# CT guided mediastinal biopsy facilitated by PET/CT imaging: Our experience

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**Abstract**
The purpose of this retrospective study is to assess the efficacy of mediastinal tumor biopsies guided by computed tomography (CT) and facilitated by positron emission tomography (PET)/CT in our hospital. We also wanted to prove the use of PET/CT in performing such biopsies. Fifty-two patients were biopsied under CT guidance with PET/CT visual co-registration (35) and facilitated PET/CT registration (17). In 49 patients, a diagnosis from the guided biopsy performed was successful and in 3 patients the results were inconclusive. Our results allow us to claim that the accuracy of CT-guided mediastinal biopsies facilitated by PET/CT allow for precise localization of higher tumor metabolism, potentially reduce the number of needle passes needed and increase the success rate of the procedure.

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## Introduction

Mediastinal masses represent a wide variety of entities with overlapping radiologic manifestations and variable prognoses. The location and composition of a lesion is crucial in order to narrow the differential diagnosis by imaging [1, 2]. Computed tomography (CT) is the most important radiological modality for the evaluation of a mediastinal mass. Computed tomography characterization is based on specific attenuation of air, fat, water and calcium, while high-resolution multiplanar reconstructions are valuable adjuncts to adequately map a lesion. Vascular abnormalities and degree of vascularization of soft tissue masses can be demonstrated and evaluated by means of intravenous contrast (IVC) administration [3].

Anterior mediastinal tumours account for 50% of all mediastinal masses, such as thymoma, teratoma, thyroid tumors and lymphoma [3]. Masses of the middle mediastinum are mainly congenital cysts and small cell lung carcinomas (SCLC) while those arising in the posterior mediastinum are usually neurogenic tumours [2]. The likelihood of malignancy of mediastinal lesions depends on the mass location, the patient age and the presence or absence of symptoms. Most patients with mediastinal masses are usually asymptomatic. However, the most common symptoms are cough, chest pain, fever and respiratory distress. Symptoms are usually secondary to tumour invasion (respiratory compromise, diaphragm and vocal cords paresis Horner syndrome, superior vena cava syndrome), while systemic symptoms are typically due to the release of excess hormones, antibodies or cytokines [1, 2].

The differential diagnosis of mediastinal lesions includes fatty, cystic and solid masses. Fat-containing masses are especially recognized by their low CT attenuation (-40 to -120HU) and include mainly lipomas in the anterior mediastinum, liposarcomas in the posterior mediastinum and thymolipomas, usually in the cardiophrenic angle [4, 5]. On the other hand, cystic lesions comprise 15%-20% of all mediastinal masses, as most of them are developmental in origin [6]. Bronchogenic, duplication, neuroenteric and thymic cysts represent the majority of cystic entities [7]. However, most mediastinal masses in the adult population are solid. Mediastinal thyroid goiters, intrathoracic thyroid masses, thymomas, rarely thymic carcinomas and thymic carcinoid constitute common neoplasms of the anterior mediastinum [8]. Accordingly, lymphomas (Hodgkin and non-Hodgkin) make up common mediastinal neoplasms and may affect any mediastinal compartment, although these usually occur in the anterior mediastinum as a part of a

more widespread disease [9]. Furthermore, germ cell tumors constitute another mediastinal entity, arising from tumoral transformation of germinal elements, sixty percent of them are benign teratomas [2]. Additionally, neurogenic tumours represent approximately 20% of all adult tumors and remain the most common cause of a posterior mediastinal mass. Neural tumors can be divided into nerve sheath tumors, ganglion cell tumors and paraganglionic cell tumors [10].

Surgical procedures such as mediastinoscopy and thoracoscopy were traditionally the methods used to biopsy mediastinal lesions. Trans bronchial needle biopsy techniques (TBNA) and trans bronchial ultrasound endoscopic techniques (EBUS) are also performed in order to biopsy mediastinal lesions. Percutaneous core needle biopsy under CT guidance has been performed for years and is less invasive than the aforementioned procedures [11]. This technique allows sufficient tissue sampling providing accurate histologic and immunohistochemical evaluation. Percutaneous CT-guided biopsy is a well-established technique for the diagnostic evaluation of mediastinal lesions as it allows access to virtually all mediastinal compartments, including those that may often be inaccessible by other methods [12]. Additionally, its diagnostic accuracy rates range from 77% to 90% with a pooled mean success rate of 83.1% [13].

Positron emission tomography/CT is a hybrid imaging modality formed through the integration of PET and CT. Fluorine-18 ($^{18}$F) is the most preferred radionuclide and fluorodeoxyglucose (FDG) is a glucose analogue labelled with the radionuclide $^{18}$F. Fluorine-18-FDG administered intravenously to the patient for PET/CT imaging accumulates in tumor cells, since these cells have a more rapid glucose metabolism than normal ones [14].

Positron emission tomography/CT is recommended for examining a variety of tumor types by National Comprehensive Cancer Network (NCCN) guidelines [15]. Its sensitivity is high, up to 90%, for the identification of malignancy, but specificity is limited to 55.17% because of false-positives such as in Castleman disease, thymic hyperplasia, non-invasive thymomas and benign neurogenic tumors [16]. Positron emission tomography/CT false-negative cases usually involve thymic cancer and invasive thymomas [17]. Most mediastinal cystic masses have true negative findings. Positron emission tomography/CT has a complementary role in the assessment of cystic lesions for further patient management.

Mean $^{18}$F-FDG uptake of malignant mediastinal tumors is significantly higher than that of benign tumors. However, the uptake of $^{18}$F-FDG is not specific for the type of tumor. Standardized uptake value (SUVmax) can be a useful marker for the differential diagnosis between malignant and benign tumors. In addition, PET/CT may reduce unnecessary invasive investigations for diagnosis in patients with low avidity $^{18}$F-FDG lesions [16].

Surgical procedures such as mediastinoscopy (sensitivity 81% and specificity 100%) and thoracoscopy were traditionally the methods used to biopsy mediastinal lesions [11]. Transbronchial needle biopsy techniques (TBNA) and endobronchial ultrasound endoscopic techniques (EBUS) are also performed during bronchoscopy and as minimally invasive alternative methods in order to biopsy mediastinal lesions [11].

Percutaneous core needle biopsy under CT guidance has been performed for years and is less invasive than the aforementioned techniques [11]. This technique allows sufficient tissue sampling providing accurate histologic and immunohistochemical evaluation. Percutaneous CT-guided biopsy is a well-established technique for the diagnostic evaluation of mediastinal lesions as it allows access to virtually all mediastinal compartments, including those that may often be inaccessible by other methods [12]. Additionally, its diagnostic accuracy rates range between 77% to 90% with a pooled mean success rate of 83.1% [13].

Using this $^{18}$F-FDG PET/CT characteristic, biopsies are conducted on various body parts with PET/CT guidance. It has been reported that use of $^{18}$F-FDG PET/CT has increased the accuracy rate of biopsies by some authors but others have stated the opposite [14, 18]. Confirmatory tissue sampling, although, is required to confirm positive PET/CT findings for a definite diagnosis [17].

The purpose of this study is to evaluate the efficacy of CT-guided biopsy in the diagnosis of mediastinal lesions compounded with PET/CT mapping prior to biopsy, within a 15-day time interval from the biopsy, in a large tertiary hospital during the last two years.

## Materials and Methods

This is our institutional single center retrospective study. Between October 2017 and October 2019, 52 patients (37 men, 15 women; mean age 49, range 21-78 years) were admitted to our department for CT-guided percutaneous mediastinal biopsy. In all patients, the diagnosis of a mediastinal mass was established by a post contrast chest CT scan. All patients underwent $^{18}$F-FDG PET/CT, (Discovery ST, GE Healthcare, Milwaukee, WI, USA) that was performed no more than two weeks before the biopsy in order to determine which approachable area of the lesion had the highest metabolism. Forty-one lesions were located in the anterior mediastinum, 7 in the posterior and 4 in the middle mediastinum. The mean tumor size was 4.2cm (range 1.5-5.5cm).

Prior to biopsy, all patients were informed about the necessity of obtaining tissue samples from the lesion, as well as the potential complications. An informed consent was obtained from all of them. A full coagulation profile (prothrombin time, partial thromboplastin time), hemoglobin level, international normalized ratio (INR), platelet count and serum for cross-matching were available before every biopsy. A platelet count of at least 50,000 and INR value of less than 1.5 were prerequisites for the procedure. In the opposite case, abnormal laboratory values were corrected before the procedure [19]. Antiplatelet or anticoagulation medication was recommended to be discontinued five days prior to biopsy. Warfarin and heparin/related products were discontinued 24 hours prior to biopsy [19].

A needle path was visually defined on the approachable

area or site of the lesion with the highest metabolism on $^{18}$F-FDG PET/CT images with respect to the surrounding anatomy. Patients were positioned in the supine, prone, or lateral decubitus position depending on the lesion location.

A pre-biopsy non-enhanced CT scan was performed on a 16- row multislice computed tomography scanner (Aquilion TSX 101A; Toshiba Medical systems, Otawara, Japan) and was sufficient in 32 patients who had already undergone diagnostic contrast-enhanced CT. However, in cases that required delineation of anatomical structures such as mammary vessels and aortic branch vessels in the projected needle path, a total volume of 100mL of non-ionic contrast medium was injected intravenously at a rate of 3mL/s by a power injector (Vistron CT injection system; Medrad, Indiannapolis, USA).

The most suitable slice was noted to access the lesion. Visual co-registration was implemented in 35 patients. Additionally, use of registration software (Oasis, Segami Corporation, Columbia, MD USA) was adopted in 17 patients (facilitated co-registration) in order to verify our visual co-registration results of the lesion with the highest metabolism and the pre-biopsy CT image. The location was marked on the skin surface with an axial laser beam localizer incorporated in the CT gantry. Local anaesthesia with 1% xylocaine was used and antiseptic (povidone iodine- draping) was applied. Continuous pulse oximetry and non-invasive blood pressure monitoring were part of the biopsy protocol. Transmission precautions in the CT suite were taken according to the CDC guidelines [20]. A 16-18-gauge tru-cut needle, 6-9cm in length (Cook, Bloomington Indiana U.S.A) was used in all patients. The selection of the needle depended on the mass depth from the skin surface, size of lesion to be biopsied and proximity to vital structures. One core was obtained in 47 patients and in 5 patients two cores were obtained. The tissue sample was directly sent to the pathology department in a formalin solution. Co-axial needles and fluoroscopy were not available [21]. A post-biopsy CT scan was performed after the needle removal to exclude possible complications. The patients were monitored for 1-3 hours after the procedure to ensure their hemodynamic stability and their respiratory status. A chest X-ray was performed prior to the patient's discharge from the hospital the same afternoon to exclude a pneumothorax.

## Results

Biopsies were performed using the parasternal approach in 41 of 52 mediastinal lesions located in the anterior mediastinum, while the trans pulmonary approach was performed in 4 patients with lesions in the middle mediastinum. Biopsy of the posterior mediastinum was achieved in 7 patients using the paravertebral approach. The angle and tract of our needle were calculated from the anaesthesia needle. Concerning the parasternal approach, the patient was in a supine position and the needle was inserted lateral to the sternum, medially or laterally to the mammary vessels (28 lateral and 13 medial to mammary vessels). For the transpulmonary approach, subpleural emphysema cysts and lung fissures were avoided when possible. The paravertebral approach was performed with all patients located in a prone position. The needle was advanced immediately lateral to the vertebral body between the endothoracic fascia and the parietal pleura. The intercostal nerve and artery, the azygos vein, and the esophagus were avoided [22].

By $^{18}$F-FDG PET/CT facilitated and visually co-registered guided percutaneous biopsy a definitive diagnosis was achieved in 49/52 patients with a 94,2% success rate. A total of 41 lesions in the anterior part of mediastinum including 28 Hodgkin lymphomas (Figures 1-4), 6 SCLC (Figure 5), 3 non-Hodgkin lymphomas, 2 thymomas, 1 hamartoma (Figure 6) and 1 sarcoma were diagnosed. The 4 cases in the middle mediastinum were 2 small cell carcinomas (SCLC) and 2 non-small cell lung carcinomas (NSCLC), while 7 lesions were located in the posterior mediastinum and consisted of 2 non-Hodgkin lymphomas (Figure 7), 2 neuromas and 3 specimens were inconclusive. The final diagnosis was non-Hodgkin lymphomas in these 3 cases were surgically confirmed. Our results are summarized in Table 1.

***Table 1:*** *Biopsies results.*

| Biopsies (52) | | |
|---|---|---|
| Anterior mediastinum (41) | Middle mediastinum (4) | Posterior mediastinum (7) |
| Hodgkin lymphomas (28) | SCLC (2) | Non-Hodgkin lymphomas (2) |
| SCLC (6) | NSCLC (2) | Neuromas (2) |
| Non-Hodgkin lymphomas (3) | | Inconclusive cases (3) |
| Thymomas (2) | | |
| Hamartoma (1) | | |
| Sarcoma (1) | | |

The procedure was well tolerated by 51/52 patients. A patient with a posterior mediastinal neuroma, due to the excessive pain lost consciousness temporarily and was treated accordingly. All patients complained of mild post procedural pain, while mild shortness of breath with no variation of pre-biopsy clinical status was observed in 3 patients. No major complications were reported [23]. In both patients, where transpulmonary approach was selected, on the post biopsy CT scan, alveolar haemorrhage was observed along the needle pathway with no further consequences (Figure 8).

## Discussion

Accurate diagnosis of mediastinal tumors, the distinction of

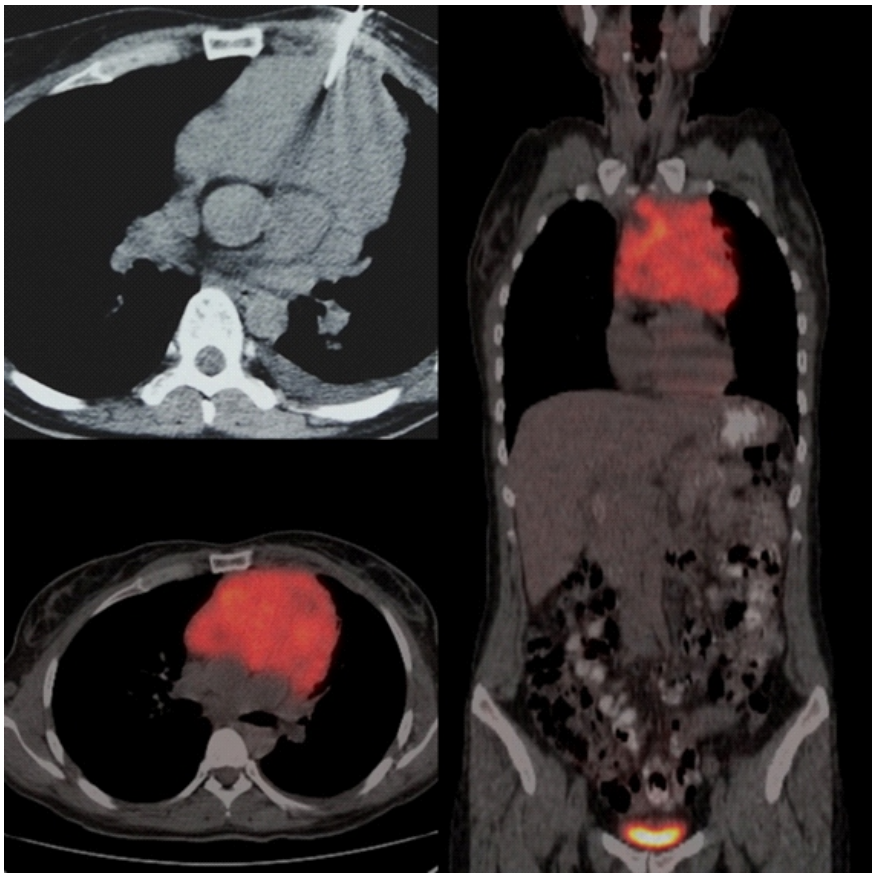

**Figure 1.** In a 36-year-old female with symptoms of weight loss, fatigue and a lesion of anterior mediastinum a CT-guided biopsy was performed with a 16/9 G needle, a paras-ternal approach lateral to the mammary arteries was performed. Positron emission tomography/CT obtained five days prior to the biopsy had shown homogenous $^{18}$F-FDG uptake in the entire lesion. The histological result was Hodgkin lymphoma.

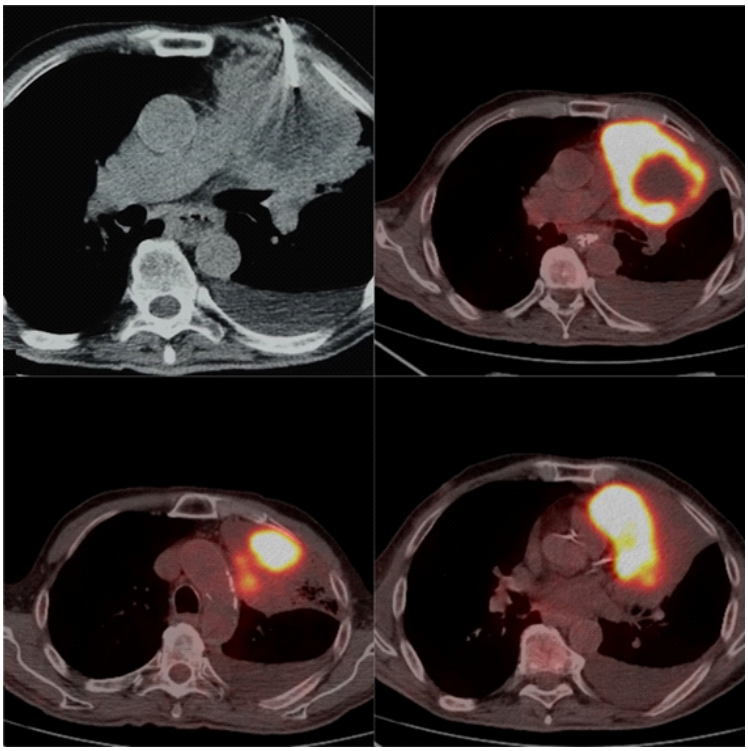

**Figure 2.** A 55-year-old male presented with a large anterior mediastinal mass. A pre biopsy PET/CT was available delineating the areas with the highest metabolic activity and a central photopenic area, representing cystic-necrotic area. The 16/9 G needle was placed in the most solid area with the highest metabolic activity. The result of the biopsy was Hodgkin lymphoma.

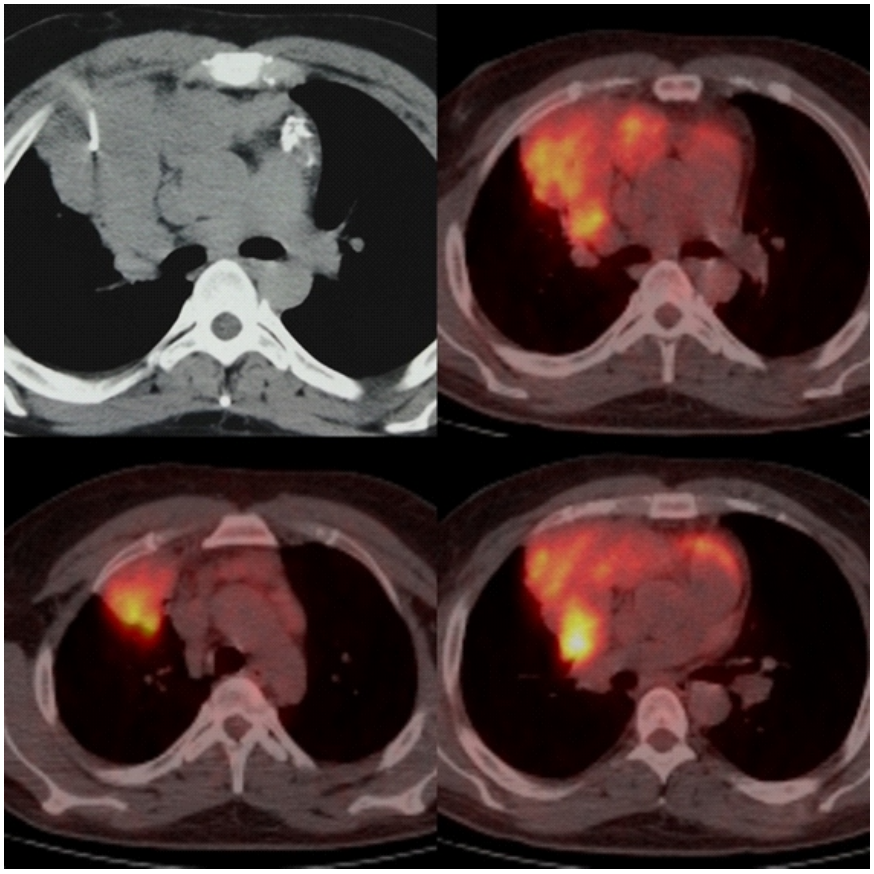

**Figure 3.** True-positive $^{18}$F-FDG uptake. A 62-year-old male presented with a large anterior mediastinal mass. A pre biopsy PET/CT was available delineating the areas with the highest metabolic activity. The 16/9 G needle was placed in the most solid area with the highest metabolic activity. The result of the biopsy was Hodgkin lymphoma.

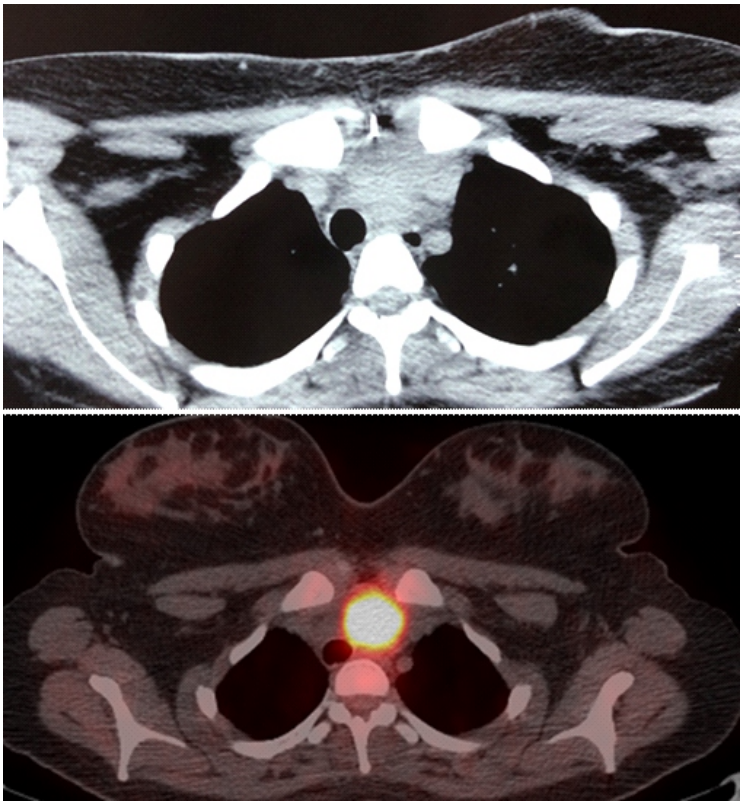

**Figure 4.** Biopsy revealed recurrent Hodgkin lymphoma in a 19-year-old female patient. The patient had undergone a mediastinoscopy previously. Positron emission tomography/CT reveals that all of the lesion is metabolically active making the biopsy easier to perform.

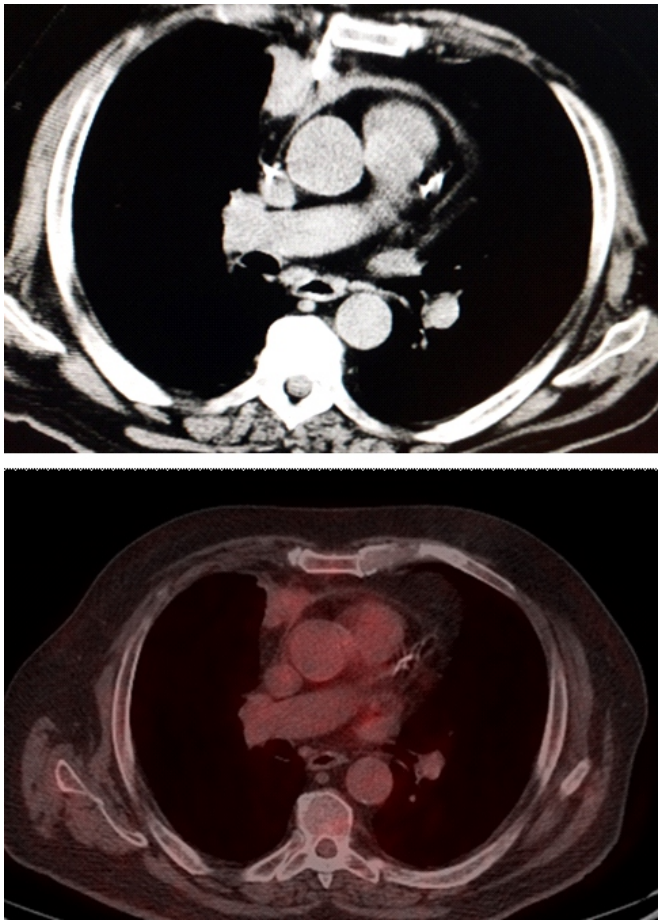

**Figure 5.** A 67-year-old male patient with a history of pericarditis and a small lesion in the anterior mediastinum. Biopsy revealed SCLC.

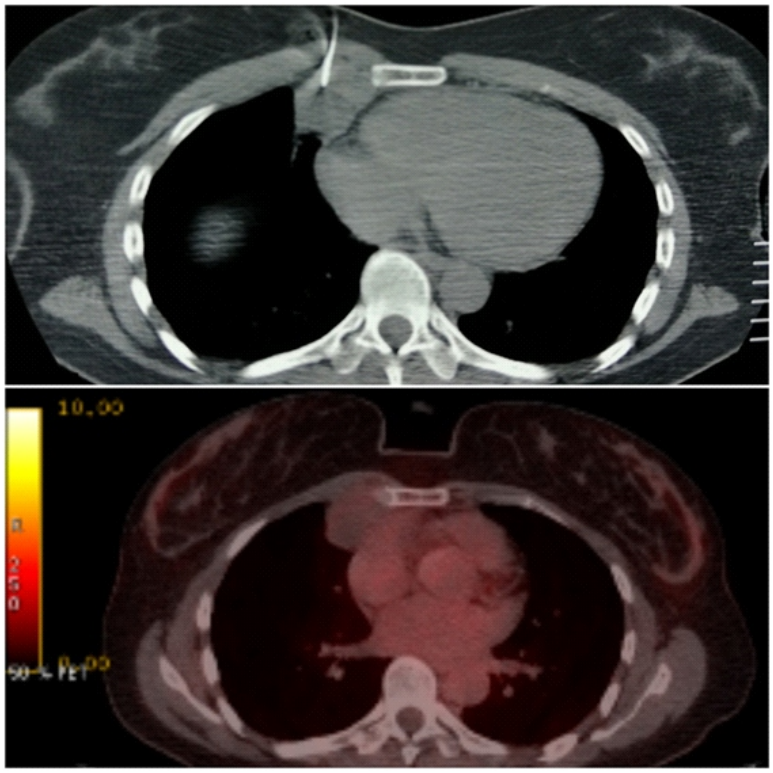

**Figure 6.** True-negative $^{18}$F-FDG uptake. A 57-year-old female, presented with a lesion in the anterior mediastinum, PET/CT did not show any $^{18}$F-FDG uptake and the possible diagnosis of benign lesion was more favoured. An 18/9 G needle was used and the first biopsy was inconclusive. A second attempt was conducted and the outcome was mesenchymal hamartoma.

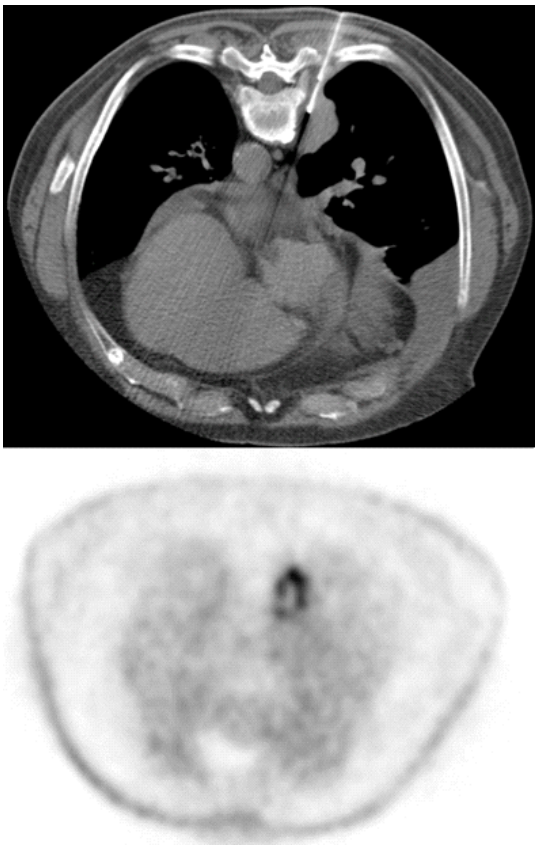

**Figure 7.** Lesion in the posterior mediastinum. Fluorine-18-FDG PET/CT revealed peripheral metabolic activity of the lesion. The needle 18/9g aimed to the area with increased metabolic activity, a neuroma was diagnosed.

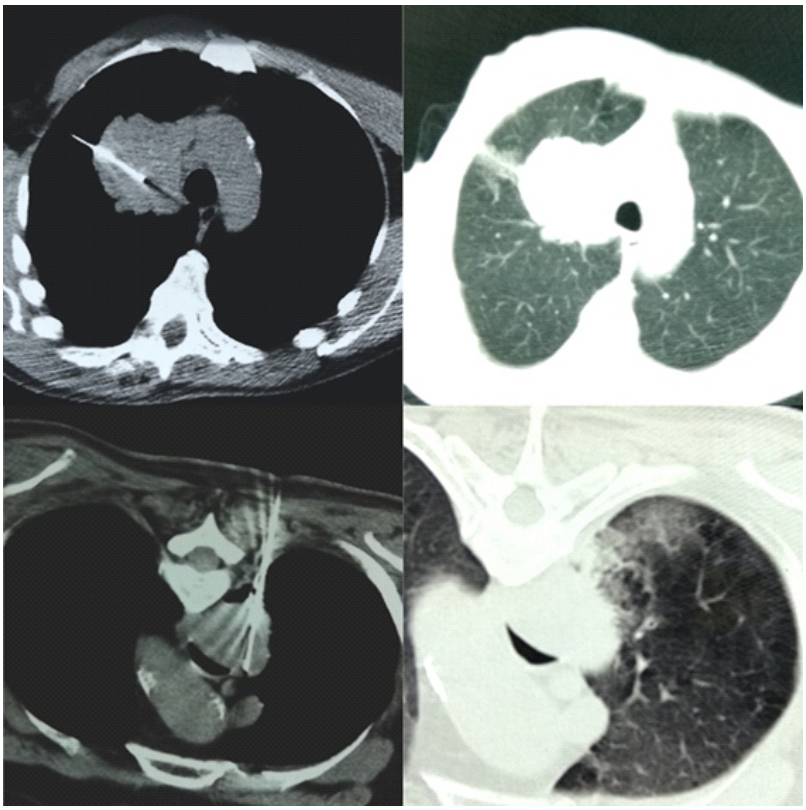

**Figure 8.** Two cases of transpulmonary approach of a lesion in anterior mediastinum and another in posterior mediastinum with 18g core biopsy needles. In both patients on the post biopsy CT scan alveolar haemorrhage was seen along the needle pathway. The first case was a SCLC and the second was inconclusive.

malignant from benign lesions, specific and early treatment are the main goals of performing $^{18}$F-FDG PET/CT in order to decrease mortality in these patients. There are several available methods for obtaining tissue specimens for cytologic or histologic diagnosis of mediastinal masses. Nowadays, CT-guided percutaneous biopsy can potentially obviate more invasive alternative techniques such as mediastinoscopy, exploratory thoracoscopy or bronchoscopic techniques such as transtracheal, transbronchial, or transesophageal fine needle aspiration, which are correlated with more complications, hospitalisation and exposure to anaesthetics [24]. Compared to the aforementioned invasive methods, CT-guided percutaneous biopsy has several advantages because it allows precise localization of the target lesions and access to virtually all mediastinal compartments [11]. Moreover, there are only a few contraindications that exclude the use of CT-guided percutaneous biopsies, such as the possibility of a hydatid cyst, bleeding diathesis, pulmonary hypertension, hypervascular tumors and the lack of patient cooperation [25].

Tissue biopsy guided only by CT anatomical data can lead to the placement of the needle into an area of necrosis or fibrosis with subsequent inadequate tissue sampling and potential false negative results, up to 20% have been reported [26]. These results are driven by the fact that anatomical imaging techniques fail to differentiate viable from non-viable regions in tumors with significant heterogeneity [26]. Furthermore, the presence and the amount of malignant cells may vary across the target lesion, whilst the mediastinal lesions may contain solid areas mixed with cystic, necrotic or fibrotic areas characterized by the absence of malignant cells [27]. In our department, regarding the patients without a pre-biopsy $^{18}$F-FDG PET/CT, the most solid areas within the lesion are selected and two needle passes are performed on average in order to improve the positive rate of the tissue sample. Our success rate in these patients is lower than the rate in patients with a PET/CT scan available before biopsy using the same needles and number of passes, 82.5 % vs 94.2%.

Current studies assess whether information provided by $^{18}$F-FDG PET/CT will decrease the false negative rate or inconclusive specimens, increase the efficacy of the biopsy procedure, decrease the number of needle passes and thus improve the accuracy of CT-guided biopsy. The diagnostic accuracy of CT-guided biopsy with and without the registration of prior PET/CT images was not statistically different reported in one study [17]. However, information with respect to the lesion's metabolic characteristics are provided in $^{18}$F-FDG PET/CT images including differentiation of metabolic from non-metabolic areas ($^{18}$F-FDG-avid, $^{18}$F-FDG-non-avid). Moreover, safer and more accessible areas, possibly in other organs, can be revealed by whole body $^{18}$F-FDG PET/CT and the CT-guided biopsy plan can be altered as seen in our study (Figure 9). Regarding the area with the highest suspicion of malignancy, tissue sampling is important according to our results and other authors in order to ensure accurate FNB results [14, 27].

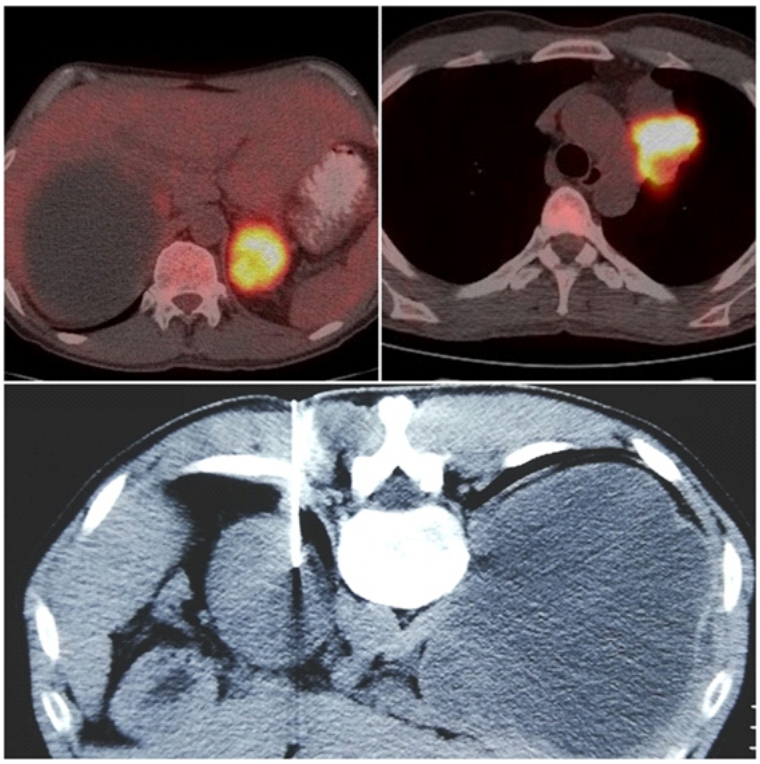

**Figure 9.** Biopsy site changed due to PET/CT. A 46-year-old patient presented with haemoptysis underwent chest CT, which revealed a lesion in the anterior mediastinum. Positron emission tomography/CT delineated the areas with the highest metabolic activity and $^{18}$F-FDG uptake in the lesion of anterior mediastinum while simultaneously pointed out other areas in the body with $^{18}$F-FDG uptake. Without the PET/CT the first approach for tissue specimen would be the lesion in the mediastinum, however PET/CT showed high $^{18}$F-FDG avidity of the left adrenal gland. Due to the easier accessibility of the left adrenal grand, a CT-guided biopsy with 18/9 G needle was performed in this area. The outcome was SCLC.

Use of software registration algorithms that register the intraprocedural CT images with the preselected PET/CT data have been adopted. Although primarily aimed at improved diagnostic interpretation, image registration also has found applications in treatment planning and interventional procedures. With the use of a co-registration algorithm, the chances of achieving a definite diagnosis are increased [28, 29]. The feasibility and potential value of 3D $^{18}$F-FDG PET/CT videos were investigated to improve the accuracy of targeted lymph node biopsy during mediastinoscopy. The results revealed that the use of PET/CT videos may reduce the frequency of false negative mediastinoscopic findings and improve the staging of lung cancer [30]. The potential use of interim $^{18}$F-FDG SUVmax for determining the need for a residual mass biopsy after dose-dense immunochemotherapy for advanced diffuse large B-cell lymphoma has been reported [31]. In addition, a case of lymphoma in which an occult lesion localization method was used for radioguided biopsy of a chemoresistant lymph node detected with interim $^{18}$F-FDG PET/CT [32]. It is worthy to mention a new in-novative technique which includes real time $^{18}$F-FDG PET/CT guidance for percutaneous biopsies of thoracic lesions under an automated robospy arm (ARA) guidance in patients with previous inconclusive biopsy results. Thus, ARA guidance proves to be promising in accurate targeting of the metabolically active tissue and avoiding unsuccessful biopsy procedures [33].

Our retrospective study provides support for the use of $^{18}$F-FDG PET/CT to improve the diagnostic accuracy of percutaneous CT-guided mediastinal biopsy, guiding the operator to the most metabolically active area of the lesion. It consequently reduces the potential need for multiple needle passes and the potential risk of complications, as targeting areas of viability and avoiding necrosis/atelectasis are accomplished. Positron emission tomography/CT can also identify early metabolic changes before obvious morphological changes appear on CT. In contrast, PET/CT does not offer additional information from CT scans concerning tumor necrosis in large tumors of the anterior mediastinum (Figure 2) in most cases but in our opinion in some cases it is of definite value when the lesion is inhomogeneous on CT (Figure 3).

In our series of patients, the success rate is high, even though in most patients (47/52) one needle pass was performed. In our opinion, a high success rate was due to the large core biopsy needle, 18-16g, and mapping the region in the tumor with the highest metabolic activity from PET/CT. These results are not in accordance with other authors such as Yokohama et al. (2014) but as stated previously, our biopsy results without a PET/CT before the procedure yielded lower success rates. Mediastinal biopsy under CT guidance should be carried out when a tumor is detected leaving the unsuccessful cases to more invasive procedures. In our series, the three unsuccessful biopsies concerned non-Hodgkin lymphoma located in the posterior mediastinum (Figure 7). Positron emission tomography/CT allows for fewer needle passes and, in some situations, changes the initial biopsy plans because it may reveal more accessible pathology for biopsy, which is in favor of patient safety (Figure 9). A limitation of our study is that it is retrospective so we could not compare the biopsy results in the same patients without the information of $^{18}$F-FDG PET/CT.

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