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Title: PET/CT guided biopsy of suspected lung lesions requires less rebiopsy than CT guided biopsy due to inconclusive results.

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ABSTRACT

The purpose of this study is to compare FDG PET/CT and CT performance in guiding percutaneous biopsies with histological confirmation of lung lesions.

Methods

We prospectively evaluated 341 patients of whom 216 underwent FDG PET/CT-guided biopsy and 125 underwent CT-guided biopsy. The pathology results, lesion size, complications and rebiopsy rate in the two groups were evaluated.

Results

Of the 216 biopsies with PET/CT guidance, histology demonstrated 170 lesions (78.7%) to be malignant, and 46 (21.3%) to be benign; In the CT guided group, out of 125 lesions, 77 (61.6%) were malignant and 48 (38.4%) were benign ($p = 0.001$). Inconclusive results prompted the need for a second biopsy in 18 patients, 13/125 (10.4%) in the CT group and 5 /216 (2.3%) in PET group (p 0.001). Complications rates were: pneumothorax (13.2%), hemothorax (0.8%) and hemoptysis (0.6%). No life-threatening adverse events or fatalities were reported. The difference between complication rates among the 2 groups was not significant ($p = 0.6$). Malignant lesions showed greater mean size than benign lesions regardless of the group ($p = 0.015$).

Conclusion

PET/CT guided biopsy of lung lesions led to fewer inconclusive biopsies in comparison with CT guided biopsy, with similar complication rates.

Keywords

CT-guided biopsy; Lung Cancer; FDG PET/CT; PET/CT-guided biopsy.

Introduction

Lung lesions represent frequent findings in clinical practice, both on radiography and CT studies, bringing concern to physicians and patients. Although pulmonary nodules might be related to conditions of low overall risk, in a non-negligible number of cases they inspire more caution. An immediate question arises from doctors and patients alike: “Could it be cancer?”. As expected, a great deal of anxiety towards the precise diagnosis is created.

Nearly 30,000 new lung cancer diagnoses were made in Brazil in 2018 and 2019 combined, representing the second most frequent cancer in men and the fourth in women (with exception of non-melanoma skin cancer). This translates into roughly 40 new reports of lung cancer in the country, daily (*1*).

Besides being highly prevalent, lung cancer is also responsible for the greatest number of cancer related deaths worldwide - both in male and female populations: around 1.8 million annual deaths (*2*). In Brazil 82% of patients do not survive the 5-year period after initial diagnosis (*3*).

Offering patients adequate treatment relies heavily on appropriate tumor classification regarding several different features including imaging and pathology evaluation (*4*). Lung cancer as an entity encompasses several different pathological categories, which demand somewhat distinct treatment strategies. Hence, tumor sampling represents a cornerstone in the diagnostic and treatment decision (*5,6*).

The appropriate biopsy technique for sampling (open, transbronchial or percutaneous) depends on a series of factors, perhaps the most important one being the tumor localization. In general, open biopsies tend to be avoided whenever possible, given its higher complexity and morbidity compared to other methods. Central and perihilar masses are routinely accessed through bronchoscopy, while percutaneous biopsy is generally preferred for more peripheral lesions.

Percutaneous biopsies guided by imaging methods are well-established procedures included in all major international societies’ lung cancer guidelines (*7-12*). These procedures yield optimal tumor sampling, with excellent performance and low complication rates (*13*).

Positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (FDG-PET/CT) has been increasingly applied in the diagnostic workup of pulmonary lung lesions, due to its

ability to better stratify the risk of malignancy and the added value for correct staging of patients in which malignancy is later confirmed (*14,15*).

For years, CT-guided biopsy has been widely accepted as an effective and safe method in the diagnostic workup in several different clinical settings. PET/CT-guided biopsy, which combines the anatomical information obtained from CT and the metabolic information from FDG-PET is a feasible procedure, which may optimize the diagnostic yield of image-guided interventions (*16,17*).

After thorough search in medical literature, we were unable to find studies directly comparing the two different approaches to percutaneous lung biopsy (i.e., guided by PET/CT or by CT-alone). In the present study, we aim to evaluate the performance of both CT and PET guiding biopsies.

Materials and Methods

The present study was approved by the Institutional Review Board and was performed in accordance with pertinent ethical guidelines. A total of 341 patients were referred to Quanta - Diagnóstico e Terapia for biopsy of suspect lung lesions: 216 underwent FDG PET/CT-guided biopsy and 125 underwent CT-guided biopsy. The study followed a prospective approach, with a minimum follow-up of patients for disease evolution of 6 months. The study followed a prospective approach, with a minimum follow-up of patients for disease evolution of 6 months.

PET/CT access was ultimately used as the randomization mechanism for our study, with patients not granted authorization for PET by their healthcare providers (public or private) being allocated to the CT-only group. CT and PET guided biopsies were performed in the same PET/CT scanner with a fluoroscopic imaging system by the same physician (JJC). Written informed consent was obtained from all patients eligible for this study between 2018 and 2020. After biopsy, samples were analyzed histologically in the same reference laboratory. Complete blood count with platelet and coagulation evaluation was requested before performing each biopsy. Exclusion criteria were platelet count less than 100,000/µl, abnormal coagulation tests, or clinical contraindication for the procedure.

Whole-body FDG PET/CT imaging was performed following an uptake period of 60–90 min after intravenous administration of 296–444 MBq (8–12 mCi) of FDG. Imaging was performed using a GE STE-

16 PET/CT scanner (GE Healthcare, Waukesha, WI) with a CT fluoroscopic imaging system. Areas of non-physiological increased FDG uptake over the background were classified as positive for disease. Technical procedure was performed as previously described (*6*). Patients were positioned according to the lesion location and biopsy planning. Light sedation was preferentially used. After antisepsis, local anesthesia was performed. A coaxial guide needle was inserted under guidance of CT fluoroscopic imaging. One bed position PET/CT images were acquired to confirm the correct position of the coaxial needle (directing the needle towards the most accessible areas of high metabolism). Four to six specimens were collected under CT fluoroscopy. After removal of the needle, manual compression was performed at the puncture site. Patients were observed for at least two hours after the procedure to ensure hemodynamic stability and monitoring the respiratory condition.

CT-guided biopsies were performed as the PET/CT guided biopsy, except for the one FDG-PET one bed position. All other steps were basically the same.

The technical success rate (acquisition of a suitable sample for histopathological evaluation) and complication rates (including pneumothorax, hemothorax and hemoptysis) were compared between PET/CT-guided biopsies and CT-guided biopsies. The histopathological results (malignant versus benign lesions) were also compared between the two techniques, searching for different malignancy detection rates. Student's t test, the chi-squared test, a two-tailed and Fisher's exact test were used for group comparisons of continuous and binomial variables, using statistical analysis software (Stata 11).

Results

The study included 341 patients that were submitted to percutaneous biopsy of lung lesions. Patients demographics and main results are summarized in Table 1.

Among the lesions sampled in the first round of biopsies, malignant results were observed in 170/216 patients in the PET/CT group (78.7%; mean SUVmax: 11.8) and in 77/125 patients in the CT group (61.6%). Benign results were found in the remaining 46 lesions in the PET/CT group (21.3%; mean SUVmax: 7.2) and in 48 (38.4%) in the CT group (p = 0.001). The mean SUVmax for all PET lesions was

10.9, with malignant lesions presenting higher mean SUVmax than benign lesions (11.8 x 7.2, p = 0.0006)

In selected patients, benign results were deemed questionable due to suspect imaging features and/or clinical expertise, and were thus considered inconclusive, prompting the need for a second biopsy. Such was the case in 18/341 (5.3%) patients total, being 13/125 (10.4%) in the CT group and 5 /216 (2.3%) in PET group (p 0.001).

In the second round of biopsy, no statistically significant differences were observed between the two groups: in the CT group, 12/13 rebiopsies turned positive results for malignancy, while the same was true for 5/5 rebiopsies in the PET/CT group (p = 0.523). A summary of the main pathology results for benign and malignant lesions (including the second biopsies, totalling 359 procedures) is provided in Table 2.

No significant differences in lesions' size were observed between the two groups in the first round of biopsies, although our data revealed statistically relevant differences in size between malignant and benign lesions, regardless of the method in which they were examined. Lesions that required rebiopsy in the PET/CT group had greater average size than those on the CT group (9.6 x 4.6 cm, p = 0.04).

All patients were followed by a minimum period of 6 months, during which at least one additional CT exam was performed and the evolution of each case was accessed through discussion with the referring physicians. All patients with initial benign pathology findings after biopsy (with exception of those deemed inconclusive) were considered truly benign on follow-up after confirmation that the suspect lesions remained stable in size and characteristics on CT, or if lesion regression was observed.

All patients were followed by a minimum period of 6 months, during which at least one additional CT exam was performed, and the evolution of each case was accessed through discussion with the referring physicians. All patients with conclusive benign pathology findings were considered truly benign on follow-up after confirmation that the suspect lesions remained stable in size and characteristics on CT, or if a lesion regression in size was observed.

PET/CT group's complication rate was 13.5% (29 patients) with 27 cases of pneumothorax (12.5%), one case of hemoptysis (0.5%) and one case of hemothorax (0.5%). Two patients had to be admitted to the hospital (one for hemoptysis observation, one for hemothorax control). In the CT group,

the complication rate was similar: 16.8% (21 patients), being 18 cases of pneumothorax (14.4%), one case of hemoptysis (0.8%) and two cases of hemothorax (1.6%). Three patients had to be admitted to hospital (one for hemoptysis control, one for hemothorax control, one for observation of pneumothorax). There were no procedure related deaths in both groups.

Discussion

To our knowledge, this comparison of FDG-PET/CT and CT-guided biopsies of lung lesions is the largest cohort published to date. We found higher rates of malignant lesions in the FDG-PET/CT guided group in comparison to the CT guided group (78.7% vs 61.6%, p = 0.001). We hypothesize a selection bias regarding the distribution of patients between the two groups, with patients in the PET/CT group presenting a higher chance of having a malignancy probably related to better accuracy of PET/CT in the evaluation of lung lesions, most noticeably regarding nodules with intermediate likelihood of malignancy presenting areas of hypermetabolism. It also must be highlighted that performing the evaluation with PET/CT carries incremental value for patients for which biopsy results will show malignancy, given PET/CT's superiority to CT regarding all 3 descriptors of the TNM staging of non-small cell lung cancer, being recommended in the workup for initial staging in all patients from stages I-IV (*18,19*).

Furthermore, we highlight that biopsy inconclusive results were different between the two groups, being higher in the CT group, prompting the need of a second biopsy in 10.4% in the CT group and in 2.3% in the PET group (*p* 0.001). Lung cancer lesions can be quite heterogeneous, especially in large masses where cancer cells is not present in the complete tumoral volume. The CT image of the lesion might contain inflammatory tissue, necrosis, normal lung tissue represented by atelectasis, when an adequate biopsy specimen must represent an actual neoplastic area in which the evaluation of metabolism by FDG-PET might improve results.

Once we integrate CT's excellent anatomical information, especially important to evaluate vessels and important structures related to the biopsy path, with the metabolic characterization provided by FDG-PET images, sampling from the hypermetabolic portion of the apparently larger morphological lesion seen

on CT becomes feasible, which is more likely to yield representative material for microscopic analysis (Figures 1,2,3) (*6,17,20-25*).

Another observation in our data is related to lesions' size. We found malignant lesions to be larger, regardless of the group, with mean size (measured in their greatest tridimensional diameter on CT) of 5.0 cm, against 4.0 cm for benign lesions (p = 0.015). Although there is statistical relevance related to this feature, we understand that such a narrow difference does not translate into a significant impact in clinical practice. Greater average size was observed in the lesions that required a second biopsy in the PET/CT group than in the CT group (p = 0.04), which might be related to tumoral cells representing a smaller proportion of the overall lesion composition in the case of large heterogeneous masses.

Lastly, we analyzed procedure safety and found similar complication rates in both groups, with no life-threatening adverse events or fatalities reported. Hence, given the size of our sample and the observed outcomes, we deem both methods quite safe overall. Regarding physician radiation safety, a similar exposure is expected among the two methods, since our approach did not require a repeat FDG-injection during the biopsy procedure, as reported elsewhere (*16*).

To the best of our knowledge, this is the first study directly comparing the performances of PET/CT vs CT-guided biopsies of lung lesions in separate groups. It must be made clear that our study presents a limitation of selection bias regarding the distribution of patients between the two groups. Access and reimbursement of PET/CT is far from being the best method for randomization but was the available method due to the Brazilian healthcare system's idiosyncrasies. Access to PET/CT examination is quite heterogeneous in Brazil. The public healthcare system (SUS) applies several restraints in order to grant clearance for PET/CT studies. Private health insurance companies also differ greatly about requirements in order to cover PET/CT expenses. It is possible that this selection bias might have contributed to higher malignancy rates in the PET/CT group.

Conclusion

PET/CT guided biopsy of lung lesions led to fewer inconclusive biopsies in comparison with CT guided biopsy, with similar complication rates.

Disclosure

There were no grants, consulting fees, travel fees, or honoraria involved in the present paper. No potential conflicts of interest relevant to this article exist.

Key Points

Question

Are there any significant differences in performance between PET/CT and CT guided percutaneous biopsy of lung lesions?

Pertinent Findings

A cohort of 341 patients was prospectively evaluated with percutaneous biopsy of suspect lung lesions, of whom 216 underwent FDG PET/CT-guided biopsy and 125 underwent CT-guided biopsy. PET/CT guided biopsy of lung lesions led to fewer inconclusive biopsies in comparison with CT guided biopsy, with similar complication rates.

Implications for patient care

Our results may influence the decision of the preferred method for guidance of percutaneous biopsy of lung lesions if both PET/CT and CT are available.

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Table 1: Patients characteristics and differences between groups.

	All Groups	CT guided biopsy	PET/CT guided Biopsy	*p* value
Age (Mean)	**65 y** (27-93)	**65.4** (SD: 13.2)	**65.9** (SD:12.1)	*p = 0.541*
Gender				
Female	**169** (49.5%)	**60** (48%)	**109** (50.5%)	
Male	**172** (50.5%)	**65** (52%)	**107** (49.5%)	*p = 0.661*
Histology (1st biopsy)				
Malignant	**247** (72.4%)	**77** (61.6%)	**170** (78.7%)	
				p = 0.001
Benign	**94** (27.5%)	**48** (38.4%)	**46** (21.3%)	
Histology (2nd biopsy)				
Malignant	**17** (94.4%)	**12** (92.3%)	**5** (100%)	
				p = 0.523
Benign	**1** (5.5%)	**1** (7.7%)	**0** (0%)	
Complications				
Pneumothorax	**45 (**13.2%**)**	**18** (14.4%)	**27** (12.5%)	
Hemothorax	**3 (**0.8%**)**	**2** (1.6%)	**1** (0.5%)	*p = 0.651*
Hemoptysis	**2 (**0.6%**)**	**1** (0.8 %)	**1** (0.5%)	

Table 2: Summary of the main pathology results for malignant and benign lesions

Malignant	
Adenocarcinoma	91/359 (**25.3%**)
Squamous cell carcinoma	26/359 (**7.2%**)
Poorly differentiated carcinoma	32/359 (**9.0%**)
Metastasis	100/359 (**27.8%**)
Other primary lung cancer	20/359 (**5.6%**)
Benign	
Inflammatory findings	37/359 (**10.4%**)
Infectious disease findings	5/359 (**1.4%**)
Other benign conditions (fibrosis, anthracosis, etc)	31/359 (**8.6%**)
Normal tissue	17/359 (**4.7%**)

Figures

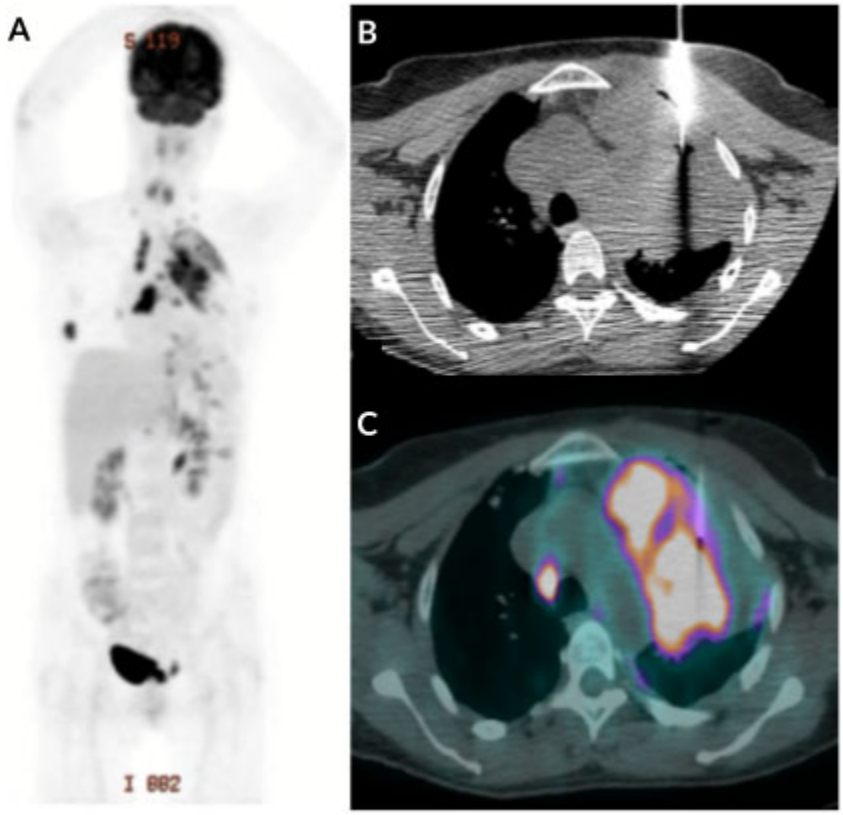

Figure 1: Patient with lung mass was referred to FDG-PET/CT. (A) Maximum intensity projection PET image shows multiple lesions in the left lung, lymph nodes and bones. (B) Axial CT thoracic image shows the placement of the coaxial guide needle in the lesion that does not differentiate atelectasis from the metabolic active lung lesion. (C) Axial PET/CT fusionated image confirms the positioning of the coaxial guide needle is appropriately positioned in the metabolic border of the lesion, assuring that metabolic active specimens will be collected with the semiautomatic needle that will be inserted 2 cm further. Pathological analysis confirmed adenocarcinoma.

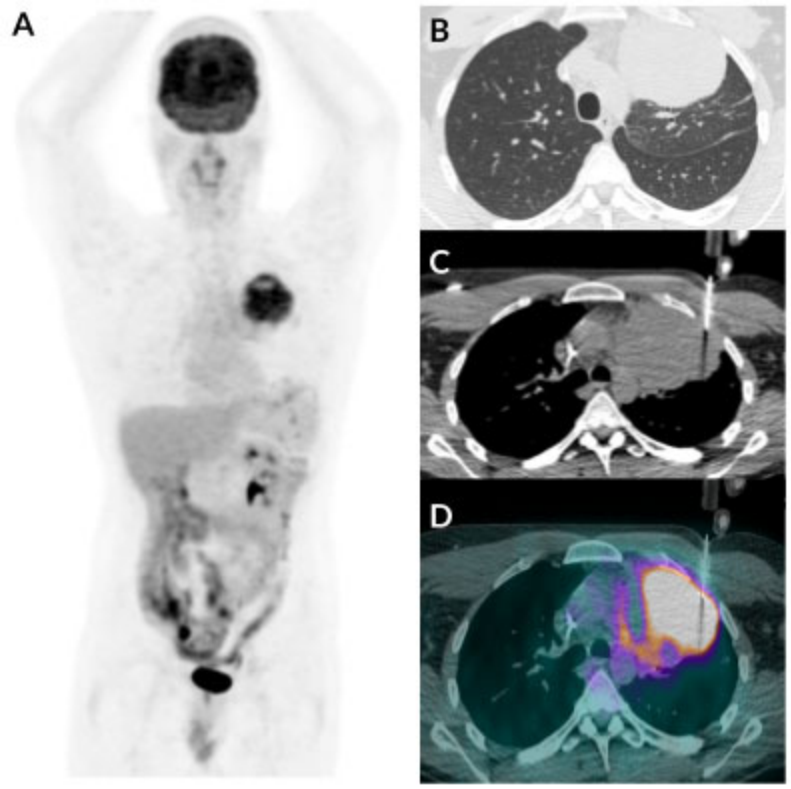

Figure 2: Patient with a previous inconclusive biopsy presented with a heterogeneous mass in the left lung, with the lateral part of the lesion presenting area of severe FDG uptake and almost absence of FDG uptake in the medial part of the lesion. FDG-PET/CT guided biopsy was performed. Through anterior access, the biopsy needle was directed to the region with highest metabolism, thus improving the odds of yielding representative neoplastic material for histopathological analysis (in this case, the results revealed adenocarcinoma). (A) Maximum intensity projection PET image. (B) CT lung window transaxial; (C) CT mediastinal window transaxial (intraprocedure). (D) FDG PET/CT transaxial fused images (intraprocedure CT image fused with previously acquired PET/CT image);

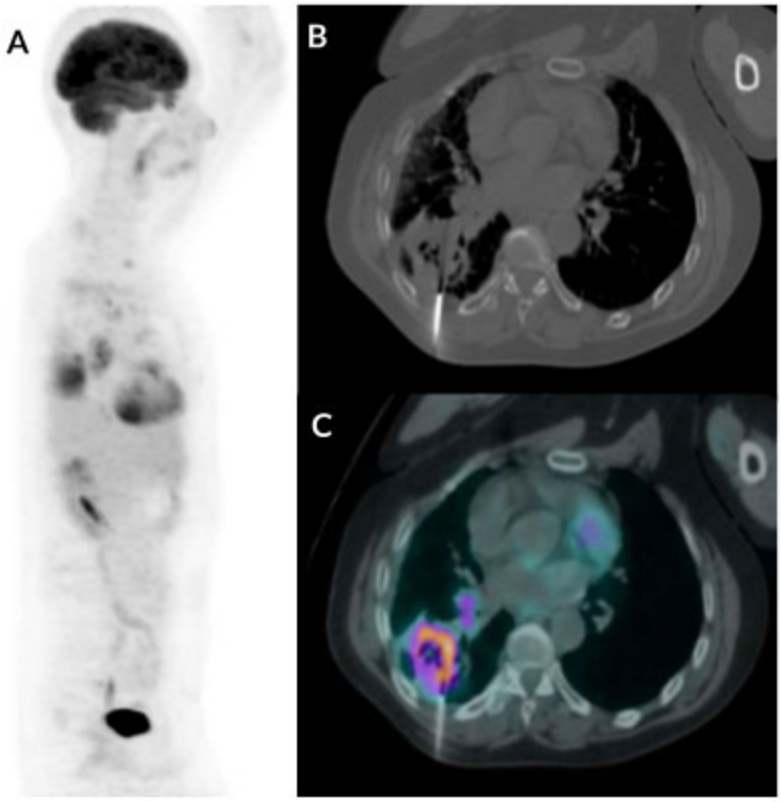

Figure 3: Patient with a cavitated lung lesion was referred to FDG-PET/CT. (A) Maximum intensity projection PET image. (B) Axial CT thoracic image shows the semiautomatic needle placed at the border of the lesion. (C) Axial PET/CT fusionated image shows the placement of the coaxial guide needle in the area with highest metabolism. Pathological analysis confirmed primary adenocarcinoma of the lung.

Graphical Abstract