

Efficacy and Limitations of F-18-fluoro-2-deoxy-D-glucose Positron Emission Tomography to Differentiate Between Malignant and Benign Bone and Soft Tissue Tumors

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Abstract. *Background/Aim:* Positron emission tomography (PET) using ¹⁸fluorine-labelled fluorodeoxyglucose (FDG), is the most widely applied molecular imaging technique in oncology. The present study assessed the efficacy and limitations of FDG-PET by comparing FDG accumulation in bone and soft tissue lesions, as well as histopathological features. *Patients and Methods:* The study included 122 patients with 165 lesions, as assessed by histopathological examinations. The maximum standardized uptake values (SUV_{max}) of benign lesions were compared to those of primary, recurrent, or metastatic sarcomas, as well as those of other malignancies. *Results:* The sensitivity, specificity, and accuracy of SUV_{max} for differentiation between benign lesions and primary sarcomas were 67.9%, 92.9%, and 80.4%, respectively. There were no significant differences between benign lesions and recurrent or metastatic sarcomas. *Conclusion:* Although FDG-PET is a useful imaging modality to differentiate primary sarcomas from benign lesions, it is difficult to differentiate residual or metastatic sarcomas from benign lesions.

Diagnostic imaging techniques including radiography, computed tomography (CT), magnetic resonance imaging (MRI), ²⁰¹thallium scintigraphy, ^{99m}Tc-MIBI scintigraphy, and positron emission tomography (PET) are widely used to assess bone and soft tissue lesions (1-5). Anatomic imaging techniques such as radiography, CT, and MRI are useful for

identifying the location, extent, and association between musculoskeletal tumors and normal tissues. Although histopathological examination is the gold standard for diagnosis, biopsy and excision of the lesion are invasive, especially for patients with benign tumors. Several studies have assessed the efficacy of radiological examinations to detect malignant lesions (6-10), however, false-positive and false-negative lesions occur when differentiating bone and soft tissue lesions using radiological examinations. ²⁰¹Thallium scintigraphy is also used to differentiate benign and malignant bone and soft tissue lesions (11). However, giant cell tumor (GCT), Langerhans cell histiocytosis (LCH), pigmented villonodular synovitis, and osteomyelitis have high accumulation profiles using ²⁰¹Thallium scintigraphy, which often results in misdiagnoses of malignant tumor (12-18). In contrast, chondrosarcoma, well-differentiated liposarcoma, chordoma, and malignant peripheral nerve sheath tumor have low accumulation profiles of the tracers.

PET with ¹⁸fluorine-labelled fluorodeoxyglucose (¹⁸F-FDG), which is the molecular imaging technique most widely applied in oncology, provides quantitative, qualitative, and functional information regarding tumor cells, based on their increased rate of glucose metabolism. FDG-PET effectively and sensitively detects, stages, and restages malignancies in patients with diverse types of cancer (19-24). Furthermore, the combination of PET and whole-body CT provides functional and anatomical information, resulting in accurate detection and staging of malignancies.

Several studies have reported on the efficacy of PET/CT for detection of malignant tumors and differentiation between malignant and benign lesions (25-29). Although ¹⁸F-FDG accumulates preferentially in malignant tumors, it is a non-specific tracer and accumulation also occurs in other physiological and non-malignant processes, including infective and inflammatory conditions such as osteomyelitis and

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arthritis (30). The aim of the present retrospective study was to determine whether integrated PET/CT reliably differentiates between malignant lesions and benign lesions, by comparing ^{18}F -FDG accumulation in bone and soft tissue lesions.

Patients and Methods

Patients. The present study included 122 patients (63 men, 59 women patients; mean age: 57.0 years; age range=13-88 years) with 165 bone and soft tissue lesions, which were assessed by PET/CT and histopathological examinations from July 2010 to November 2015. The 165 lesions included 137 malignant lesions and 28 benign lesions. The 137 malignant lesions comprised 28 primary tumors, 34 recurrent or residual tumors, 43 metastatic tumors, and 32 other malignancies including carcinomas and lymphomas. The study was approved by the Kanazawa University Ethical Committee. All participants provided written informed consent.

Integrated PET/CT acquisition. Integrated PET/CT was performed after fasting for at least 6 h, if the serum glucose level was ≤ 200 mg/dl. Each patient was injected with 4.0 MBq/kg (0.11 mCi/kg) of ^{18}F -FDG, and whole-body PET/CT was performed using a PET-CT system (Discovery PET/CT 690; GE Healthcare, Milwaukee, WI, USA) 60 and 120 min after injection. PET/CT was performed only at the 60 min timepoint in cases without significant accumulation of ^{18}F -FDG.

Image analysis. PET and CT images were reviewed by a physician with experience in nuclear medicine. The maximum standardized uptake value (SUV_{max}) was determined in each region of interest (ROI). SUV_{max} was calculated using the PET scanner software, using the following formula: $\text{SUV}_{\text{max}} = C (\mu\text{Ci/mL}) / ID (\mu\text{Ci}) / w (\text{kg})$, whereby C is the activity at a pixel within the tissue defined by an ROI, ID is the injected dose, and w is the patient's body weight in kg. SUV_{max} values within the selected ROI are reported.

Statistical analyses. Values are expressed as means \pm standard deviations. Comparisons of SUV_{max} between 2 groups were analyzed using Student's t -tests. Comparisons of ≥ 2 groups were assessed using analysis of variance. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and accuracy were calculated; and 95% confidence intervals (CIs) were determined for each parameter, based on the binomial distribution. SUV_{max} for malignant lesions were compared with that of benign lesions. Furthermore, SUV_{max} of primary, recurrent, or metastatic sarcomas, as well as carcinomas, were compared with those for benign lesions. The optimal cutoff levels for SUV_{max} were defined as the index values that minimized the number of false results by receiver operator characteristic analyses. Correlations between SUV_{max} and histological evaluation were analyzed using measure of sensitivity, specificity, accuracy, PPV, and NPV. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using EZR statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Comparisons of SUV_{max} between benign and malignant lesions. The mean SUV_{max} for benign lesions and malignant tumors were 4.9 ± 3.4 and 8.8 ± 6.7 , respectively (Figure 1).

Although there was a significant difference between values for benign and malignant lesions ($p = 0.001$), considerable overlap was observed. For malignant tumors, the mean SUV_{max} of primary sarcomas, recurrent sarcomas, metastatic sarcomas, and the other malignancies were 13.1 ± 7.6 , 6.2 ± 5.7 , 6.6 ± 5.1 , and 10.8 ± 6.7 , respectively (Figure 2). Primary sarcomas and other malignancies had significantly higher SUV_{max} compared to benign lesions (Figure 2; $p < 0.01$), whereas no significant differences occurred between benign lesions and recurrent or metastatic lesions (Figure 2).

Sensitivity, specificity, and accuracy of FDG-PET. The sensitivity, specificity, PPV, NPV, and accuracy of SUV_{max} for differentiating between benign lesions and malignant tumors were 92.9%, 43.8%, 96.8%, 25.2%, and 52.1%, respectively, with an optimal cutoff SUV_{max} value of 8.2 (Figure 3A; Table I). The sensitivity, specificity, PPV, NPV, and accuracy of SUV_{max} for differentiating benign lesions from primary sarcomas were 67.9%, 92.9%, 90.5%, 74.3%, and 80.4%, respectively, with an optimal cutoff SUV_{max} of 8.6 (Figure 3B; Table I).

False positives and false negatives using PET/CT. Although SUV_{max} for malignant lesions ROIs were significantly higher compared to those for benign lesion ROIs, considerable overlaps in SUV_{max} were observed (Table II). There were 2 false positives among the benign lesion cases, including 1 each of GCT and LCH. There were 9 false negative cases among the primary sarcomas, including the following types of sarcomas: 2 extraskelatal myxoid chondrosarcomas, 2 Ewing's sarcomas, 1 chondrosarcoma, 1 leiomyosarcoma, 1 osteosarcoma, 1 epithelioid endothelioma, and 1 undifferentiated pleomorphic sarcoma (UPS). In the present study, 1 case of LCH and 4 cases of GCT were categorized as benign lesions. Therefore, the mean SUV_{max} for LCH was 14.8 and the mean SUV_{max} for GCT was 8.4 (range=3.6-13.8) (Figure 4), which was higher than for the other types of benign lesions. Cases of multiple lesions including malignancies also made it difficult to differentiate between benign lesions and metastatic lesions. For example, PET/CT in a 68-year-old patient indicated multiple lesions (Figure 5), and histological examinations of the thyroid, left buttock, and ilium revealed thyroid cancer, undifferentiated pleomorphic sarcoma, and sclerotic bone without tumor, respectively.

Discussion

PET SUV_{max} has been proposed as diagnostic tools to differentiate between benign and malignant lesions (31, 32). Cho *et al.* (31). reported that PET/CT is an adjunctive diagnostic method for differentiating malignant lesions from vertebral compression fractures. Additionally, Tian *et al.* reported that malignant lesions have higher SUV_{max} than

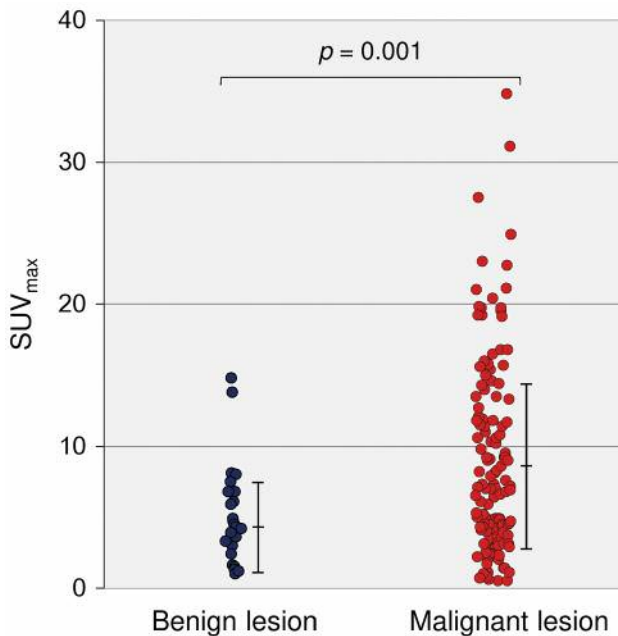


Figure 1. Maximum standardized uptake values (SUV_{max}) in benign and malignant lesions. Malignant lesions included primary sarcomas, recurrent sarcomas, metastatic sarcomas, and other malignancies. The data are expressed means \pm standard deviation (SDs). Statistical analyses were performed using Student's *t*-tests.

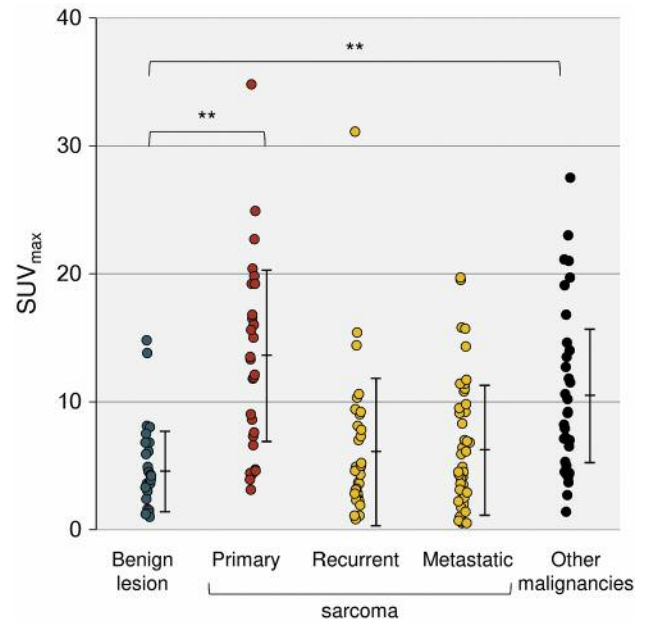


Figure 2. Maximum standardized uptake values (SUV_{max}) in benign lesions, primary sarcomas, recurrent sarcomas, metastatic sarcomas, and other malignancies. The data are expressed means \pm standard deviation (SDs). Statistical analyses were performed using analysis of variance (ANOVA). ** $p < 0.01$.

Table I. Efficacy of SUV_{max} for differentiating between benign and malignant lesions.

	Benign and malignant lesions*		Benign lesions and primary sarcomas	
	Value	95%CI	Value	95%CI
Sensitivity	43.8%	40.9-44.8%	67.9%	56.5-72.9%
Specificity	92.9%	78.7-98.0%	92.9%	81.5-97.9%
PPV	96.8%	90.4-99.1%	90.5%	75.4-97.2%
NPV	25.2%	21.4-26.6%	74.3%	65.2-78.3%
Accuracy	52.1%	47.3-53.9%	80.4%	69.0-85.4%

*Malignant lesions included primary sarcomas, recurrent sarcomas, metastatic sarcomas, and carcinomas. SUV_{max} : Maximum standardized uptake value; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

Table II. False-positive and false-negative cases assessed by positron emission tomography/computed tomography.

	Pathological diagnoses	SUV_{max}
False positive cases	Langerhans cell histiocytosis	14.8
	Giant cell tumor	13.8
False negative cases	Chondrosarcoma (grade 2)	3.1
	Extraskeletal myxoid chondrosarcoma	3.9
	Epithelioid endothelioma	4.3
	Osteosarcoma	4.4
	Extraskeletal myxoid chondrosarcoma	4.6
	Undifferentiated pleomorphic sarcoma	4.7
	Ewing's sarcoma	6.6
	Ewing's sarcoma	7.3
	Leiomyosarcoma	7.6

benign lesions (malignant lesions, 6.8; benign lesions, 4.5), although considerable overlap was observed (32). Our data also demonstrate significant differences in SUV_{max} between benign and malignant lesions, although we also observed considerable overlap in SUV_{max} between groups. Among malignant lesions, the mean SUV_{max} for primary tumors,

recurrent tumors, and metastatic tumors were 13.1 ± 7.6 , 6.2 ± 5.7 , 6.6 ± 5.1 , and 10.8 ± 6.7 , respectively. Most primary sarcomas in our study were large masses at the time of diagnosis. In contrast, the recurrent and metastatic tumors in our study were small masses, primarily because most patients had follow-up examinations such as CT and MRI to

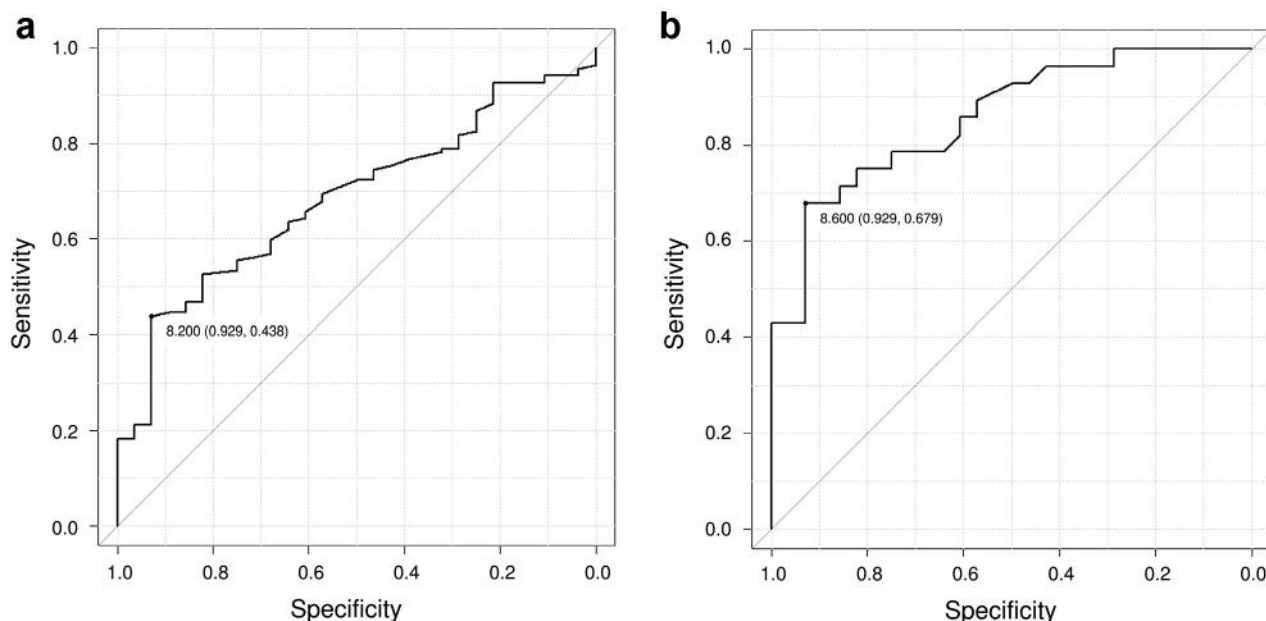


Figure 3. Receiver operator characteristic (ROC) analysis to differentiate between benign and malignant lesions. A: Benign lesions and malignant lesions. Malignant lesions included primary sarcomas, recurrent sarcomas, metastatic sarcomas, and other malignancies. B: Benign lesions and primary sarcomas.

detect lesions. Therefore, the differences in SUV_{max} between primary, recurrent, and metastatic sarcomas may be related to tumor size.

Discrepancies between SUV_{max} and malignancy determination have been reported for some tumors (33-35). In our study, LCHs had the highest SUV_{max} among benign lesions, and the mean SUV_{max} for GCTs was higher (8.4, range=3.6-13.8) than for other benign lesions. Cellular uptake of FDG in human tumor cells is associated with expression of glucose transporter protein (GLUT)-1, hexokinase II, and with gene upregulation for these proteins (34, 36). Ong *et al.* found significantly greater GLUT-1 and hexokinase II in 5 different human cancer cell lines (37). However, other studies have demonstrated an up-regulation of GLUT-1 in human monocyte-derived macrophages (38-40), and the high monocyte/macrophage content within GCTs may explain the FDG uptake (34, 35). Therefore, GCT and lesions containing active macrophages should be considered in differential diagnoses of intensely FDG-avid neoplasms. In contrast, SUV_{max} values for liposarcoma and chondrosarcoma are usually lower in PET studies, compared to values for other types of malignancies (41). However, SUV_{max} cut-offs may enable prediction of malignancies in lipomatous and cartilaginous tumors. In a previous report assessing SUV_{max} in lipomatous tumors, a cut-off value of 0.81 for FDG-PET significantly differentiated between benign lesions and well-differentiated liposarcoma (41). Feldman *et al.* reported that the sensitivity, specificity, and accuracy of FDG-PET for

distinguishing benign and malignant cartilage neoplasms with a cutoff SUV_{max} values of 2.0 were 91%, 100%, and 97%, respectively (42). Therefore, cases of suspected lipomatous or cartilaginous tumors indicated by MRI or CT should use a low SUV_{max} cut-off to differentiate between benign and malignant tumors.

Although our data demonstrate significant differences between benign and malignant lesions, considerable overlaps in SUV_{max} were observed. Furthermore, the inclusion criteria for the present study were limited. The first inclusion limitation was that PET/CT was performed only for lesions that were suspected as malignancies; most of the benign lesions that were suspected as malignant tumors before PET were aggressive tumors such as GCTs. The second inclusion limitation was that the present study included only lesions that were confirmed by histopathological examinations. Exclusion of conventional benign tumors from the study may have influenced SUV_{max} .

In conclusion, PET is a useful imaging modality for differentiation between benign lesions and primary sarcomas, with 80.4% accuracy. However, differentiation between benign lesions and recurrent or metastatic lesions is difficult because of low FDG uptake in many types of lesions. Therefore, combinations of PET and other methods such as enhanced MRI are preferable for determining diagnoses.

Conflicts of Interest

The Authors declare that they have no competing interests.

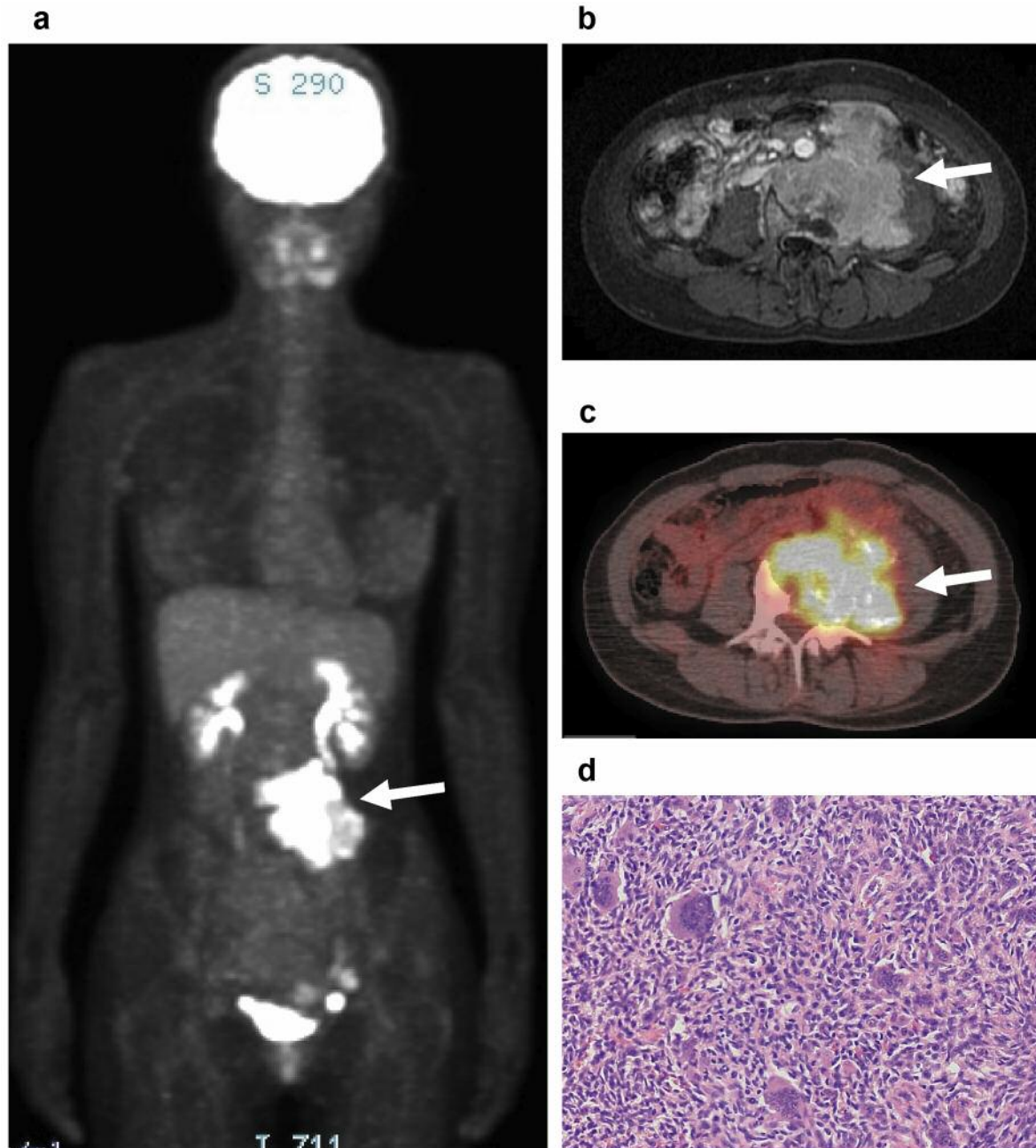


Figure 4. A 25-year-old woman with giant cell tumor (GCT) in lumbar vertebral bone. A: A whole-body positron emission tomography (PET) shows fluorodeoxyglucose (FDG) accumulation in lumbar vertebrae. B: Magnetic resonance imaging (MRI) shows a large mass on the lumbar vertebrae (white arrow). C: Fused positron emission tomography/computed tomography (PET/CT) image. Maximum standardized uptake value (SUV_{max})=13.8 (white arrow). D: Hematoxylin and eosin (HE) staining.

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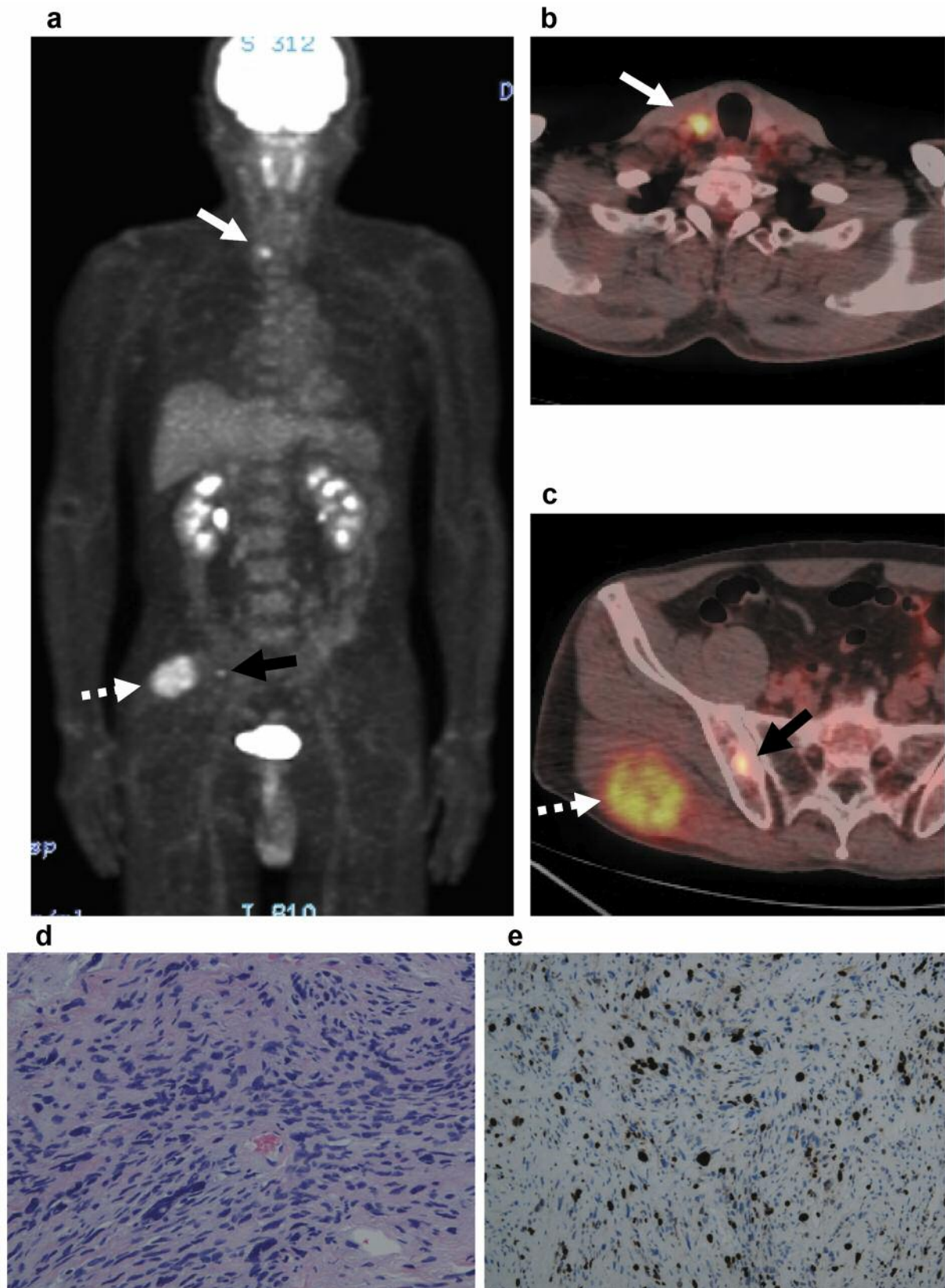


Figure 5. *Continued*

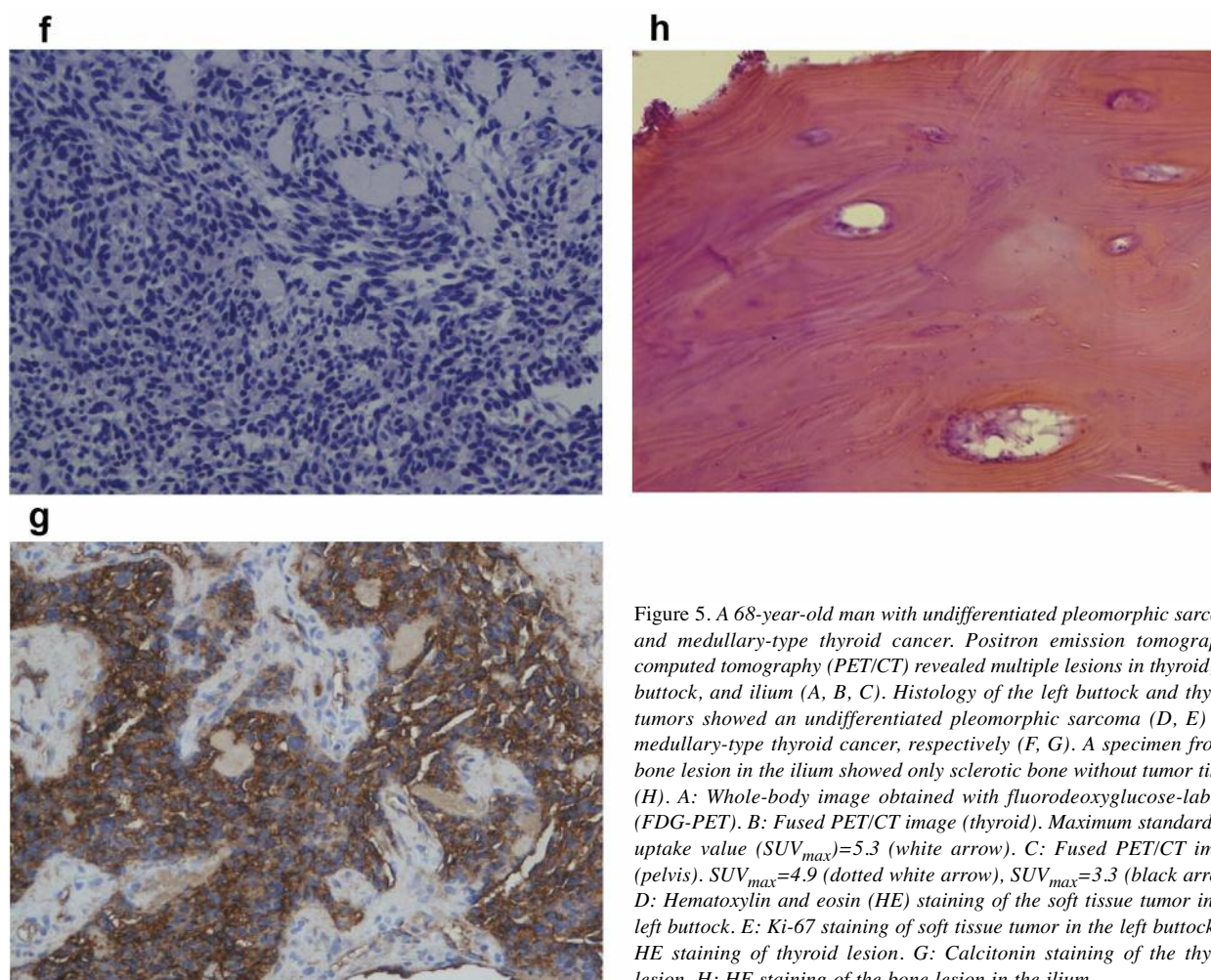


Figure 5. A 68-year-old man with undifferentiated pleomorphic sarcoma and medullary-type thyroid cancer. Positron emission tomography/computed tomography (PET/CT) revealed multiple lesions in thyroid, left buttock, and ilium (A, B, C). Histology of the left buttock and thyroid tumors showed an undifferentiated pleomorphic sarcoma (D, E) and medullary-type thyroid cancer, respectively (F, G). A specimen from a bone lesion in the ilium showed only sclerotic bone without tumor tissue (H). A: Whole-body image obtained with fluorodeoxyglucose-labeled (FDG-PET). B: Fused PET/CT image (thyroid). Maximum standardized uptake value (SUV_{max})=5.3 (white arrow). C: Fused PET/CT image (pelvis). SUV_{max} =4.9 (dotted white arrow), SUV_{max} =3.3 (black arrow). D: Hematoxylin and eosin (HE) staining of the soft tissue tumor in the left buttock. E: Ki-67 staining of soft tissue tumor in the left buttock. F: HE staining of thyroid lesion. G: Calcitonin staining of the thyroid lesion. H: HE staining of the bone lesion in the ilium.

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