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Performance of intra-procedural 18-fluorodeoxyglucose PET/CT-guided biopsies for lesions suspected of malignancy but poorly visualized with other modalities

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Abstract

Purpose—We sought to evaluate the safety and the diagnostic success rate of percutaneous biopsies performed under intra-procedural 18F-deoxyglucose (FDG) positron-emission tomography/computed tomography (PET/CT) guidance for lesions difficult to see with conventional cross-sectional imaging.

Methods—From 2011 to 2013, consecutive clinically indicated percutaneous PET/CT-guided biopsies of 106 masses (mean size, 3.3 cm; range, 0.7–15.9 cm; SD, 2.9 cm) in bones (n=33), liver (n=26), soft tissues (n =18), lung (n=15) and abdomen (n =14) were reviewed. The biopsy procedures were performed following injection of a mean of255 MBq(SD, 74) FDG. Mean maximal standardized uptake value (SUV) of lesions was 8.8 (SD, 6.3). A systematic review of the histo-pathological results and outcomes was performed.

Results—Biopsies were positive for malignancy in 76 cases (71.7 %, 76/106) and for benign tissue in 30 cases (28.3 %, 30/106). Immediate results were considered adequate for 100 PET/CT biopsies (94.3 %, 100/106) requiring no further exploration, and for the six others (5.7 %, 6/106) benign diagnoses were confirmed after surgery (n=4) or follow-up (n=2). The consequent overall sensitivity and the diagnostic success of biopsy were therefore 100 %. No significant differences in terms of detection of malignancy were observed between the different locations. Lesions > 2 cm or with SUV>4 were not significantly more likely to be malignant. Complications occurred after four biopsies (3.7 %, 4/106).

Conclusion—Intra-procedural PET/CT guidance appears as a safe and effective method and allows high diagnostic success of percutaneous biopsies for metabolically active lesions.

Keywords

Biopsy; Cancer; Interventional radiology; PET/CT

Introduction

Targeted percutaneous biopsies under computed tomography (CT) and ultrasound (US) guidance are commonly used to obtain definitive tissue diagnoses. High diagnostic success rates have been reported for lesions visible on CT imaging, often higher than 90 % [1–4], with rates of false-negative results ranging from 3.3 % in bone [5] to 6.7 % in abdomen or chest [6]. However, many lesions are not easily visualized on non-contrast CT imaging used for needle guidance during biopsy procedures, even after careful review of CT, magnetic resonance (MR) or US investigations [7]. In these circumstances, anatomic landmarks can be used to guide tissue sampling, though confirmation of accurate needle positioning may be unattainable. This resulted in more false-negative biopsy results compared to lesions with good visualization [8]. Intra-procedural intravenous contrast may be administered to improve target conspicuity; however, depending upon lesion size and location, transient contrast enhancement may be insufficient to ensure accurate targeting [9], in particular for small lesions (less than 2 cm) [8]. Alternatively, navigation tools may be used to fuse

different imaging modalities, though breathing motion or positional differences can reduce target alignment [10].

For ^{18}F-deoxyglucose (FDG) avid lesions, the use of positron-emission tomography/computed tomography (PET/CT) has been shown to enable targeting of tumors that are not well visualized with CT or other imaging methods [11–13]. The advantage of such technique is related to the fact that FDG can be used to distinguish benign from malignant masses, viable from non-viable, or biologically aggressive from non-aggressive regions of malignant masses [14]. Another advantage of PET/CT may be to demonstrate abnormalities that are not visible on anatomic images, or before morphologic or radiographic changes may be evident. Pre-procedure PET/CT can be fused to intra-procedural CT with reasonable fidelity, though subject to the similar alignment challenges [15–18]. In order to overcome these issues, percutaneous biopsy or ablation procedures can be performed with-in the PET/CT suite [7, 13, 19]. The in-suite PET/CT-guided biopsies may avoid the challenges of fusion with previously acquired PET images due to the different placement and position of the patients during the biopsy procedures. Biopsies performed in suite may also allow a direct control of the tumor uptake position and needle placement in real time, which may improve the accuracy of such biopsies.

Although the potential to target masses or specific regions of masses suggests a wide range of possibilities for interventional PET/CT-guided procedures in the future, using either FDG or other radiopharmaceutical tracers [14], the literature on the efficacy of PET/CT-guided interventions is limited [7, 13]. The purpose of this study is therefore to evaluate the safety and the diagnostic success rate in several anatomic locations of percutaneous biopsies performed under intra-procedural PET/CT guidance for lesions that are poorly visualized with conventional cross-sectional imaging but highly suspected of malignancy.

Material and methods

Patients

The Institutional Review Board approved this Health Insurance Portability and Accountability Act-compliant retrospective study with a waiver of informed consent. From 2011 to 2013, 105 consecutive patients underwent FDG-PET/CT-guided biopsy at our institution for diagnostic evaluation of 106 FDG avid lesions.

Over the study period, there were 48 female and 57 male patients ranging in age from 7 to 78 years (mean 59 years, SD 15). All patients had a pre-procedure PET/CT prior to the biopsy (mean 24.4 days prior, range 2–112, SD 22.1). Out of 105 patients, 102 had a known malignancy, including lymphoma (n=25), cancers of breast (n=17), lung (n=13), head and neck (n=11), colon (n=6), esophageal (n=5), sarcoma (n=5), prostate (n=4), melanoma (n=3), endometrium (n=2), gastric (n=2), myeloma (n=2), rectal (n =1), pancreas (n=1), small bowel (n=1), skin (n=1), thyroid (n=1), vulva (n =1), germ cells (n =1) and kidney (n =1).

Following a multidisciplinary effort and targeted biopsy consultation, a recommendation for PET/CT guidance was based on existing image review, including PET/CT and challenges

anticipated using CT, MR or ultrasound modalities for procedural guidance due to the lack of visualization of the targets with these imaging modalities. Biopsies were performed for restaging (n =100), for initial diagnosis of a lesion suspected of malignancy identified with diagnosis PET/CT (n=3), for lesions that had a high suspicion for cancer, and a non-diagnostic biopsy using another imaging tool (n=2), or for post-treatment response assessment (n=1).

Therefore, in the 105 patients studied, FDG PET/CT-guided biopsies were performed in 106 masses (mean size of the uptake zone 3.3 cm, range 0.7–15.9, SD 2.9). Among all lesions, 47 measured less than or equal to 2 cm and 59 more than 2 cm. Ten lesions measured less than or equal to 1 cm. Anatomically, biopsy targets were located in bone (n=33; 31.1 %), liver (n=26; 24.5 %), soft tissue (i.e., lymph nodes or subcutaneous tissue, n=18; 17 %), lung (n =15; 14.1 %) and abdomen (n=14; 13.2 %). Each patient had one lesion biopsied, except for one patient who had two sites biopsied, both in bone, in two different procedures with a 12-month interval. Patient and tumor characteristics are summarized in Table 1.

PET/CT-guided biopsies

Three board-certified interventional radiologists performed the biopsies in a PET/CT suite dedicated for interventional procedures. Patient positioning was based upon factors including target location, optimal needle path and shortest skin-to-target distance. A radiopaque grid (Beekley, Bristol, Conn, USA) or custom needle-localizing device was placed on the patient's skin. No patient received iodinated intravenous contrast agents for biopsy procedures. Intra-procedural fluorine-18-deoxyglucose (Cardinal Health, Woburn, Mass) PET/CT imaging with a mean injected activity of 255 MBq (range, 144–488; SD, 74) was performed for all patients. Only ten patients received a dose > 277 MBq. Patients were asked to fast for at least 8 h before intravenous FDG injection. PET/CT (Discovery ST; GE Medical Systems, Milwaukee, WI) was performed with a mean of 81 min (range 35–183 min, SD 24.6 min) after FDG injection, depending on uptake time. Plasma glucose was measured prior to administration of FDG (mean 108 mg/dl, range 60–194 mg/dl, SD 23.9 mg/dl).

Patients with a whole body PET/CT within 8 weeks of the biopsy procedure (98 biopsies) had only limited PET/CT imaging (one to two position beds) over the biopsy region of interest. If the patient did not have a PET/CT within 8 weeks, the patient received a whole body PET/CT to take advantage of the administered dose, which required longer uptake than observed for limited PET/CT imaging. An initial non-contrast CT for attenuation correction and anatomic co-registration without oral or intravenous contrast material was obtained in every case (imaging parameters: 120kVp, 115 mA, 1.25 mm collimation, reconstructed as 3.75 mm thick slices using a 512*512 matrix). Immediately after CT, PET imaging was acquired in three-dimensional mode (slice 128×128 matrix; voxel size 4.24 mm×4.25 mm×3.27 mm).

Standardized uptake values (SUV) were normalized to patient body weight and a maximum SUV (SUVmax) in a given disease site was calculated after rescaling overall activity concentration ($Bq.ml^{-1}$). Uptake values from all abnormal regions were recorded. For comparison, the mean liver uptake values were also recorded (mean 2.4, range 1.7−3.6, SD

1.2) and compared to PET/CT imaging obtained prior to the biopsy procedure. All targeted tumors were well visualized on intra-procedural scans with a mean SUV of 8.8 (range 1.9–44.4, SD 6.3).

After PET/CT images were acquired from one or two relevant bed positions, insertion and guidance of the needles were performed with CT. However, intermittently, intraprocedural CT images of the needle were fused with the initial PET data set to confirm intended needle position within the FDG-avid target volume. A coaxial 11 gauge bone biopsy system (Madison, Laurane Medical, Westbrook, Conn, USA) was used for all bone biopsies performed under local anesthesia. For other biopsies, needle diameter varied from 18 to 20 G (Temno Evolution, Carefusion, San Diego, CA, USA). The mean number of needle passes for all biopsies was three (range 1–10, SD 1.3).

Histopathology

All samples were reviewed in the pathology department at our institution. Lesions were initially classified as malignant or benign according to tissue pathology reports. When malignancy was not initially diagnosed by biopsy, or when the initial biopsy was non-diagnostic, a medical record review was performed in order to determine whether additional procedures clarified the nature of the lesion. Final classification took into account results of surgical procedures, as well as follow-up imaging.

Statistical analysis

All patient data were retrospectively acquired through review of medical records, imaging, and pathology reports. Means, standard deviations, and medians were evaluated for the distribution of the quantitative continuous variables. Descriptive statistics were used to summarize the results.

Procedure-related complications were noted and classified on the basis of criteria proposed by the Society of Interventional Radiology [20] and the National Cancer Institute Common Terminology Criteria Adverse Events (CTCAE, version 4.0).

Tumors were subcategorized into small lesions (≤2 cm) and large lesions (> 2 cm) and into lesions with SUV ≤4 and SUV>4 to evaluate the performance of PET/CT in these subcategories. Statistical analysis was conducted with Fisher exact test, χ^2 for independent variables, a Mann-Whitney U test for nonparametric variables and $p<0.05$ was considered statistically significant. Diagnostic accuracy was reported in terms of sensitivity, specificity, negative and positive predictive values (PPV). The PPV was defined as the proportion of malignant lesions in each group of locations, and was calculated with 95 % confidence intervals (CIs) using the Wilson method. For each anatomic location, the rate of malignancy within the group was compared with the rate for all lesions outside of the group via a chi-square test with Bonferroni correction (STATA© software, College Station, Texas, USA).

Results

PET/CT-guided biopsies

All needle placements were performed in the area of metabolic activity for biopsy. For all biopsies, adequate necessary specimens for pathological profiling were obtained. Among all biopsies performed, biopsy procedures were positive for malignancy in 76 cases (71.7 %, 76/106) (Figs. 1 and 2) and positive for benign tissue in 30 cases (28.3 %, 30/106). The 76 biopsies with malignant diagnoses included 53 carcinomas, 16 lymphomas, three melanomas, three sarcomas and one myeloma. The 30 biopsies with benign findings corresponded to inflammatory (n=12), fibrotic (n = 7) or granulomatous tissue (n=5) and benign bone marrow (n=6) (Fig. 3). The results are summarized in Tables 2 and 3.

There were 100 PET/CT biopsies (94.3 %, 100/106) that were considered as adequate on medical report, requiring no further exploration. The six remaining biopsies, which were possibly falsely negative (non-malignant findings but high suspicion of malignancy), were further evaluated surgically in four cases and by clinical and imaging follow-up in two cases (Table 3 and Fig. 3). These subsequent investigations confirmed the absence of malignancy in the targeted zone in all six of these patients.

Therefore, the diagnostic success of biopsies performed under PET/CT guidance was 100 % (106/106) after taking into account the outcomes and follow-up results. Moreover, as no biopsies were considered false-negative results, the consequent overall sensitivity of biopsy was 100 % (76/76).

Complications

Complications were observed after four biopsies (3.7 %, 4/106). All were considered at level 2 according to CTCAE classification. Three pneumothoraces (two after lung biopsies, one after liver biopsy) and one self-limited hematoma after liver biopsy were reported. The pneumothorax required chest tube placements for one patient. All pneumothorax patients were discharged on the day after the biopsy.

Accuracy of PET/CT as a diagnostic tool

The data from this study also permitted an analysis of diagnostic PET/CT as a predictor of tissue malignancy. PET–CT allowed for only low prediction of malignancy: detection rate of malignancy with PET/CT is summarized in Table 2 according to the different locations. Despite the different anatomic locations, no significant differences were observed by anatomic location. Moreover, for tumors less than or equal to 2 cm (n=47), the detection rate was 68.1 % (32/47), whereas for tumors > 2 cm (n=59), it was 74.6 % (44/59) (p=0.58). For tumors less or equal to 1 cm, the detection rate was 60 % (6/10). For SUV less than or equal to 4 (n=20), the detection rate was 50 % (10/20), whereas for SUV>4 (n=86), it was 76.7% (66/86) (p=0.15).

Discussion

For many patients requiring histologic confirmation of radio-graphic lesions that are poorly visualized on ultrasound or non-contrast CT scans, PET/CT imaging guidance can contribute

to successful biopsies [21, 22]. We describe in this retrospective report a large series of patients with lesions highly suspected for malignancy undergoing PET/CT-guided biopsies in a dedicated interventional PET/CT scanner and in a variety of anatomic locations.

As shown in our large study cohort, PET/CT-guided biopsies can be performed safely and accurately. The complication rate is low and seems comparable with the rate observed after CT-guided biopsies [1–6]. Targeted biopsies were positive for malignancy in 71.7 % of cases. In the study population, if a malignant lesion existed, the biopsy always identified it (sensitivity 100 %). Our study confirmed, therefore, the high sensitivity of diagnostic FDG-PET to detect malignancy, even if other radiographic techniques failed to identify a lesion [22]. Although prior reports of high success rates with other techniques of guidance of percutaneous biopsies have been reported [1–6], performance of direct PET/CT guidance may be higher yet, because no false-negative biopsies were observed. It may be related to the fact that needle positioning in the specific focus of highest FDG uptake is possible, and can be confirmed in real−time using fused PET/CT images, regardless of patient position in the scanner [11,13,23]. Relative to other image−fusion techniques, in−suite direct PET/CT biopsy is less susceptible to registration bias or misalignment [24–26].

In our clinical practice, we administer FDG doses of 222–259 MBq (6−7 mCi) of FDG for PET/CT-guided biopsies. Although this differs from the standard diagnostic dose of 444 MBq (12 mCi) used in our institution and from other PET/CT-guided biopsy studies [7, 13], this protocol allowed adequate results. Early in our experience we used the diagnostic PET dose of ~440 MBq; however, later in our experience, we moved to a lower FDG dose as we realized that this was sufficient to visualize our target. All patients had a prior high quality diagnostic PET/CT scan, so the purpose of this scan was purely for identifying an already identified lesion and guiding the biopsy. This targeting dose of 222−259 MBq (6−7 mCi) was chosen on the basis of the FDG half-life, uptake time and mean biopsy procedure length. Such a “low dose” protocol may limit the cost of the procedure and the radiation exposure due to the radiotracer to the patient, physician, nurses, anesthesiologists, technologists, and trainees. As it is possible that the dose may be lowered, further standardized prospective studies are needed to determine a lower and best FDG dose sufficient to visualize the lesions during the procedure.

A particular advantage of FDG-PET/CT imaging guidance is the ability to differentiate and selectively sample the most metabolically active component of a lesion. This can be beneficial for heterogeneous targets, and may reduce the false-negative biopsy rate [13] and improve disease stratification [12, 27–32]. It may be particularly useful in cases of evolving or previously treated disease, when new avid lesions must be adequately differentiated from others. Due to better visualization, targeted biopsy with PET/CT imaging might reduce the time of procedures for lesions with equivocal imaging findings with other modalities, and subsequently radiation exposure to the patient and physicians [33]. Further comparative studies may evaluate these parameters specifically. On other hand, it is well known that diagnostic PET/CT scans have limited specificity and often highlight areas of non-malignant lesions, such as areas of inflammation. In our patient cohort, the high rate of non-malignant FDG avid disease (28.8 %), confirmed by histopathology or subsequent imaging appearance, correlates with published rates [34–36]

There are several limitations to this study. First, our study is limited because of its retrospective nature. Intra-procedural PET acquisitions were not standardized. Variable dosage of FDG and time of acquisition after injection may have influenced the SUV measurements and the statistical results on subcategorized lesions within SUVmax. The uptake time variability reflects a busy interventional practice where workflow timing is complex. Since patients had pre-procedural diagnostic quality PET/CT, it was less critical to have the consistent imaging algorithm. Secondly, our population was highly selected; all but three (2.8 %, 3/106) of the patients included in this study had a cancer diagnosis prior to biopsy. However, prior studies have reported that PET positive predictive value was not significantly affected by history of malignancy [22]. We included all patients consecutively to minimize bias, but patients were selected based on the operator's belief that the biopsy would be facilitated by PET guidance. Third, generalizability of our findings may be limited by the fact that dedicated interventional PET/CT suites are not widespread. Studies such as this may provide additional clinical justification for interventional PET imaging facilities in the future. Another limitation is that FDG activity may not be detectable in all cancers [21], such as in small (< 5 mm) tumors or in tumors recently treated with chemotherapy; therefore, the techniques studied here are not always applicable [18]. For very small lesions, image registration errors between CT and PET may be also reduced. However, as shown in our study even for small tumors < 1 cm, spatial accuracy of this technique seemed sufficient to display clinically relevant image guidance information during biopsy. The cost-effectiveness in terms of time, cost and radiation dose has not been evaluated in our study and is warranted. Findings of such a study must be weighed against the potential to decrease the number of non−diagnostic or false-negative results observed after PET/CT-guided biopsies.

In conclusion, this study demonstrates that intra-procedural PET/CT-guided biopsy is feasible and can be safely performed with complication rates comparable to traditional CT-guided biopsies. PET/CT imaging guidance can be used to biopsy metabolically active lesions with excellent diagnostic success. Detection of malignant tissue with FDG is high, allowing a high overall sensitivity, but a high rate of false positives remain due to the lack of specificity of FDG. Relative to diagnostic PET imaging, lower doses of FDG are sufficient for visualization of percutaneous biopsy targets.

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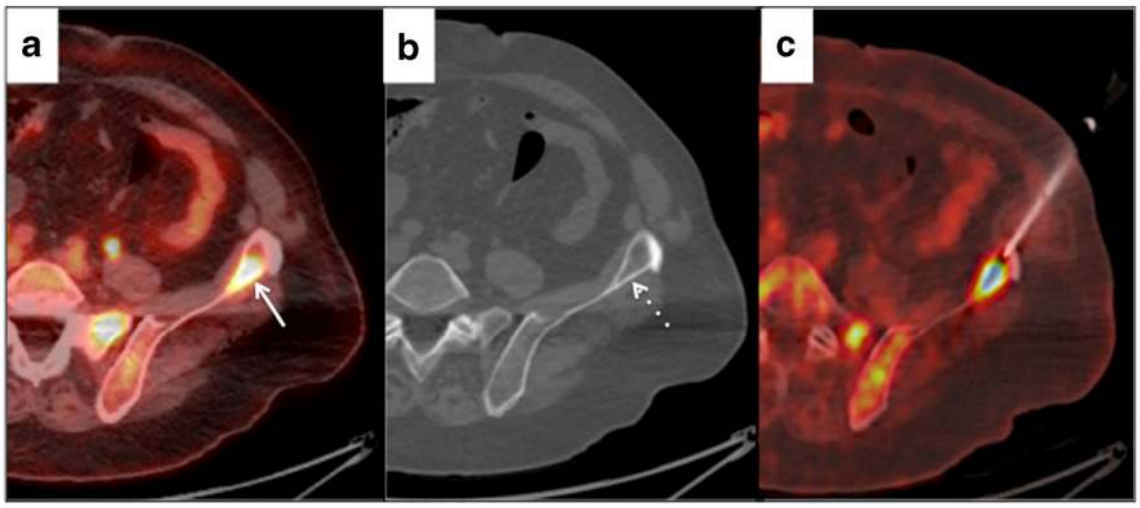

Fig. 1.

PET/CT-guided bone biopsy in a 60-year-old man with history of oropharyngeal carcinoma. **a** Axial FDG PET/CT image showed uptake (10.2) on the left iliac bone (*arrow*) with high suspicion of metastasis. **b** Axial non-contrast CT scan showed no imaging correlate in the corresponding region (*discontinuous arrow*). **c** CT image showing the needle into the lesion. The pathologist concluded to a carcinoma metastasis

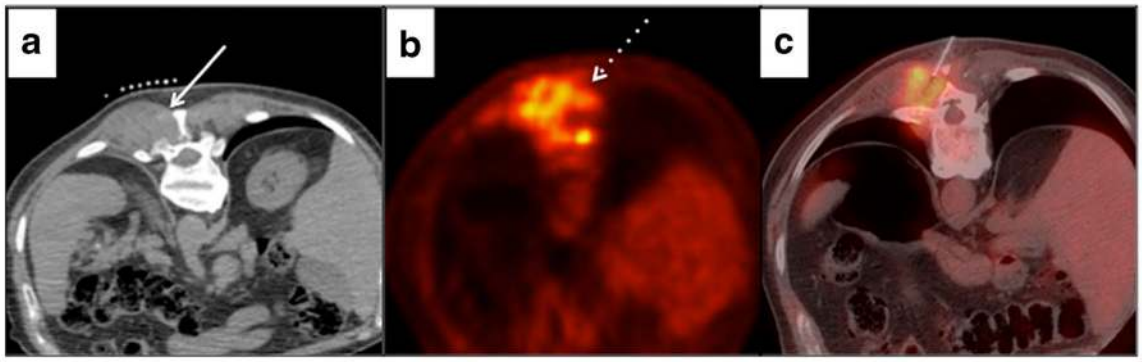

Fig. 2.

PET/CT-guided soft-tissue biopsy in a 73-year-old man with history of lymphoma and back pain. **a** Axial non−contrast CT-scan showed no imaging correlate (*arrow*). **b** FDG PET image showed uptake in the left paraspinal muscle (SUV 10.4) (*discontinuous arrow*). **c** Axial PET/CT fusion image with needle. The 10.8 cm lesion corresponded to a recurrence of a B-cell lymphoma

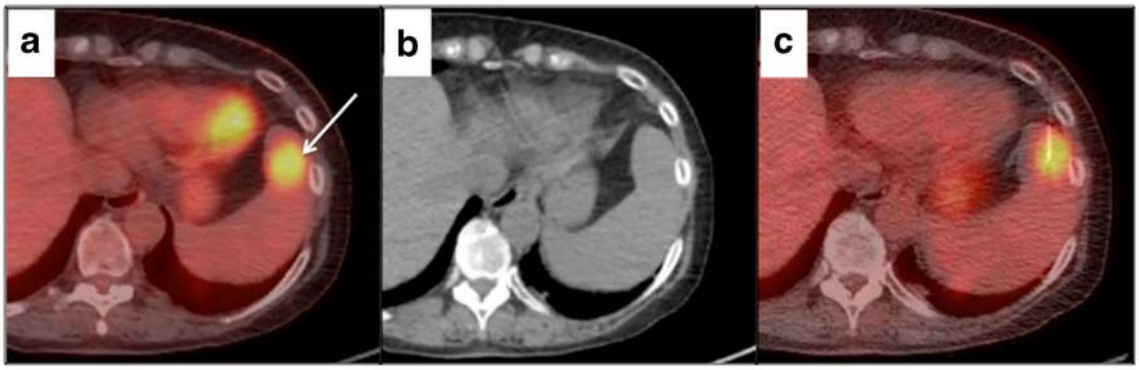

Fig. 3.

PET/CT-guided splenic biopsy in a 70-year-old woman with history of follicular lymphoma. **a** Axial FDG PET/CT fusion image showed a 2 cm uptake (SUV 8.2) in the spleen *(arrow)* with high suspicion of new localization. **b** Axial non-contrast CT-scan showed nothing suspicious in the corresponding region. **c** Corresponding PET/CT image showing the needle into the lesion. The pathologist concluded to granulomatous reaction and normal spleen tissue. A splenectomy performed subsequently confirmed this result without lymphoma recurrence

Table 1

Patients and tumor characteristics

Characteristics	Datum	% or Range
Total no. of patients	105	
No. of men	57	54.3 %
No. of women	48	45.7 %
Median age (y)[a]	61.5	(7–87)
Median plasma glucose (mg/dl)	103	(60–194)
No. of lesions	106	
Median lesion size (cm)[a]	2.4	(0.7–15.9)
Median SUV[a]	7.2	(1.9–44.4)
Indication		
Restaging	100	94.4 %
Initial diagnosis	3	2.8 %
Previous non-contributive biopsy	2	1.9%
Post-treatment response	1	0.9 %
Lesion location		
Bone	33	31.1 %
Liver	26	24.5 %
Soft-Tissue	18	17%
Lung	15	14.1 %
Abdominal	14	13.2%
Initial malignancy		
Lymphoma	25	23.6 %
Breast carcinoma	17	16%
Lung carcinoma	13	12.3 %
Head and neck carcinoma	11	10.4 %
Colon carcinoma	6	5.7 %
Esophageal carcinoma	5	4.7 %
Sarcoma	5	4.7 %
Prostate carcinoma	4	3.8 %
None	3	2.8 %
Melanoma	3	2.8 %
Plasmocytoma	2	1.9%
Endometrium carcinoma	2	1.9%
Gastric carcinoma	2	1.9%
Rectal carcinoma	1	0.9 %
Pancreas carcinoma	1	0.9 %
Small bowel carcinoma	1	0.9 %
Skin carcinoma	1	0.9 %
Thyroid carcinoma	1	0.9 %

Characteristics	Datum	% or Range
Vulva carcinoma	1	0.9 %
Germ cells carcinoma	1	0.9 %
Renal carcinoma	1	0.9 %

SUV standardized uptake value

[a]Data in parentheses are ranges

Table 2

Biopsy results

Location	No.	Malignant	Benign	Initially considered as adequate	*p**
Bone	33	24 (72.7 %)	9 (27.3 %)	30 (90.9 %)	0.09
Liver	26	23 (88.5 %)	3 (11.5 %)	26 (100 %)	0.24
Soft-Tissue	18	13 (72.2 %)	5 (27.8 %)	17 (94.4 %)	0.06
Lung	15	8 (53.3 %)	7 (46.7 %)	14 (93.3 %)	0.13
Abdominal	14	8 (57.1 %)	6 (42.9 %)	13 (92.9 %)	0.06
Total	106	76 (71.7 %)	30 (28.3 %)	100 (94.3 %)	NA

*Rate of malignancy identified with biopsy within the group wascompared with the rate for all lesions outside of the group via a chi-square test with Bonferroni correction

Table 3

PET/CT-guided biopsy results considered initially as non-diagnostic (n=6) and subsequent surgical explorations and/or outcomes

Patient No.	Type	Size (cm)	Location	History	SUV	Pathological result	Additional imaging diagnosis	Follow-up (months)	Outcomes
1	Bone	1.5	8th left rib	Breast cancer	6.9	Benign bone marrow	Fracture	18	Spontaneous resolution
2	Bone	2.2	Right femur	Lung cancer	4.1	Hypercellular bone marrow	-	-	Surgical curettage
3	Bone	2.1	Left Femur	Lymphoma	8.3	Hypercellular bone marrow	-	-	Surgical curettage
4	Soft-tissue	2	Anterior mediastinum	Lymphoma	14.2	Fibrotic tissue	-	-	Surgical resection
5	Lung	2.3	-	Lung cancer	3.5	Aspecific inflammatory tissue	Post radiotherapy	6	Stable with bronchograms
6	Abdomen	2	Spleen	Lymphoma	8.2	Granulomatous reaction	-	-	Splenectomy

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