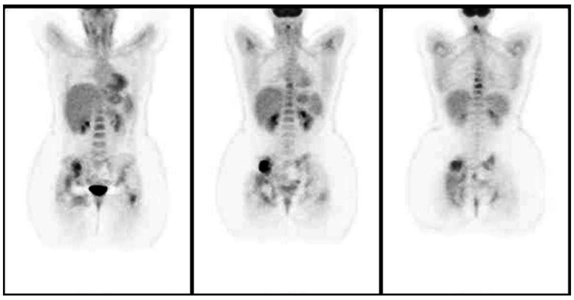

Figure 6 **FDG PET has the capability of screening for metastatic disease in both soft tissue and bone site. This patient had previously received chemotherapy and limb-sparing surgery for an osteosarcoma of the proximal right femur. Follow-up PET scanning demonstrates multiple bone metastases.**

Conclusion

Molecular imaging techniques and particularly the exciting new technology of PET/CT offer a number of practical advantages in the evaluation of soft tissue and bone sarcoma. Further studies are required to determine how best to use these techniques to complement conventional imaging or, in some situations, to replace existing investigative paradigms.

It needs to be remembered that there are currently no functional imaging scans that are specific for 'cancer'. They all evaluate pathophysiologic or biochemical processes that are more pronounced in tumours than normal tissues. Thus, while enhanced glucose metabolism is a hallmark of cancer, it is also seen in infection, actively healing tissues and in many normal tissues. Thus, it is not realistic to expect that FDG PET will not have 'false positive' results. In the same way that a bone scan demonstrates the increased osteoblastic activity that accompanies infection, healing fractures, active arthritis and bone invasion by tumours, the interpretation of FDG PET needs to be based on the clinical scenario (pre-test probability of disease) and the pattern of abnormality. To interpret PET scans purely on the basis of SUVs is akin to relying on Hounsfield units alone to interpret CT. The diagnostic process in cancer is a complex one and one that is all the more difficult in sarcoma. Intelligent pattern recognition and correlative imaging are vital if maximal clinical benefit is to be delivered to sarcoma patients.

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