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Cone-beam CT Fusion/navigation for real-time PET guided Biopsies and Ablations: A Feasibility Study

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Abstract

Purpose—PET guided biopsies may be useful for pathological confirmation of imaging findings when anatomical abnormalities with focal features are absent on conventional imaging. A novel technique for multimodality PET fusion-guided interventions is described combining cone-beam CT (CBCT) with pre-procedural PET-CT.

Methods—Subjects were selected among patients scheduled for a biopsy or ablation. The lesions were not visible with conventional imaging methods or did not have uniform uptake on PET. Clinical success was defined by adequate histo-pathological specimens for molecular profiling or diagnosis and by lack enhancement on follow-up imaging for ablations. Time to target (time elapsed between the completion of the initial CBCT and first tissue sample or treatment), total procedure time (time from the moment the patient is on the table until they are off the table) and number of needle repositioning were recorded.

Results—Eight procedures were performed on seven patients (2 ablations and 6 biopsies). Registration and procedures were completed successfully in all cases. Clinical success was achieved in all biopsy cases and in one of the two ablations. The needle was repositioned once in one biopsy case only. On average the time to target was 38 minutes (range: 13–54 minutes).

Total procedure time was 95 minutes (range: 51–240 minutes, which includes composite ablation). On average, fluoroscopy time was 2.5 minutes (range: 1.3–6.2 minutes).

Conclusions—An integrated CBCT software platform can enable PET-guided biopsies and ablations without the need for additional specialized hardware.

Keywords

PET-CT fusion; Image guide procedures; Navigation; Cone Beam CT

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Background

With the advent of molecular profiling and targeted therapies, obtaining specimens from metabolically active areas of a lesion has increased importance. ^{18}F -fluoro-deoxy-glucose (FDG)-PET-CT is an integral diagnostic tool for oncologic staging and response assessment (1). Pathological correlation of PET abnormalities may be necessary since FDG uptake is not specific to cancer (2). However, until recently, PET-guidance for biopsies and ablations was not possible unless a corresponding abnormality was also present on conventional imaging(3). PET guided biopsies and ablations have recently been described using electromagnetic (EM) tracking, procedural PET-CT or retrospective off-line registration (3–6). EM tracking and cone-beam CT (CBCT)-based fusion both provide real-time feedback in relation to the PET-data although EM tracking requires additional hardware and disposables. Direct PET imaging during the procedure is impractical, increases radiation and is not accompanied by real-time navigation. Off-line registration techniques are also not truly real-time or integrated on the CBCT or CT.

The 3D imaging data set of a cone-beam CT generated by C-arm may be fused with fluoroscopy for real-time navigation capabilities without the need for additional hardware or disposables (7–10). With recent developments, fusion (registration and co-display) of a procedural CBCT with previous imaging (such as MRI and CT) allows for real-time navigation during image-guided interventions. The feasibility and early experience of this novel technique during biopsies and ablations is reported.

Materials and Methods

This study was compliant with the Health Insurance Portability and Accountability Act with all patients under a protocol reviewed and approved by the Institutional Office of Human Subjects Research Protection.

Patients

Seven patients were selected from patients referred for biopsy and / or ablation to our interventional radiology section between January 2011 and September 2011. Patients who underwent CBCT-PET guidance had lesions only seen on PET-CT or did not have uniform FDG-18 uptake. In addition these CBCT-PET guided procedures also had lesions not visible with US and/or it was deemed that real-time fluoroscopy would offer an added advantage i.e. detection of a potential pneumothorax during lung biopsy. All participants were at least 18 years of age. All patients were being investigated for a suspected malignancy, or for molecular profiling requiring high quality cellular specimens for tissue characterization or validation of drug effect.

Two patients were referred for ablations of a single hepatic metastatic lesion (one adrenocortical carcinoma and one metastatic lung carcinoma). In both cases the lesion was not visible on diagnostic CT and in one case, the lesion was not visible on MRI either. The patient referred for ablation of the metastatic lung carcinoma also underwent a PET-guided biopsy for molecular profiling. The remaining five patients were scheduled for biopsies as part of their staging (2 patients), or for molecular profiling as part of another clinical trial (3 patients). In five patients, the lesions did not demonstrate uniform PET activity. It was presumed that targeting the PET-avid portion of the lesion could have a higher diagnostic yield.

Targeted lesions were located in the liver (n=2), adrenal gland (n=1), retroperitoneum (n=1), pulmonary parenchyma (n=2) and mediastinum (n=1). Mean lesion greatest diameter was 42.5 mm in greatest diameter (range: 15–82 mm). Software on the CBCT workstation

enables the operator to semi-automatically segment a tumor in all three planes based on previous imaging or procedural CBCT and determines its volume based on that segmentation. Measurements were performed by a single board-certified radiologist. Median lesion volume measured by segmentation tool was 41.5 cm³ (range: 0–120 cm³) on conventional imaging and the median PET avid volume per lesion was 24.3 cm³ (range: 6.33–57.87 cm³). When the lesion was not visible on conventional imaging, the volume was marked as zero. A visual manual threshold was used to define PET avid volumes.

PET-CT imaging

The mean duration between PET-CT and the PET-guided biopsy or ablation was on average 19.5 days (range: 1–94 days, median: 6 days). For PET-CTs performed at our institution, patients fasted for at least 6 hours before intravenous injection of F18-FDG (Cardinal Health Inc., Beltsville, MD) with a mean injected dose $\pm$ standard deviation, 11.1mCi $\pm$ 2.58mCi. PET-CT had been performed at our institution in all but two patients in which cases an outside PET-CT was registered. Institutional PET/CT (Discovery ST; GE Medical Systems, Milwaukee, WI) was performed a mean of 60 minutes (range: 58–65 minutes) after the F18-FDG injection. CT was performed first with the patient laying supine and shallow breathing. The CT images are acquired from the head to the proximal thighs, for attenuation correction and anatomic co-registration without oral or intravenous contrast material. Imaging parameters were 120 kVp, 115 mA, and 1.25 mm collimation, with reconstruction as 3.75mm thick slices using a 512 *512 matrix. Immediately after CT, PET images of the same volume were obtained in two-dimensional mode (slice 128×128 matrix; voxel size 4.24 mm × 4.25 mm × 3.27 mm). For each lesion, a maximum standardized uptake value (SUV) was generated after rescaling of activity concentration (Bq ml⁻¹). The mean SUV maximum of the tumor was 7.62 (range: 2.3–11.82).

CBCT-PET Fusion procedures

Two board-certified interventional radiologists performed all the cases (NAJ, BW with 3 and 13 years of experience post-fellowship respectively) in an interventional radiology suite equipped with CBCT and navigation capabilities (Allura Xper FD20 Philips Healthcare, Best, NL). Patient positioning was determined by the radiologist based upon lesion location, accessibility and the shortest skin-to-target distance.

Two ablation cases were performed under general anesthesia with intravenous contrast (Isovue 320, Bracco, Princeton, NJ). The biopsies were performed with conscious sedation (Midazolam, Roche, Nutley, NJ; and fentanyl citrate, Hospira, Lake Forest, Ill) and without contrast. A CBCT centered on the lesion was obtained. In each case, a previous PET-scan was imported into the CBCT workstation and manually fused with a procedural CBCT (XperCT, Philips HealthCare, Best, NL). In this initial prototype version of the software, image fusion was performed by manually registering the CBCT to the PET series of the PET-CT directly. Image fusion was accomplished with manual rigid registration using anatomical landmarks.

Using navigation software (XperGuide, Philips Healthcare, Best NL) a needle path was determined based on PET and CBCT fused data and overlaid on real-time fluoroscopy enabling real-time navigation of the needle to the PET-active target under fluoroscopy/CBCT/PET feedback (figure 1). The operator faded and blended the registered volume in or out during real-time navigation, altering the relative weighted mixture or blend of each modality. The system corrected for table motion by internally tracking the table position. Visually matching anatomic landmarks on registered 3D volume and real-time fluoroscopy facilitated the tracking of respiratory volumes during needle manipulations. Thus the

operator waited until the ribs and/or diaphragm were matched between the CBCT and fluoroscopy to advance the needle.

A 22 Gauge Chiba needle (Cook Medical Inc., Bloomington, IN) was used for fine needle aspirations. A co-axial 17/18 Gauge Temno biopsy system (Cardinal Health, Dublin OH) was used for all core biopsies. A 24-cryoprobe (Endocare, Healthtronics, Austin TX) and a 17-gauge single 15–3cm Cool-tip RF probe (Covidian, Boulder CO) were utilized during the ablation cases.

The *time to target* was defined as the time elapsed between the completion of the initial CBCT and first tissue sample or treatment. The total procedure time, number of needle repositioning and diagnostic accuracy of the biopsies were recorded. Of note, the total procedure time is defined as the time elapsed from the moment the patient is placed on the table to the time the patient is off the table and includes preparation, anesthesia induction and recovery. Lack of enhancement on follow-up imaging and lack of FDG-uptake on PET-CT constituted success for the ablation cases. Cytology and surgical pathology results were reviewed for adequacy of specimen and diagnostic ability when correlated to clinical and imaging features over time.

Results

We performed 2 ablations and 6 biopsies on seven patients (4 men and 3 women) with average age of 64.5 years (range: 24–83 years) (table 1). Two patients underwent fine needle aspiration and core biopsy, three patients underwent core biopsy alone, one underwent ablation alone and one underwent ablation and core biopsy.

The registration was successful in all cases. The lesion was reached on the first pass in all cases but one biopsy case where the needle was repositioned. On average the time to target was 38 minutes (range: 13–54 minutes).

Total procedure time was 95 minutes (range: 51–240 minutes, which includes composite ablation). On average, fluoroscopy time was 2.5 minutes (range: 1.3–6.2 minutes).

In all biopsies, adequate diagnosis and necessary specimens for molecular profiling were obtained. Of the six biopsies, five were positive for neoplasia and one revealed benign disease, thought to be true negative based on clinical presentation and imaging follow-up. This patient had a history of renal cell carcinoma and a new discrete retroperitoneal psoas abnormality on PET-CT (SUV of 2.3). The biopsy revealed normal muscle without evidence of tumor. On 6 month follow-up imaging, no lesion was identified.

Both ablations were technically successful initially, but only one had a successful clinical outcome. Despite numerous overlapping cryoablation zones, a 4 cm segment-8 hepatic dome metastasis recurred at the cranial margin with incomplete treatment. Image fusion guidance had demonstrated and predicted an inadequate margin cranially, however due to the risk induced by lesion touching the cardiac structures, no additional ablations were performed. Follow-up PET-CT indeed confirmed a rim of residual uptake at the cranial/ cardiac margin of the lesion, as expected. The second ablation was an adrenocortical carcinoma metastasis to the liver successfully treated with complete absence of enhancement and evidence of necrosis in the ablation zone on 2 months follow-up imaging (figure 2).

Discussion

PET-fusion guidance with CBCT navigation is feasible and may facilitate certain biopsies and ablations. Registration for image fusion was successfully performed with this approach

in all cases. The hardware/software combination enabled real-time navigation with fluoroscopy based on PET information, with real time feedback of needle location in relation to the registered PET activity. In this case series, the lesions were either visible only on PET-CT or did not demonstrate uniform FDG uptake. Without PET-CT information, needle positioning might have otherwise been less precise if based on nearby landmarks alone (3). Incongruent needle positioning in relation to PET activity could otherwise result in false negative biopsies or incomplete ablation because the needle or ablation probe might be inaccurately positioned in an area with no or minimal FDG uptake (3, 4). The clinical value of PET-CT guided interventions has been demonstrated previously (11, 12). In the era of personalized medicine, PET-CT can potentially offer early insight into chemotherapy response (11, 13, 14). Thus accurate sampling of PET-avid regions could be an important tool in drug discovery, validation of drug effects, or early biomarker for prognostic validation. PET-CT has played an increasing role in oncologic management of patients because it provides functional imaging (11, 13, 15). PET guided biopsy could expand the role of PET in predicting drug effects, prognosis, or tumor sensitivity (16). Although PET-CT is very sensitive, it is not specific to neoplasia (17) and correlation with biopsy also improves accuracy of diagnosis and management (18).

Multimodality fusion with CT, MRI and PET for image-guided interventions has theoretical and proven advantages (19–22). PET-CT guided biopsies are of a particular interest since PET-CT offers functional information that may or may not have an anatomical correlate on conventional imaging (13). PET-CT guided procedures may be performed with real-time PET in the PET scanner (5, 12, 23, 24), with image fusion using off-line software(5) or by using electromagnetic or optical tracking navigation software(3, 20, 25). Most publications are small series not in excess of 25 patients but all suggesting feasibility or benefit (3–5, 12, 20, 23–26).

PET-guided biopsies performed in the PET-scanner (5, 12, 23, 24, 26) were done for different indications, with small numbers of patients and varying techniques. Some authors combined diagnostic PET-CT and PET-guided biopsy to minimize patient radiation and FDG injection; however coordinating physician with PET-CT room availability may be logistically difficult (5, 26). Others did not combine diagnostic PET-CT and PET-guided biopsies simultaneously therefore the patients required additional FDG injection (12, 23, 24).

Performing PET-guided procedures in PET scanners should however reduce registration errors. Indeed PET-CT typically consists of a PET and CT acquired separately and co-registered automatically post acquisition (27). Registration errors with PET-CT due to respiratory and cardiac motion can be significant because the PET is obtained over a prolonged time period in shallow breathing, whereas CT is just one phase of the respiratory cycle (5). Data exists demonstrating that the errors of registering the PET and CT portions of a PET-CT are significant and can be up to 14.7mm, but this may be mitigated with respiratory bellows monitored breath-holds (28). Therefore PET-guided interventions directly in the PET scanner may minimize the registration errors since the needle position can be confirmed with additional injection of FDG. However this technique requires access to a dedicated PET-CT and repeated FDG dosing. Moreover, this approach is ergonomically and practically limited by the narrower and longer PET-CT gantry (compared to conventional CT gantry), which may limit in-gantry needle manipulations (5). Additional radiation exposure to operator and patient may be inevitable, and additional radiation protection equipment can be cumbersome and limit operator mobility (12, 26). Radiation exposure to the physicians and staff is often unreported (5, 12) or is simply acknowledged as increased (26) without any details on the measurement technique. Direct PET guidance in

the PET-CT gantry is also more time consuming and may impact patient throughput and scheduling (12, 26).

Peri-procedural off-line registration has also been reported in 14 patients who underwent PET guided abdominal biopsies with rigid registration of a previous PET-CT with a procedural CT using online software (4) with encouraging results. This method does not require additional radiation and the procedure is performed in a regular CT, however the registration may be time consuming and sometimes difficult. Scoliosis precluded registration in one patient (4). More importantly the registration with previous PET-CT is a rigid, static one-time reference. The important real-time feedback of the needle position in relation to PET abnormality is not available with this technique as opposed to EM tracking techniques or CBCT fusion techniques.

Electromagnetic tracking (EM) tracking sometimes-called “medical GPS” (6) utilizes an electromagnetic generator and small sensors to track a needle, ultrasound transducer and patient position in a virtual magnetic space. An advanced imaging modality may be semi-automatically registered in the virtual magnetic space using fiducial patches (19). EM tracking also enables image fusion with anatomic landmarks. The operator can therefore determine a target on pre-procedure imaging such as a PET-CT. The PET-CT is fused with a procedural CT, which is registered in the virtual magnetic space using the fiducial patches (6, 19). The physician can then navigate in the virtual magnetic space while referencing in real-time the previous PET-CT (6). Most publications of multi-modality image fusion with EM tracking do not specifically pertain to PET-guided interventions (6, 20, 21, 25) with the exception of at least two series describing PET fusion with EM tracking during bronchoscopic biopsies (25) and during percutaneous biopsy and ablation (3). In the latter series of 25 patients, registration was successful in all cases. The total procedure time was on average 122 minutes, which is acceptable for complex procedures such as ablations and included a learning curve for using new software. However, this EM based technique requires additional hardware (EM field generator and tracking workstation), additional software and disposables (tracked devices and fiducial patches), not be readily available in most interventional oncology suites.

CBCT-based technique offers the advantage of being widely accessible, and only requires the addition of software to standard high-end C-arm suite with table tracking that many interventional radiologists are equipped with. Moreover the registration is automatically updated and navigation of the needle is performed with real-time PET information overlaid on fluoroscopy. The dedicated PET gantry guidance technique requires an actual interventional PET scanner (12) and the static off-line registration technique provides intermittent PET information based upon a one-time static registration (5). Although not reported in this paper, the registration time decreased in general with experience. More recent software (not used in this series) allows for registration of the CBCT directly with the CT series of the PET-CT. This may shorten the registration time and time to target by simplifying matching anatomic landmarks. Our procedure times were likely influenced by complex procedures, early prototype software, and a learning curve but were still comparable to previous publications (3) although direct retrospective comparison is meaningless since the type of procedures and cases are highly variable. CBCT PET-fusion navigation utilizes radiation while EM tracking does not. However registration into the virtual space usually requires a CT that delivers more radiation than a CBCT.

CBCT PET fusion guided interventions were feasible, but this small study has limitations. Larger studies will be needed to document accuracy or relative benefits compared to other techniques. Follow-up was short however biopsy results were confirmed by definitive histopathological diagnosis (or complete regression of PET abnormality).

PET image fusion with CBCT for image-guided procedures can be used to bring PET spatial information into the interventional suite without additional hardware, which makes this approach widely accessible to interventional radiologists.

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Figure 1. CBCT Guided Lung Biopsy of PET-Avid Part of Tumor

Images 1a and 1b are axial images of a diagnostic CT and procedural CBCT demonstrating a large pulmonary infiltrate in the middle lobe. Image 1c is axial image of the CBCT with the PET-CT image fusion. During needle advancement, the virtual needle path based on target and entry point chosen with PET information is overlaid on real-time fluoroscopy. Once target is reached, adequate needle location is confirmed as seen on axial image of CBCT (figure 1d).

Figure 2. CBCT Fusion Guided Hepatic Tumor Ablation

Figures 2a and 2b are axial arterial and venous phase images of a diagnostic CT and figure 2c is an axial CBCT image demonstrating that the lesion is not visible on any of these modalities. It was only seen on PET. Figure 2d and 2e show the tumor segmented (green circle) on PET-CT and overlaid on procedural CBCT images. However in figure 2e the PET-CT has been faded out and an ablation zone is seen. The virtual needle path for a probe and a thermocouple are also depicted. Figure 2f is an axial confirmation CBCT with overlaid PET showing the needle in ideal position. Once finished, the treated area can be segmented in all planes as seen in figure 2g. It can then be overlaid on the pre-treatment segmented tumor. Figure 2h and 2i are sagittal and 3D representations of the tumor volume (green circle) and the ablated volume (yellow volume) respectively.

Table 1

summarize s patient and procedure characteristics

Patient	Gender, Age	Procedure	Site	Days PET-Procedure	Fluoroscopy time	Technical /Clinical Success	
1	M, 24	Biopsy	Mediastinum	1	2.5	Yes/ Yes (Staging)	
2	M, 83	Biopsy & ablation	Liver	21	4.6	Yes/ Yes biopsy (MP [*]) No ablation (rim of residual enhancement)	
3	F, 68	Biopsy	Adrenal gland	5	2.6	Yes/ Yes (MP [*])	
4	F, 55	Ablation	Liver	6	5.1	Yes/ Yes (no enhancement on 6 week follow-up)	
5	M, 73	Biopsy	Lung	3	1.8	Yes/ Yes (MP [*])	
6	M, 69	Biopsy	Retroperitoneum	94	2.2	Yes/ Yes (Staging)	
7	F, 79	Biopsy	Lung	3	1.3	Yes/ Yes (MP [*])	

* MP stands for molecular profiling