Original Article

Ex vivo Measurement of the Radioactivity of PET/CT-Guided Biopsy Specimen: Is it Helpful to Confirm the Sampling from a Viable Region of the Tumor and the Nature of the Lesion?

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Abstract

Objective: *Ex vivo* radioactivity measurement of positron emission tomography/computed tomography (PET/CT)-guided biopsy tissue specimen to check the viable tumor sampling and predict the nature of the biopsied lesion. **Materials and Methods:** We prospectively evaluated the retrieved tissue specimens during PET/CT-guided biopsies for the presence of radioactivity. The qualitative radioactivity was measured by acquiring PET/CT images of the specimen. For quantitative analysis, a multichannel-analyzer (MCA) was used, and a counting-factor (CF) in counts/mCi.mm^3 was calculated based on background-corrected net-counts, tissue-volume (mm^3), and exponential tracer-activity during biopsy (mCi). The CF-values were compared with the 2-(fluorine-18) fluoro-2-deoxy-D-glucose-avidity in the target lesion and correlated with the histopathology. **Results:** A total of 49 patients (30 males) aged 51.8 ± 17.8 years were recruited for the biopsy, and radioactivity was measured. All the specimens revealed the presence of radioactivity on PET/CT images of the specimens and MCA counting. The mean CF-values were 17.2 ± 15.6 counts/mCi.mm^3. One sample had meager counts with a CF-value of 0.162 and was subjected to re-biopsy after repositioning the coaxial needle to the hypermetabolic site. Pathological diagnosis was established in all the patients (malignancy-29, benign-20). The CF-values were significantly higher in malignant lesions than benign (21.45 ± 18.05 vs. 10.76 ± 8.96 counts/mCi.mm^3, P = 0.025). CF-values and maximum standardized uptake value had a significant correlation (Pearson's r = 0.457, P = 0.001). **Conclusion:** The *ex vivo* measurement of the radioactivity of retrieved tissue specimens during PET/CT-guided biopsy helps to confirm the sampling from viable region and a highly practical approach to avoid erroneous sampling of a lesion with a large necrotic area. It is also helpful in predicting the nature of the biopsied lesion before the histopathological analysis.

Keywords: *Biopsy, ex vivo, fluorodeoxyglucose, positron emission tomography computed tomography, radioactivity*

Introduction

For individualized therapy planning in oncological practice, accurate tissue diagnosis and tumor staging is the utmost requirement. Although many laboratory investigations, including tumor markers and anatomical imaging modalities, are used to determine metastatic disease, histopathology remains the gold standard to confirm a malignancy.[1] Conventional imaging (CI) modalities such as ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI) are commonly used for image-guided tissue sampling.[2] CT-guided tissue sampling has long been the standard technique to obtain tissue from a lesion.[3] The results can be variable and affected by the size of the lesion and the part of the lesion biopsied.[4] Moreover, these CI modalities cannot discriminate between a viable and nonviable part of the tumor and often may lead to falsely negative image-guided biopsy and ensuing a fall in diagnostic accuracy.[5]

2-(fluorine-18) fluoro-2-deoxy-D-glucose positron emission tomography/CT (FDG PET/CT) is a vital imaging modality that provides the anatomical along with functional details of the tumor or part of the tumor. It is now an established imaging modality for staging, restaging, and response assessment in various tumors.[6,7] FDG PET/CT helps in the early diagnosis of malignancies since it reveals changes at the tissue level before any significant

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changes appear at morphological levels.[8] FDG avidity in a lesion is not specific to malignancy, and many benign inflammatory or infective etiologies may also show FDG uptake, which affects the overall diagnostic performance of PET/CT.[9] Hence, before planning individualized treatment, the nature of FDG uptake in a lesion needs to be confirmed with histopathological examination. PET/CT-guided biopsy from a tracer avid lesion, or viable portion of the tumor, is an emerging interventional modality to confirm the histopathological nature of the lesion.[10-14] PET/CT-guided biopsies can increase the chance of achieving definitive diagnosis and reduce the chance of false negativity with a reported success rate of 98.2% for bone lesions and 96.5% for abdominopelvic lesions with nonrepresentative sampling in approximately 3.5% of the patients leading to false-negative results.[10,11] Small numbers of these false-negative lesions might be attributed to technical error due to the displacement of the biopsy needle and sampling from nonavid lesions.

An *ex vivo* measurement of the radioactivity of the biopsy specimen may be an ideal approach to reduce these sampling errors. The present study aimed to evaluate the *ex vivo* measurement of radioactivity in PET/CT-guided biopsy specimens to confirm whether the sampling was from a viable portion of the tumor.

Materials and Methods

Patient population

In this prospective study, patients who underwent FDG PET/CT-guided biopsies were recruited from October 2018 to April 2019 to measure the radioactivity of the retrieved tissue specimen. The institute ethics committee approved the study and informed written consent was obtained from the patients for the biopsy procedure, explaining the procedure-related complications, risks, and benefits. The inclusion criteria for the study were the presence of FDG-avid lesion on whole-body PET/CT imaging, normal or corrected coagulation profile, and age more than 18 years. Patients with uncorrected or abnormal coagulation profile, hemogram <8 mg/dl, and platelet count <80,000 μ/dl were excluded from the study.

Patient preparation and positron emission tomography/computed tomography imaging

Patients were kept fasting for 4–6 h, and anticoagulant medications (if any) were stopped for at least 4 days before the procedure. A whole-body PET was acquired in patients with no prior PET/CT scan using a dedicated PET/CT scanner (Discovery MIDR, GE Medical Systems, Milwaukee, WI, USA) after injecting 296–370 Minimum Base Quantity (MBq) (8–10 mCi) of F-18 FDG intravenously. PET/CT-guided biopsy procedure was performed 4–6 h later to reduce radiation exposure to the interventionists. For patients with a previous PET/CT scan, a low dose of FDG, i.e., 111–150 MBq (3–4 mCi), was injected, and the biopsy procedure was done after 60–90 min.

Biopsy procedure

The whole-body FDG PET/CT images were reviewed and trajectory for biopsy was planned after considering the size of the lesion, area with maximal FDG avidity, nearby vasculatures, and patient safety.

Patients were positioned into prone/supine/lateral positions depending upon planned trajectory and immobilized. A regional PET/CT image of the region of interest was acquired. During the biopsy procedure, CT parameters were 40 mA and 120 kVp, rotation time 0.8 s, 1.25 slice thickness, 512 × 512 matrix followed by PET acquisition (60 s/bed position, 3.75 mm slice thickness, and 128 × 128 matrix). For biopsy planning, the regional PET/CT images were transferred to Automated Robotic Arm (ROBIO-EX, Perfint healthcare Pvt. Ltd, Chennai; India). The preplanned trajectory was then executed on the ROBIO-EX console, and the robotic arm was placed automatically for execution along the planned path. A suitable coaxial biopsy needle was introduced manually under the robotic arm guidance. A low-dose check CT (40 mA tube current) was acquired to verify the position of the needle. After confirming the position of the needle to a viable area of the tumor, adequate tissue cores were taken. The whole procedure was done under surgical asepsis and after giving local anesthesia. For soft tissue biopsies, 18G and 16G needle biopsy instrument was used with a throw of 10 mm or 20 mm tissue length. For bone biopsies, 11G needles were used.

Calculation of tissue volume

The volume of the retrieved tissue sample was calculated based on the gauge and length of the biopsy needle, as provided by the manufacturer (BARD, BD interventional). For an 18G needle with a 10 mm core, one core would be equal to 8.231 mm^3, and a 20 mm core would be equivalent to 16.462 mm^3. For a 16G needle with 10 mm and 20 mm core, the volume would be equal to 13.083 mm^3 and 26.126 mm^3, respectively. For 11G needles, the volumes equivalent to 10 mm and 20 mm core would be 41.671 mm^3 and 83.340 mm^3, respectively.

Radioactivity measurement and counting procedure

The retrieved tissue samples were collected in a test tube containing 12 ml of formalin. The qualitative radioactivity measurement of the retrieved specimens was done by acquiring the PET/CT image of the specimen container after the biopsy procedure under the PET/CT scanner. Radioactivity was measured using a multichannel analyzer (MCA) for quantitative measurements at an operating voltage of 750V. Before measuring radioactivity, the MCA was calibrated with Cs-137 standard source. For each specimen, two counts were taken (C1 and C2) for a preset time of 60 s and at a 20% window centered over photopeak of 511 keV. Background counts were also taken for the same period and photopeak window. A counting factor (CF) measured in counts/mCi. mm^3 was calculated based on background-corrected sample counts, decay corrected radioactivity at the time of biopsy,

which is calculated by exponential law of radioactivity (mCi) and volume of retrieved core tissue (mm^3) to eliminate variation in injected activity, differences in duration of biopsy after injection of activity and variation in the number of cores taken from each patient.

The time duration between radiotracer injection and tissue sampling, numbers of the core samples, the biopsy site, and maximum standardized uptake value (SUVmax) of the target lesions were recorded for each patient. The gold standard for evaluating the result was a final histopathological report, and data were categorized into two groups (malignant and nonmalignant). An independent *t*-test was applied to see differences in CF and SUVmax in both groups. Furthermore, Pearson's correlation was calculated between CF and SUVmax of the target lesion.

Results

Patient population

A total of forty-nine patients (30 males, 19 females) aged (mean ± standard deviation [SD]) 51.8 ± 17.78 years were recruited prospectively in the present study. Of these 49 patients, 30 underwent lung biopsies, nine lymph nodal biopsies, five bone biopsies, and the remaining five patients underwent biopsy from miscellaneous sites (retroperitoneal lesion-1, adrenal mass-1, muscle mass-3). All the procedures were well tolerated with slight pain and minimal bleeding; however, no life-threatening complication was noted in any patient. A dose of 3.88 ± 1.68 mCi of F-18 FDG was injected, depending on whether the patient had undergone a previous PET/CT scan. The duration between FDG injection and performing a biopsy procedure was 3.46 ± 1.34 h. Patient characteristics are listed in Table 1.

The values of radioactivity, maximum standardized uptake value, retrieved tissue volume, and calculated counting factor

The measured value of the injected tracer activity (mean ± SD) at the time of biopsy was 1.1 ± 0.5 mCi. The target lesion's uptake value (SUV max) was 13.6 ± 9.7 (mean ± SD) on whole-body images. A total of 4–6 biopsy cores were retrieved in each patient, and the mean volume of the tissue was 66.5 mm^3. All the retrieved specimens revealed radioactivity on a qualitative analysis of PET/CT images of retrieved biopsy specimens [Figure 1].

For quantitative analysis, radioactivity in each specimen was measured using MCA. Based on the counts in each specimen, CF values were calculated that had a nonzero value, i.e., minimal value and maximal values varying from 0.162 to 77.3 counts/mCi.mm^3. Of the total 49 specimens, one had a meager value of CF (0.162 counts/mCi.mm^3) and this patient underwent repeat sampling in the same sitting, which revealed a CF-values of 25.5 counts/mCi.mm^3. The calculated values of CF (mean ± SD) were 17.2 ± 15.6 counts/mCi.mm^3.

Table 1: Patient characteristics and key variables

Parameter	Value
Total numbers of patients	49
Gender (male/female)	30/19
Age (years), mean±SD	51.8±17.78
Dose of F-18 FDG injected (mCi), mean±SD	3.88±1.68
Time to perform the procedure after tracer injection (h), mean±SD	3.46±1.34
Sites of biopsy	
Lung	30
Bones	5
Lymph nodes	9
Miscellaneous (retroperitoneal lesion-1, adrenal-1, and muscle-3)	5

SD: Standard deviation, F-18 FDG: 2-(fluorine-18) fluoro-2-deoxy-D-glucose

Histopathology analysis

Pathological diagnosis was established in all the patients. Of the total forty-nine patients, twenty-nine were malignant on pathology, while the remaining 20 were benign. Of the 29 malignant lesions, eight (27.5%) were adenocarcinoma, seven (24.1%) were lymphoma, five (17.2%) were squamous cell carcinoma, two (6.8%) had small cell carcinoma, and the remaining seven (24.1%) had diverse tumors, i.e., myeloma, leukemia, synovial sarcoma, papillary cystadenoma, myofibroblastic tumor.

Correlation of counting factor, radioactivity, and maximum standardized uptake value of lesions with histopathology

For patients with malignant histology, the value of radioactivity at the time of biopsy was 1.00 ± 0.655 mCi, lesion SUVmax 15.10 ± 9.19, and the measured CF was 21.45 ± 18.051 counts/mCi.mm^3 [Figure 2]. For patients with

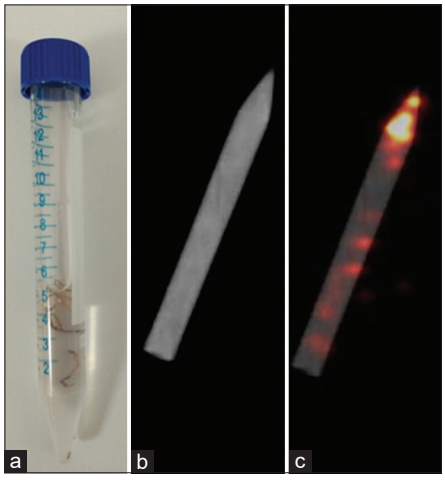

Figure 1: Container (a) showing the retrieved tissue specimen after positron emission tomography/computed tomography-guided biopsy, Sagittal computed tomography and positron emission tomography/computed tomography (b and c) revealed FDG avidity in the retrieved specimen, confirming the sampling from the viable tumor

benign histological findings, the radioactivity, SUVmax, and CF values were 1.05 ± 0.590 mCi, 11.39 ± 10.27, and 10.76 ± 8.96 counts/mCi.mm^3 [Figure 3], respectively. However, based on qualitative analysis of PET/CT images of the retrieved tissue specimen for the presence of radioactivity, differentiation between benign and malignant lesions is not possible.

The value of Karl Pearson's correlation coefficient between CF and SUVmax was found to be 0.457, with a $P = 0.001$. These values suggested a statistically significant moderate positive correlation between the CF and SUVmax.

Comparison of counting factor, radioactivity, and maximum standardized uptake value of lesions in malignant and benign groups

An independent *t*-test was applied to see if a significant difference in the value of activity injected SUVmax and CF in malignant and benign groups. There was no significant difference in exponential decay corrected activity at the time of biopsy in both groups ($P = 0.788$). Similarly, no significant difference was noted in the SUVmax of the lesion in the two groups ($P = 0.216$). However, there was a statistically significant difference in CF-values of the

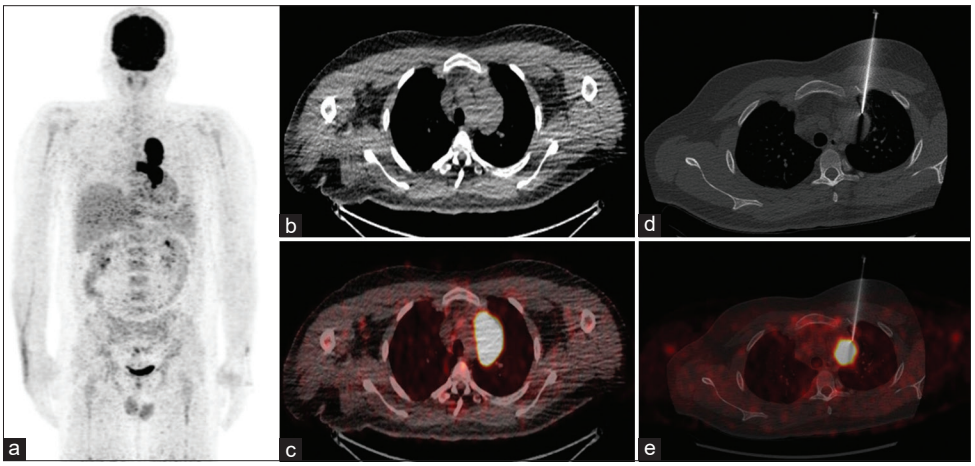

Figure 2: A 32-year-old male presented with chronic cough with dilated cardiomyopathy with monomorphic ventricular tachycardia. He had clinical suspicion of sarcoidosis and the NCCT chest revealed mediastinal lymph nodes. He was referred for FDG positron emission tomography/computed tomography and guided biopsy. A maximum intensity projection (a) image of positron emission tomography/computed tomography revealed FDG-avid lesions in the thoracic region. Transaxial computed tomography and fused positron emission tomography/computed tomography images (b and c) revealed FDG-avid mediastinal lymph nodes with maximum standardized uptake value 36.6. Transaxial computed tomography and fused computed tomography images (d and e) show the biopsy needle positioned to the FDG avid mediastinal lymph node. The counting factor of the retrieved specimen was 18.1 counts/mCi. mm^3. Histopathology demonstrates the caseating granulomatosis suggestive of tuberculosis

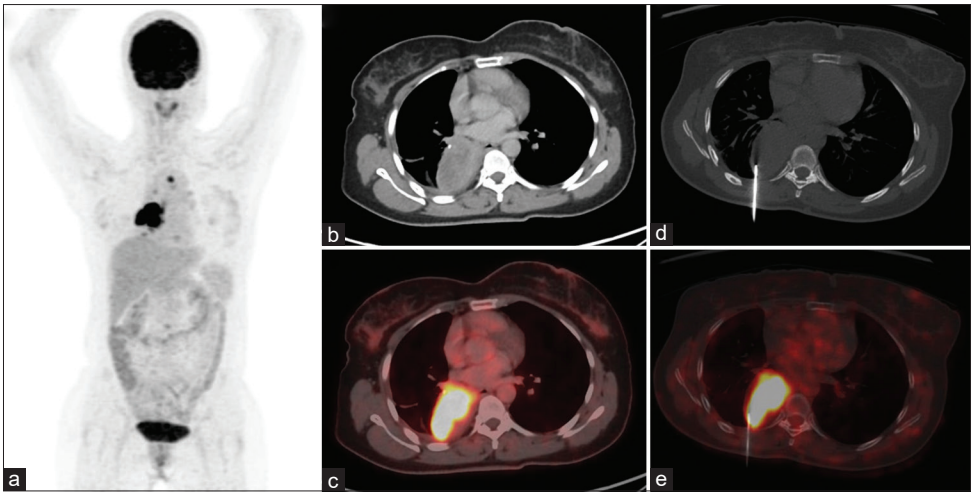

Figure 3: 50-year-old female presented with cough, weight loss, and hemoptysis for 1 year. Enhanced computed tomography demonstrated soft tissue density in the run-length limited with segmental collapse and right pleural effusion. Computed tomography-guided fine-needle aspiration was inconclusive. She was referred for FDG positron emission tomography/computed tomography and positron emission tomography/computed tomography-guided biopsy if amenable. Maximum intensity projection image of positron emission tomography/computed tomography (a) revealed FDG-avid lesions in the thoracic region. Transaxial computed tomography and fused positron emission tomography/computed tomography images (b and c) revealed FDG-avid mediastinal lymph nodes with maximum standardized uptake value 19.3. Transaxial computed tomography and fused computed tomography images (d and e) show the biopsy needle positioned to the FDG-avid mediastinal lymph node. The counting factor of the retrieved specimen was 29.5 counts/mCi. mm^3. Histopathology confirmed the diagnosis of adenocarcinoma lung

malignant and benign lesions (P = −0.025). A comparison of these parameters with histopathology is shown in Table 2.

The receiver operating characteristic (ROC) curve analysis [Figure 4] revealed that a CF value >11.2 counts/mCi.mm^3 could predict the malignancies with a sensitivity of 72.4% and specificity of 65%, and the area under the ROC curve was 0.70. Similarly, SUVmax greater than or equal to 8.52 had a sensitivity and specificity for detecting malignancies, 75.9% and 60%, respectively, with an area under the ROC curve of 0.65.

Discussion

The present study demonstrated that *ex vivo* measuring the radioactivity of PET/CT-guided biopsy specimens facilitated accurate sampling from a viable part of the tumor and helped to establish a pathological diagnosis. Qualitatively on PET/CT images of the retrieved specimen, all the specimens had radioactivity. However, on quantitative analysis, the radioactivity was noticed in all the samples except one having minimal count on MCA and meager CF-value. After repositioning the coaxial needle to the hyper-metabolic portion of the tumor in the same sitting, this patient underwent resampling and the retrieved specimen demonstrated adequate CF value. Finally, an accurate pathological diagnosis was established in all the recruited patients. The results anticipated that there would be a significant fall in the counts if there is any technical error while sampling or any displacement of the tip of the needle from the viable to nonviable non-FDG avid part of the tumor. The novel parameter of CF values of biopsy specimens of malignant lesions was significantly higher than benign (21.45 ± 18.05 vs. 10.76 ± 8.96 counts/mCi.mm^3) with a P = 0.025, suggesting that higher the CF values, there is more chance of malignancy in a lesion. These findings suggested that one can predict the nature of the biopsied lesion (malignant vs. benign) based on quantitative analysis of radioactivity on MCA (CF values) before the histopathology analysis. However, on qualitative analysis of radioactivity of the specimen, the nature of the biopsied lesion cannot be predicted. In addition, ROC curve analysis revealed that predicting the malignancy in the specimen at a CF cut-off value of 11.5counts/mCi.mm^3 of biopsy cores has a sensitivity and specificity of 72.4% and 65%, respectively.

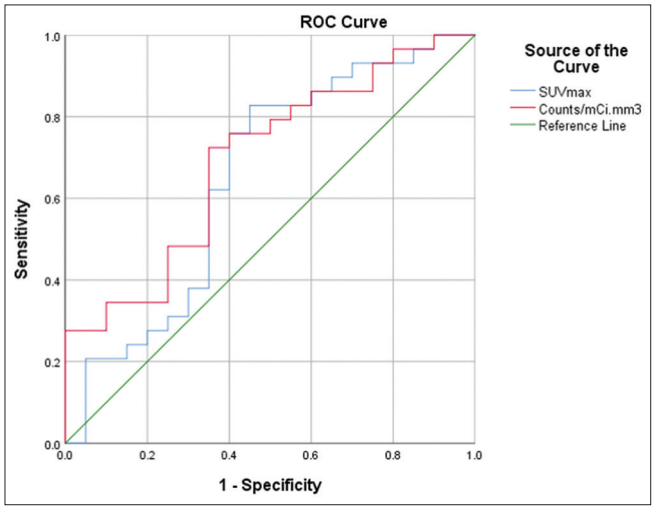

Figure 4: The receiver operator characteristic curve was drawn based on counting factor values and maximum standardized uptake value of the target lesion. The sensitivity was taken along the Y-axis and 1-specificity along the X-axis. The area under the curve of counting factor was 0.70 while for maximum standardized uptake value was 0.65

Conventional image-guided biopsies using USG, CT, MRI are well-established and safe procedures with high diagnostic yield.[15] These modalities have less sampling error or inconclusive results than open biopsy with a reduced risk of complications.[16] The accuracy of CT-guided biopsy of the thoracic lesion is 96.8%, while MR-guided prostate biopsy had a sensitivity of 93.0%.[3-17] CI cannot provide the functional details of the tumor and sampling from a nonrepresentative site, ensuing a fall in diagnostic accuracy.[5]

FDG PET/CT has the ability to show the malignant changes in an organ even before the appearance of discernible anatomical changes and is hence used as a frontline investigation in current oncological practices. The functional information provided by FDG PET/CT can facilitate the accurate retrieval of a tissue sample from the most metabolically active area within a heterogeneous lesion to expedite the early pathological diagnosis.[18] A biopsy procedure is designated as successful if the retrieved tissue specimen is adequate to establish a pathological diagnosis and immune histochemistry and tumor grading.[19]

PET/CT-guided biopsies from the various lesion, including bones, abdominal pelvic lesions, even with prior inconclusive CI-guided biopsies, have shown a very high diagnostic performance.[10,11,13] It has been documented that there is no significant difference in the rate of complication and tissue retrieval between PET/CT and CT-guided biopsies, and these modalities have shown a success rate of 96.8% versus 93.8%.[20] Despite many advantages, PET/CT-guided biopsies also have few concerns, like radiation exposure to the interventionist due to PET radiotracer and success rate may not always be 100% due to inadequate

Table 2: Comparisons of various parameters with histopathology

Parameters	Histopathology, mean±SD		*P*
	Malignant (*n*=29)	Benign (*n*=20)	
Activity at the time biopsy (mCi)	1.00±0.66	1.05±0.59	0.78
SUV_{max} of target lesion	15.10±9.19	11.39±10.27	0.21
CF (counts/mCi/mm^3)	21.45±18.05	10.76±8.96	0.02

SD: Standard deviation, CF: Counting factor, SUV_{max}: Maximum standardized uptake value

sampling or sampling from a nonrepresentative area of the tumor. The reported radiation exposure to the interventionist was within limits specified by the regulatory authorities.[21]

The reported success rate of PET/CT-guided biopsies varies depending upon the target organ and abdominal and pelvic lesion; it has a success rate of 96.5% with nonrepresentative samples in 3.5% of the cases.[11] During PET/CT-guided biopsy, to minimize the errors while sampling, the ideal approach is to measure the *ex-vivo* radioactivity of retrieved specimens.

Hu *et al*. revealed that the SUV max values of 3.5 helped predict malignancies in solitary pancreatic lesions with sensitivity and specificity of 92.6% and 76.9%, respectively.[22] No significant difference was observed in FDG avidity (SUVmax values) of target lesions in the present study to differentiate malignant and benign etiology on PET/CT images (P = 0.216). However, we noted a significant correlation between CF and SUVmax of the target lesion and the CF could help predict the nature of the lesion.

The study also has few limitations, i.e., the small number of recruited cohorts for the study. The recruited population had heterogeneity in the target sampled lesions based on the site and histology. In addition, the measurement of *ex vivo* radioactivity to confirm the sampling from a viable portion of the tumor may increase the time taken for biopsy and might be a reason for increased complications in these patients. However, no life-threatening complication was noticed in the present study.

The present study provides a proof of concept for *ex-vivo* measuring the radioactivity of PET/CT guided biopsy specimen helped to increase the sampling accuracy and establish a pathological diagnosis. To the best of our knowledge, this is the first study for *ex vivo* measurement of the radioactivity of PET/CT-guided biopsy cores for characterizing the retrieved specimen, which can help to predict the nature of the disease.

Conclusion

The present study demonstrated that the *ex vivo* measurement of the radioactivity of retrieved tissue specimens during PET/CT-guided biopsy helped in predicting the sampling from a viable portion of the tumor. The quantitative measurement of radioactivity also helped in predicting the nature (malignant vs. benign) of the biopsied lesions. It is a highly practical approach for accurately sampling the target lesion with a large necrotic area and justifiable to avoid inaccurate sampling.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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