Metabolic PET/CT guided lung lesion biopsies - impact on diagnostic accuracy and rate of sampling error

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Short Title: PET/CT guided lung lesion biopsies.
ABSTRACT

CT-guided fine needle aspiration (FNA) of lung lesions is subject to sampling errors. Current study assesses whether information provided by FDG-PET/CT will decrease the false negative rate and thus improve the accuracy and of CT-guided FNA.

Methods: Data of 311 consecutive patients with lung nodules who underwent FDG-PET/CT and CT-guided FNA within an interval of less than 30 days were retrospectively assessed. An in-house developed software co-registered CT images used to guide FNA (CT-FNA) with corresponding PET/CT data. The quality of registration was rated on a scale of 1(excellent) to 5 (mis-registration). Only cases scored 1-2 were further evaluated. The software provided the highest Standard Uptake Value (SUV) within the lesion and at the location of the tip of the aspirating needle. The distance (mm) between the tip and the area with the highest SUV within the lesion was measured. The mean distance from the tip of the needle to the focus with the highest SUV as well as the mean difference between the SUVmax in the whole lesion and at the needle tip were calculated and compared for cases with true positive (TP) and false negative (FN) FNA results. Anatomic and metabolic parameters of lesions included in these two groups were also compared.

Results: There were 267 patients (86%) with score 1 and 2 registration quality of CT-FNA and CT-PET/CT images, including 179 TP studies (67%), 5 false positive (FP, 2%), 49 true negative (TN, 18%) and 34 FN (13%) FNA results. The distance between the location of the needle tip and the focus with the highest SUV in the lesion was significantly greater in the FN group (15.4 ±14mm) as compared to the TP group (5.9 ±
13.4 mm, p < 0.001). The SUV max at the location of the aspirating needle tip were significantly higher in the TP group, 6.4 ± 6.4, as compared to the FN group, 4 ± 4.7, p < 0.05.

**Conclusion:** Present results demonstrate a relationship between the degree of metabolism at the site of tissue sampling aspiration in lung lesions and the accuracy of FNA results. Anatomo-metabolic based FNA guidance using information provided by both FDG-PET and CT may improve the accuracy of histological examinations, decrease the rate of FN results and thus increase the probability of achieving a definitive diagnosis.

**Key words:** Biopsy; PET/CT; Lung; CT guided biopsy
INTRODUCTION

Percutaneous CT-guided fine needle aspiration (FNA) of a lung lesion is a routinely used, relatively safe method for diagnosis of benign and malignant processes (1). The diagnostic accuracy of CT-guided FNA for malignant lung tumors varies between 64% and 97% (2), depending on factors such as the size and depth of the lesion as well as the number of needle paths (1, 2). FDG imaging provides information with respect to the metabolic characteristics of lung lesions (3). Its inherent advantages include the early detection of malignancy and differentiation from non-malignant areas within a mass representing fibrosis and necrotic tissue (3-5). FDG-PET/CT has a high sensitivity of approximately 90% in characterizing solitary pulmonary nodules but its specificity is hampered by FDG accumulation by various non-malignant processes (6, 7). CT used for guiding of FNA does not provide information regarding the metabolic characteristics of the lesion, in particular the specific location of functionally active cells within the tumor (8). Tissue aspiration guided only by anatomical data can therefore lead to placement of the needle into a nonviable area of the lesion with subsequent inadequate tissue sampling and potentially false negative (FN) FNA results (8, 9).

The success rate of image-guided biopsies could be improved and multiple attempts at biopsy avoided if the functional information obtained from the FDG-PET/CT study is used to direct the positioning of the tip of the needle to the region with the highest metabolism within a lesion (9). The purpose of this study was to demonstrate that FDG-PET/CT can provide the additional information that will decrease the false negative rate and improve the accuracy of CT-guided FNA of lung lesions.
MATERIALS AND METHODS

Study Population

The institutional FDG-PET/CT and CT-guided biopsy databases between the years 2007 to 2010 were retrospectively searched for patients who underwent whole-body FDG-PET/CT for characterization of pulmonary nodules and CT-guided FNA of the lung lesion within a time interval of less than 30 days. Data of 311 consecutive patients who met the above criteria were retrieved. After identification of the specific patient population, data regarding cytology results of samples obtained at CT-guided FNA and histology of the same lesions obtained at surgery, when performed, as well as clinical and imaging follow-up were retrieved from their medical records. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived.

CT-Guided FNA Procedure

CT-guided FNA was performed as a non-enhanced CT procedure (Philips MX 8000 4 slices or Philips IDT 16 slices) by senior radiologists with experience ranging between 9 and 20 years. A 22-gauge needle, 9 cm or 15 cm in length, was used. A cytologist was present to evaluate the initial aspiration and to prepare the slides. Cytology results were categorized as positive if malignant cells were identified, benign if a specific non-oncologic diagnosis could be made and negative if only respiratory cells or macrophages were present. FNA results were considered true positive (TP) if malignant cells were detected and further confirmed at surgery or by imaging and clinical follow-up and true negative (TN) if no evidence of malignancy was found on cytology and the patients had
either a benign lesion at surgery or no evidence of cancer was found for a clinical follow up to 5 years. In false positive (FP) cases the presence of malignant cells was reported on FNA results with no further evidence of malignancy while in false negative (FN) cases no malignant cells were found on aspiration but cancer was diagnosed in that lesion at surgery.

**PET/CT Acquisition and Processing**

Patients were instructed to fast, except for glucose-free oral hydration, for 4-6 hours prior to the injection of 370-555 MBq (10-15 mCi) 18F-FDG. Diabetic patients were instructed to keep their regular glucose-controlling drug schedule. Blood glucose levels were measured before injection. PET and non-enhanced CT were acquired consecutively 60-90 minutes after the injection of FDG, using a PET/CT system (Discovery LS, or Discovery 690, GE Healthcare, Milwaukee, USA). The patients were instructed to breathe normally during the PET/CT acquisition. For the purpose of this research, all studies were reviewed retrospectively with knowledge of the patient’s clinical history and results of previous imaging tests, blinded to the results of the FNA examination. FDG activity in the lung lesions was graded as homogenous, inhomogenous or absent. Each lung lesion was assessed on CT for size and pattern as solid, semisolid or ground glass opacity (GGO).

**Registration Between PET/CT and CT-guided FNA Data**

An in-house developed software was used to register CT images performed for the FNA procedure (CT-FNA) with corresponding slices of the PET/CT study. The software was implemented on the Xeleris work-station (GE Healthcare, Milwaukee, USA). The
registration process was performed by a radiologist and took less than one minute per patient using the last slice of the CT-FNA series. In this image the needle’s tip location within the investigated lung lesion represented the site of aspiration. The operator then manually scrolled through the CT slices of the PET/CT study to identify the image in which the contours of the CT-FNA matched those of the PET/CT. The quality of registration was rated visually by the operator on a scale of 1 to 5 as follows: 1- excellent, if the registration contours matched the lesion, lungs and mediastinum, 2- good, if the registration contours matched the lesion with no accurate match of the lungs and mediastinum, 3- fair, if the registration contours included the lesion but with no accurate match of its perimeter, 4 – poor, if the registration contours included the lesion but with significantly inaccurate match, 5 - no registration could be obtained. Only cases scored 1 and 2 were further evaluated and included in the final data analysis. After registration a matched CT-FNA and FDG-PET image was available for each patient. The software further provided measurements of the following parameters: 1. maximum Standard Uptake Value (SUVmax) in a 3x3 pixel cube around the location of the tip of the aspirating needle, 2. SUVmax of the whole lesion, 3. distance (mm) between the location of the tip of the needle and that of the highest FDG uptake within the lesion.

**Statistical Analysis**

Data are presented as mean, minimum and maximum values and standard deviation (SD). Lesion size, SUVmax and the mean distance between the location of the highest SUVmax in the lesion and the location in which the tissue sample was obtained were measured and compared between the group of patients with TP and FN results of FNA
using the Mann-Whitney non-parametric test with a p-value <0.05 statistically significant. Lesions’ size and FDG uptake patterns were compared between the TP and FN groups using the Chi square test.

RESULTS

The PET/CT and CT-FNA database search identified 311 patients (185 men and 126 women) aged 19 to 95 (average 67 years) that met the inclusion criteria. Ninety patients (29%) had lesions in the right upper lobe, 83 (27%) in the left upper lobe, 75 (24%) in the right lower lobe, 53 (17%) in the left lower lobe and 10 patients (3%) in the right middle lobe. The size of the lung lesions, in their largest diameter, ranged from 6.5 mm to 148.6 mm (average 32 mm). On CT, 229 lesions (74%) demonstrated a solid pattern, 72 (23%) were semisolid and 10 (3%) had a ground glass appearance. On PET, 113 lesions (36%) demonstrated homogenous FDG uptake, 160 (51%) were inhomogeneous and 38 (12%) showed no abnormal FDG uptake. CT-FNA positioning was prone in 155 patients (50%), supine in 113 (36%), left decubitus in 23 (7%) and right decubitus in 20 patients (6%).

The registration score of CT-FNA and CT-PET/CT images was 1 (excellent) in 129 patients (41%), 2 (good) in 138 (44%), 3 (fair) in 23 (7%), 4 (poor) in 19 (6%) and 5 (no registration) in 2 (0.64%) patients. A total of 267 patients (86%) had score 1 and 2 registration quality and were further analyzed.

FNA results were consistent with cancer in 184 (69%) patients and showed no malignant cells or were equivocal in 83 (31%) patients. Of the positive FNA results, 179/184 were further confirmed as malignancy on biopsy obtained at surgery or based on follow up imaging and clinical assessment (TP, 67%) while 5 were diagnosed as benign.
processes (FP, 2%). Forty-nine negative FNA results were further confirmed as benign processes at surgery or on clinical follow up (TN, 18%) while 34 lesions were malignant (FN, 13%). The sensitivity, specificity and accuracy of FNA for diagnosis of pulmonary lesions were 84%, 91% and 85% respectively.

The distance between the location of the tip of the needle and the focus with the highest SUVmax within the lesion was significantly greater in patients with FN results of FNA (15.4 ±14mm) as compared to the cases with TP results (5.9 ± 13.4mm, p<0.001). The SUVmax in the tumor and in the location of the aspirating needle tip were significantly higher in the TP group (12.4 ± 10) and (6.4 ± 6.4) as compared to the FN group (9.2 ± 7.3, p<0.05) and (4 ± 4.7, p<0.05) respectively. There was no statistically significant difference in lesion size and FDG uptake pattern between cases with TP and FN results of FNA (Table 1, Figures 1 and 2).

DISCUSSION

CT-guided FNA and FDG-PET/CT examinations are performed routinely in patients with pulmonary lesions, both for diagnosis or staging. Accuracy of these tests is critical to ensure selection of the most appropriate management plan for an individual patient. Tissue sampling of the area with highest suspicion of malignancy is important to ensure accurate FNA results. However, the presence and amount of malignant cells may vary across or between lung masses. A larger lesion may contain malignant, highly active areas mixed with necrotic or fibrotic regions characterized as a rule by low or absent metabolic activity (9). Similarly, in patients with multiple lung lesions these may have
varying levels of metabolic activity and their random sampling may not provide the most appropriate tissue for correct diagnosis resulting in false negative FNA tests.

FDG-PET/CT can detect and correctly localize foci of high metabolic activity within a lung lesion and thus distinguish viable, mainly malignant from non-malignant tissue, thereby reducing the sampling error and increasing the diagnostic accuracy of image-guided biopsy. Alternatively, in patients with multiple lesions, PET/CT can be used to target the most metabolically active lesions, with the highest FDG uptake, for biopsy.

The results of FNA obtained in present study population, based only on CT-guided aspiration, showed sensitivity, specificity and accuracy of 84%, 91% and 85% respectively, for diagnosis of pulmonary malignancy, similar to previously reported literature data (2, 10). However, this study aimed to examine whether combining CT-guided FNA and FDG-PET/CT data had an added value in order to improve the tissue sampling accuracy. Present results demonstrate that the distance between the aspirating needle’s tip location and the area with the highest metabolic activity within the lesion was significantly greater in patients with FN as compared to those with TP FNA results. In addition, SUVmax in the location of the aspirating needle’s tip was significantly higher in the TP as compared to the FN group. These results demonstrate the relationship between the degree of metabolism at the site of aspiration within lung lesions and the accuracy of FNA results. Interestingly, there were no significant differences in lesion size and tissue heterogeneity between the TP and the FN groups. This is in contrast to the accepted assumptions that the larger and more heterogeneous the lesion is, the higher the
probability for sampling error, and, that a lower FNA accuracy is expected in small lesions, mainly due to the partial volume effect (11, 12). This lack of heterogeneity differences between the TP and FN groups further emphasis the need for quantitative measurements as a tool for more accurate tissue sampling in addition to the visual analysis of the assessed lesion.

Previous studies have examined the value of PET-guided biopsy in malignant lesions in the bone. In a retrospective study FDG-PET-directed skeletal biopsies resulted a higher number of TP and a lower number of FP biopsies as compared to sampling directed by bone scintigraphy (13). In a case report of a patient with medullar and trabecular bone metastases, only the use of FDG-PET/CT allowed to localize the area for biopsy that produced a conclusive tissue specimen containing viable tumor while CT, MRI and bone scintigraphy failed to reliably detect bone marrow infiltration (14).

Present study provides support for the use of FDG-PET/CT to improve the diagnostic accuracy of FNA in lung lesions. In addition to guiding the operator to the most metabolically active area of a neoplasm, there are additional advantages to the use of FDG-PET/CT to guide FNA. The use of PET/CT allows identifying the most easily accessible lesion, thereby reducing the potential need for repeat invasive procedures and the risk of complications. PET/CT can assist in guiding the operator to the metabolically active region in a lesion that is hard to locate, such as anatomical alterations after surgery or radiation therapy, or to lesions that have only minimal morphological changes on diagnostic CT. Because FDG-PET/CT can detect malignancy before significant
morphological changes occur, the use of this test to guided biopsy could also contribute
to providing an earlier histologic diagnosis of small tumor load malignancies.

While FDG-PET/CT is used for diagnosis and staging of lung malignances, some
metabolically active benign processes can, as well, show high FDG uptake \((7, 15-17)\).
Differentiating inflammatory and infectious processes of benign tumors from malignancy
may be difficult but confidence that the aspirating needle has been placed in the right
location, higher if FNA is guided by FDG imaging is important in these cases as well.
Although there is increasing evidence to support a role for FDG-PET/CT to guide
biopsies, the logistics of integrating this imaging modality into routine clinical FNA
procedures is more complex. Recent reports have presented potential solutions.
Previously acquired FDG-PET/CT images have been digitally registered with the intra-
procedural CT images to guide needle placement during biopsy of abdominal masses
\((18)\). An additional study also used co-registered, previously acquired FDG-PET/CT
images with intra-procedural CT images and reported that in approximately 50% of
biopsies performed in various organs, the availability of metabolic information was
beneficial and improved the diagnostic accuracy as compared to CT-only guided biopsy
\((9)\). Registration of separately performed PET/CT and procedural CT data can show a
few limitations. In present large series sub-optimal registration of FDG-PET/CT and CT-
FNA was found in 14% of cases and was related to changes in the size, shape and
metabolic characteristics of the lesion that occur during the time interval between the
PET/CT and the biopsy procedure. Additional potential registration errors occurring from
respiratory and cardiac motion and the different position of various body parts during the
PET/CT and biopsy procedures performed at two different time points are also possible
drawbacks. In patients in whom biopsy is considered as the next diagnostic step studies should be performed within a short time interval and, whenever possible in the same position used for the interventional procedure. The potential role of respiratory and cardiac gating for improved co-registration needs also to further investigated in more depth.

These potential limitations could probably be minimized with real-time PET/CT guidance. A recent case report demonstrated the use of intra-procedural real-time FDG PET/CT in the biopsy of bone metastases from esophageal cancer (19). The technical feasibility, clinical success and complication rates of PET/CT-guided biopsies were evaluated in a large series of 126 patients, including 50 lung masses (20). The target lesion and the biopsy needle location were reconfirmed using a dedicated real time PET/CT image. The authors reported a success rate of obtaining representative tissue samples in 93% of the lesions and complication rate of 14% and concluded that biopsy guided by a real time PET/CT data seems to be feasible and may optimize interventional procedures. Moreover, PET positive lesions with no clear CT correlate may be accessible to tissue sampling using PET/CT information (20).

The routine clinical use of real time PET/CT guided FNA is currently limited, in part, by the fact that PET imaging for FNA procedures may require a relatively long machine time and, additionally, ionizing radiation fields close to the patient can be substantial for several hours after radiopharmaceutical injection, with potentially higher radiation exposure of the personnel performing the procedure. The development of PET scanners with higher sensitivity could shorten scan times thus increasing scanner
availability and also require less radioactivity that needs to be administered. In the method proposed in the current study, since the diagnostic PET/CT acquisition is registered with the FNA CT, these limitations do not necessarily apply. In an optimal setting it would require just a suitable workstation and easy-to-use software located in the procedure room.

CONCLUSION

Present study supports the concept that anatomo-metabolic guidance of FNA (using information provided by both FDG-PET and CT) may improve the accuracy of tissue sampling, decrease the incidence of false negative results and thus may increase the probability of achieving a definitive diagnosis. Future work should focus on defining the technique and protocol to enable the clinical application of PET/CT to image-guided biopsy.
REFERENCES:

Figure 1: True positive (TP) CT-guided FNA in a 44x42 mm lesion in the left lung. 
(A) CT-FNA demonstrates the location of the aspirating needle (arrow), (B) registered CT-FNA slice with the corresponding CT-PET/CT (red contours, score 1) (C) corresponding FDG-PET slice demonstrating high and homogenous FDG uptake at the site of the needle tip. SUVmax at the tip of the needle: 9.1; highest SUVmax in tumor: 11.0, distance between tumor SUVmax and tip of needle: 3.77 mm. FNA results: adenocarcinoma. Histology obtained at surgery: poorly differentiated adenocarcinoma.
**Figure 2:** False negative (FN) CT-guided FNA in a 58x37 mm lesion in the left lung.

(A) CT-FNA demonstrating the location of the aspirating needle (arrow), (B) registered CT-FNA slice with the corresponding CT-PET/CT (red contours, score 2), (C) corresponding FDG-PET slice demonstrating that the tip of the needle is inside an area of the lesion with low metabolic activity. SUVmax at tip of the needle: 2.4; highest SUVmax in tumor: 6.9; distance between tumor SUVmax and tip of needle: 11.85 mm.

FNA results: macrophages and respiratory cells. Histology obtained at surgery: moderately differentiated squamous cell carcinoma.
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* No surgery was performed
** Others include: metastases, lymphomas, non-specific malignant cells
TP – True positive, FN- False Negative, FNA – Fine Needle Aspiration
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