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Long Half-life ^{89}Zr Labeled Radiotracers Can Guide In Suite Percutaneous Molecular Imaging PET/CT-guided Biopsies Without Reinjection of Radiotracer

Running title: In Suite ^{89}Zr PET/CT-guided Biopsies

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ABSTRACT

Rationale:

To evaluate the feasibility of in suite Zr^{89} labeled radiotracer positron emission tomography-computed tomography (PET/CT)-guided biopsies performed without reinjection.

Methods:

From 2013-2016, 12 patients (7 males, 5 females; mean age 61 years, range 40-75) with suspected metastatic prostate or breast carcinoma on either imaging or biochemical progression underwent 14 percutaneous biopsies after diagnostic PET/CT using ^{89}Zr labeled radiotracers (mean dose: 180MBq; range: 126-189MBq) targeting prostate specific membrane antigen (PSMA) (n=7) or human epidermal growth factor receptor 2 (HER2) (n=5). Biopsies were performed in a PET/CT suite without radiotracer reinjection.

Results:

Biopsies were performed without complications a mean of 6.2 days (range, 0-13) after injection of radiotracers in bone (n=7), pleura (n=3), lymph nodes (n=2) and liver (n=2). All biopsies were positive for malignancy on pathology. A concordance between the initial diagnostic imaging findings and biopsies results was observed. The additional radiation (mean dose length product) due to CT procedures was 1581 mGy/cm (379-2686). No complications were reported.

Conclusion:

Molecular imaging PET/CT-guided biopsies using ^{89}Zr labeled radiotracers are safe and effective without tracer reinjection.

Keywords: Biopsy; PET/CT; interventional radiology; ^{89}Zr; metastasis

INTRODUCTION

PET/CT guided interventions are promising for radionuclide avid lesions not well visualized with CT[1–3]. However when ^{18}F labeled radiotracers are used, such as the 2-^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), a new injection is required prior to the intervention due to the short physical half-life of ^{18}F (109.8 minutes). Zirconium-89 (^{89}Zr) may be more attractive in comparison due to its longer physical half-life of 78.4 h [4]. After ^{89}Zr diagnostic scan are performed and interpreted, avid lesions retain activity for several additional days, enabling PET-guided biopsies at a later date utilizing the original injection of ^{89}Zr labeled agent[5].

In patients with metastatic cancer, ^{18}F-FDG-PET may fail to detect sites of disease because of a small lesion size and subsequent partial volume effect, a low or heterogeneous utilization of glucose, and as ^{18}F-FDG is non-specific [6]. Conventional imaging, such as CT, can also fail to detect metastases or insufficiently differentiate between aggressive and indolent lesions [7]. Therefore, the potential of using other PET tracers with unique biological specificities has been evaluated [8–10]. Agents capable of specific binding, such as monoclonal antibodies, have shown promise for clinical use [9,10]. Recently, we reported preliminary findings involving HER2–targeted PET tracer (trastuzumab) for HER2-positive metastases in patients with primary breast cancer and humanized third-generation PSMA-specific antibodies for soft tissue and bone metastases [9–11].

The purpose of this study was to evaluate the feasibility of performing delayed molecular imaging-guided biopsies using dedicated in suite PET/CT guidance without radiotracer reinjection in patients presenting with metastatic prostate or breast cancer.

MATERIALS AND METHODS

Patients

All patients were enrolled in an Institutional Review Board approved protocol. This protocol was Health Insurance Portability and Accountability Act compliant. The prospective protocols for molecular imaging were performed under an Investigational New Drug process [9–11].

From 2013-2016, 12 patients (mean age 61 years, range 40-75) with positive findings from ^{89}Zr labeled anti-PSMA (J591 antibody or minibody, 7 males) or trastuzumab PET/CT imaging (5 females), were referred to interventional radiology for biopsy confirmation of metastasis detected on imaging and to obtain optimal molecular profiling of the tumor. The seven male patients had a history of prostate cancer and all presented with a rising level of prostatic specific antigen (PSA) despite treatment with testosterone-lowering hormonal therapy. Five female patients with confirmed HER2-negative primary breast cancers underwent biopsies to assess for ^{89}Zr-trastuzumab foci suggestive of HER2-positive disease.

Exclusion criteria included previous anaphylactic reaction to PET imaging or radiotracers, patients on any new anticancer therapy (GnRH analog allowed) while on the study, abnormal hepatic lab values (Bilirubin>1.5 ULN, AST/ALT >2.5 ULN, Albumin < 2 g/dL, GGT > 2.5 ULN if Alkaline Phosphatase >2.5 ULN), abnormal renal lab values (Creatinine > 1.5 ULN), or other severe acute or chronic medical condition that may increase the risk associated with study participation or investigational product administration. Patient characteristics are summarized in Table 1.

Pre-procedural imaging

Patients received radiolabeled antibody with a mean administered activity of 180MBq (range: 126-190MBq). A single dose of 10mg of anti-PSMA antibody (J591) [11] or mini-antibody (df-IAB2M) [9] or 50mg of HER2 targeted PET tracer (trastuzumab) [10] labeled with 185MBq of ^{89}Zr was administrated intravenously over 5-10 minutes.

All scans were performed on the same PET/CT scanner (Discovery DSTE, GE Medical Systems, Milwaukee, WI). A CT protocol designed for attenuation correction with iterative reconstruction was used for anatomic localization of PET abnormalities. Thus, each patient underwent one single 80 mA CT scan followed by 10 mA CT scans performed on the remainder of the days of imaging.

Molecular Image Guided Interventional Procedures

Targeted lesions were determined based on ^{89}Zr labeled radiotracer PET/CT positivity and accessibility of the lesions upon factors including target location, target size, optimal needle path and shortest skin-to-target distance by consensus at a multidisciplinary conference comprised of oncologists, interventional radiologists and nuclear medicine physicians.

Procedures were performed in an interventional radiology suite equipped with a PET/CT scanner (Discovery 690; GE Medical Systems, Milwaukee, WI) without radiotracer reinjection. Patients had limited PET/CT imaging (1-2 position beds) over the biopsy region of interest. A 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 3.75mm 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) with 7 min/FOV. Insertion of biopsy needles was performed under local anesthesia and conventional CT or CT-fluoroscopy guidance but CT images were intermittently fused with the PET dataset.

A coaxial 11G bone biopsy system (Madison, Laurane Medical, Westbrook, Conn, USA) was used for bone biopsies, whereas for other biopsies, needle diameter varied from 18-20G.(Temno Evolution, Carefusion, San Diego, CA, USA). Following an institutional protocol, 2

biopsies were requested in bone and 3 in soft tissue, but additional biopsies could be taken. Pathological evaluation of biopsied tissue was performed at the time of biopsy.

Procedure-related complications were noted and classified based on criteria proposed by the Society of Interventional Radiology and the National Cancer Institute Common Terminology Criteria Adverse Events (version 4.0) [12].

Statistical analysis

Diagnostic accuracy was reported in terms of sensitivity and positive predictive value (PPV). The PPV was defined as the proportion of malignant lesions and was calculated with 95% confidence intervals using the Wilson method.

RESULTS

Targeting of lesions

Biopsies were performed a mean of 6.2 days (range, 0-13) after the diagnostic injection of ^{89}Zr . All lesions were successfully visualized (Figures 1, 2 and 3). The ^{89}Zr tracer positive lesions were targeted for biopsy. Biopsies were performed in all cases without complication. The mean number of needle passes for all biopsies was 3 (range, 2-5). The additional radiation (mean dose length product) due to CT procedures was 1581 mGy/cm (range, 379-2686).

Pathological results

For all positive biopsies, adequate specimens for pathological and molecular profiling were obtained. Diagnosis of prostate or breast carcinoma metastases was confirmed for all lesions biopsied (n=14). A concordance between the initial diagnostic imaging findings and biopsies results was observed. Biopsy performance is summarized in table 2.

DISCUSSION

As shown in this preliminary study, in-suite delayed molecular imaging PET/CT-guided biopsies can be accurately performed using ^{89}Zr labeled radiotracers. In this study, ^{89}Zr anti-PSMA or trastuzumab radiotracers were accurate for both early identification of metastases [9–11,13] and biopsy guidance. Moreover, unlike ^{18}F-FDG which would require an additional injection of isotope prior to the delayed PET/CT-guided procedure, ^{89}Zr allows for biopsies to be performed without reinjection after the initial injection due to the long half life of ^{89}Zr. A workflow that allows for diagnostic PET/CT followed by PET/CT guided biopsy several days later after multi-disciplinary review meeting is feasible and efficient for patients.

This study is limited by the small size of our highly selected population. All patients had a known cancer diagnosis prior to biopsy. These results are therefore probably not translatable to other populations or other situations. Although not evaluated, the additional radiation exposure related to the use of ^{89}Zr labeled radiotracers has been estimate to 68 mSv effective dose per scan in average [11]. This brief communication is presented as a proof of concept, but larger studies will be needed to further evaluate the value of these biopsies.

CONCLUSION

In summary, in-suite molecular imaging PET/CT-guided percutaneous biopsies can be safely and accurately performed without reinjection of radiotracer after a diagnostic ^{89}Zr labeled radiotracer PET/CT. ^{89}Zr labeled radiotracers targeting specific proteins may be useful for both detection and molecular profiling in high risks patients presenting with widely disseminated disease. Studies such as this may provide additional clinical justification for implementing molecular imaging in interventional oncology as well as developing access to interventional PET imaging facilities in the future.

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Figures

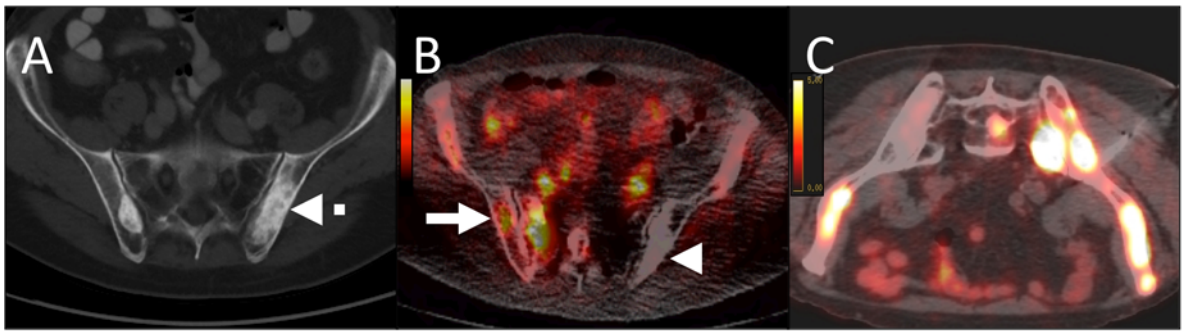

Figure 1: Delayed molecular imaging PET/CT-guided biopsy of a bone metastasis of prostate carcinoma

A) Axial CT scan shows suspicious increase of density (dashed arrow) on the iliac bones in a 64-year-old man with high suspicion of metastatic prostate carcinoma (PSA: 91 ng/ml) without history of bone radiotherapy.

B) Axial Zr-89 anti-PSMA targeted PET/CT fusion image showing new lesions on right iliac wing and sacrum (arrow). Interestingly, the lesions identified with CT scan presented no uptake (arrowhead).

C) Axial Zr-89 anti-PSMA targeted PET/CT fusion image performed 7 days after injection shows the lesions including one that was biopsied. Pathology confirmed metastasis of prostate carcinoma.

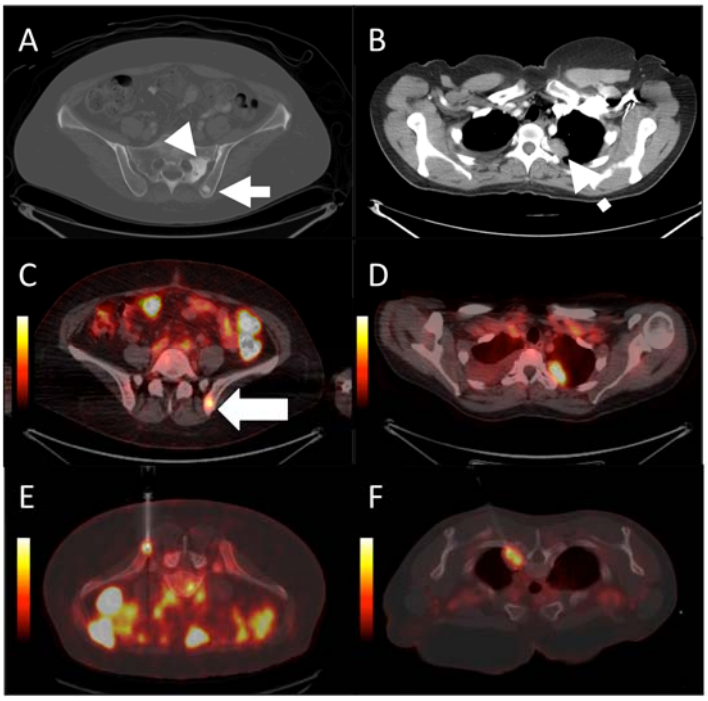

Figure 2: Delayed molecular imaging PET/CT-guided biopsies of a bone and lung metastases of breast carcinoma

A-B) Axial contrast-enhanced CT scan showing bone lesions of the left iliac wing (arrowhead) and sacrum (arrow) in a 51-year-old woman with metastatic breast carcinoma. A thoracic mass is observed (dashed arrow).

C-D) Axial Zr-89 anti-human epidermal growth factor receptor 2 targeted PET/CT fusion image showing left iliac crest (large arrow) and lung metastases. No lesion was observed in the sacrum.

E-F) Corresponding in suite PET/CT biopsy was performed 2 days after injection. A residual uptake is still observed during the procedure on the fusion image. Pathology confirmed metastasis of breast carcinoma.

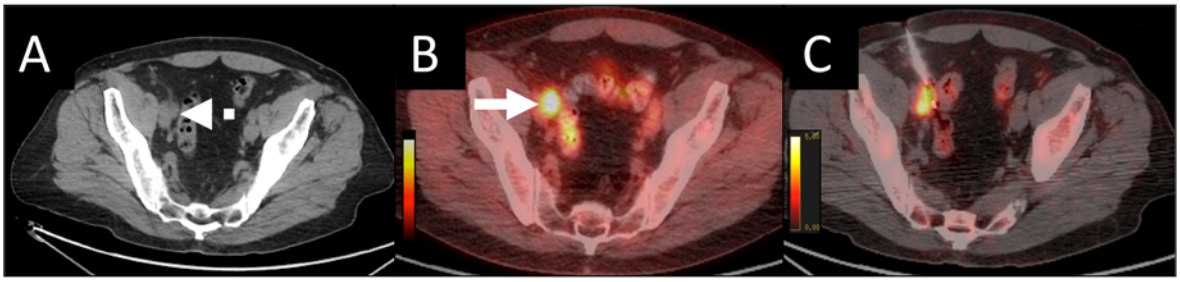

Figure 3: Delayed molecular imaging PET/CT-guided biopsy of a lymph node metastasis of prostate carcinoma

A) Axial CT scan showed a 15mm right iliac lymph node (dashed arrow) in a 75-year-old man with high suspicion of metastatic prostate carcinoma (PSA: 10 ng/ml).

B) Axial Zr-89 anti-PSMA targeted PET/CT fusion image shows the lymph node (arrow)

C) Corresponding in suite PET/CT biopsy was performed 6 days after injection. A residual uptake is still observed during the procedure on the fusion image. Pathology confirmed metastasis of prostate carcinoma.

Table

Table 1

Patient characteristics

	In suite ^{89}Zr targeted biopsies
Number of biopsies	14
Number of patients	12
Gender	7 male / 5 female
Mean age (years)	61.1 (40-75)
Mean PSA (ng/mL) **for the 7 male patients**	88.8 (2-323)
Mean dose (MBq)	179.5 (125.8-189.8)
Mean delay after injection (days)	6.2 (0-13)
Biopsy guidance	PET/CT
Location	Bone (n=7); Pleura (n=3); LN (n=2); Liver (n=2)

Note – PSA= Prostatic Specific Antigen; LN: lymph nodes

Table 2

Results and performances of biopsies.

	Number of biopsies	Number of biopsies positive for malignancy	Number of biopsies negative for malignancy	Sensitivity	PPV	Accuracy
In suite ^{89}Zr-targeted biopsies	14	14	0	100%	100% [52-100]	100%

Note – PPV= Positive predictive value with confidence interval 95%