Percutaneous Ultrasound-Guided Biopsies in the Evaluation of Thoracic Tumours after PET-CT: A Prospective Diagnostic Study

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Key Words

Computed tomography • Positron-emission tomography • Thoracic malignancies • Ultrasound-guided biopsy

Abstract

Background: Lesions detected by positron emission tomography-computed tomography (PET-CT) during the analysis of thoracic tumours are often impalpable at physical examination, and subsequent ultrasound (US) may aid in finding these lesions for pathologic evaluation. **Objectives:** The success rate of percutaneous US-guided biopsies of palpable and non-palpable lesions and the impact on tumour stage were studied prospectively. **Methods:** Lesions, significant for diagnosis and disease stage, with metabolic activity on PET-CT and presumed appropriate for percutaneous approach under US guidance were selected for cytologic aspiration or tissue core biopsies. **Results:** In 127 patients, 134 lesions (subdivided into 24 local thoracic, 74 supraclavicular and 36 distant metastatic lesions) were biopsied percutaneously under US guidance. Malignancy, benign disease and inadequate biopsies were found in 80% (106/134), 14% (19/134) and 7% (9/134), respectively. In 55% (56/102) of patients, biopsies confirmed the disease stage. Fifty-one percent (18/35) of distant lesions and 54% (43/68) of supraclavicular lesions were impalpable on physical examination.

Conclusions: US-guided biopsies in patients with suspected thoracic malignancy on PET-CT provide an excellent tool for obtaining a pathological diagnosis, leading to a definitive disease stage in over half of the patients.

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Introduction

2-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) integrated with computed tomography (CT) provides both anatomic and metabolic information, making it an extremely important tool in characterizing both local thoracic as well as metastatic disease. It has been demonstrated to have a higher diagnostic accuracy than PET or CT alone [1–4]. Therefore, it can be considered the most important imaging tool in the analysis of thoracic tumours. Nevertheless, due to the low specificity of PET, pathological confirmation is necessary to establish a definitive diagnosis and/or to provide a tumour stage [5].

While a careful physical examination is considered standard of care, metastatic lesions are often missed and discovered only on PET. The visualization of both palpable and non-palpable lesions by ultrasound (US) allows for real-time biopsy. This technique enables safe patho-

logic sampling with fine needle aspiration (FNA) or tissue core biopsies (TCB) of thoracic tumours in contact with the thoracic cage but also supraclavicular metastatic disease and various sites of distant metastatic disease.

Pulmonologists in Europe have become increasingly familiar with US imaging as endoscopic and endobronchial US are nowadays established procedures in the diagnosis and staging of lung cancer. Although US-guided percutaneous biopsy and aspiration in the diagnosis of pleural disease are broadly practised by pulmonologists, the technique is seldom applied to other thoracic indications. A recent guideline of the American College of Chest Physicians recommends confirmation of a suspected lung cancer by obtaining tumour cells or tissue with FNA or biopsy if feasible [6]. If pulmonologists become proficient in US-guided biopsy they can expand their role in lung cancer diagnosis and staging.

This study is a prospective analysis of the value of percutaneous US-guided FNA and TCB in patients with PET-CT-suspected thoracic neoplasms as performed by pulmonologists. The evaluating and procedural pulmonologist determined the lesions to be sampled based on their accessibility and visibility by US-guided biopsy and their importance in diagnosis and/or staging. It was hypothesized that US-accessible lesions (no matter if palpable or not) detected on PET-CT will provide a definitive pathological diagnosis and pathological proof of disease stage.

Patients and Methods

Study Population

Patients that were selected for US-guided sampling had all undergone PET-CT scans for suspected thoracic tumours. The selection was discussed in meetings of the nuclear physician and pulmonologist and was based on PET-CT results.

The lesions observed on PET-CT that were approached for pathologic US-guided sampling had to fulfill three criteria.

First, they were judged by a pulmonologist to be accessible by US-guided FNA or biopsies (for instance adjacent to the thoracic wall or located in the supraclavicular or axillary region). Second, only lesions with increased FDG uptake were selected. Third, the lesions had to be significant for tumour staging. Preferably, the obtained material delivered a pathological diagnosis and stage verification at once.

If PET-CT showed obvious and extensive metastatic disease, there were occasional deviations from this principle. In these cases, the easiest accessible lesions were approached (for example, some widespread metastasized stage IV tumours were diagnosed according to this strategy with supraclavicular aspirations).

The diagnostic strategy was based on recommendations in the guidelines on the initial diagnosis of lung cancer of the American College of Chest Physicians.

According to legal criteria for medical research, our institutional review board stated that approval was not necessary for this study.

Methods

PET-CT scans were performed on an integrated PET-CT scanner (GE Discovery ST PET-CT scanner, General Electric, Milwaukee, Wisc., USA).

Percutaneous US-guided FNA was performed by a pulmonologist with a Hitachi probe (EUP-C532) with a EZU-PA532 Hitachi Biopsy attachment and a Hitachi EUB-5500 processor. TCB and FNA were obtained under direct vision.

Needles used were Spinocan 0.9 × 88 mm/20 gauge × 8 cm for cytology. For histologic biopsies, Bard core tissue biopsy needles 14 gauge × 13 cm were used with a Bard magnum biopsy instrument (fig. 1).

A local physical examination was performed, before the application of US, to determine if lesions were palpable or not.

All biopsies and aspirations were performed under local anaesthesia of the skin with lidocaine 2%. For local thoracic tumours, specimens were preferentially obtained with core tissue biopsy needles for histologic analysis. Two or 3 TCB were taken as a rule for histologic sampling. Supraclavicular and distant metastatic lesions were usually approached with FNA. Specimens obtained with FNA were smeared on slides for morphologic analysis and deposited in a fixative for immunohistochemical staining in cases where subtyping was necessary. Two to 4 needle passes into each lesion were taken. There was no on-site evaluation of the samples by a pathologist.

The numbers of adequate (enough tissue or material to make a diagnosis as assessed by a pathologist after microscopy) and inadequate biopsies (not enough tissue or material or no accessible tumour or lymph node by US) were counted. In the case of inadequate aspirates or biopsies, CT-guided biopsies, endoscopic biopsies or surgical procedures were performed. When these additional investigations had to be performed, this was considered as a failure of the US procedure. In case such an approach was not feasible, clinical follow-up data were available to substantiate the diagnosis.

Stage categories as defined by the American Joint Committee on Cancer Staging [7] and the sixth edition of the Union Internationale Contre le Cancer [8] were applied.

Results

Between March 2006 and May 2009, a total number of 127 patients out of 1,056 patients (12%) in whom PET-CT was performed to image suspected thoracic malignancies were considered suitable for US-guided biopsies.

In these patients, a total number of 134 lesions were approached for US-guided biopsies (FNA, $n = 107$; TCB, $n = 22$; not detectable with US, $n = 5$). In 5 patients, US-guided biopsies were performed on more than one lesion (1 patient had 3 biopsies on different lesions and 4 patients had 2 biopsies on different lesions). Table 1 shows the distribution of FNA and TCB in the subcategories lo-

Fig. 1. Devices used for US-guided aspirations and core tissue biopsies. **a** Biopsy attachment with a 20-gauge needle mounted on US probe. **b** Biopsy attachment with core tissue biopsy needle.

Table 1. US-guided aspirations and biopsies from PET-CT-observed lesions

Location	n	US-observed lesions	Lesions not detectable with US	FNA	TCB	Palpation performed	Palpation negative
Local thoracic lesions	24	22 (92)	2 (8)	4	18	NA	NA
Supraclavicular nodes	74	71 (96)	3 (4)	71	0	68 (92)	37 (54)
Distant lesions	36	36 (100)	0	32	4	35 (97)	18 (51)
Total	134	129 (96)	5 (4)	107	22		

Figures in parentheses are percentages. NA = Not applicable.

Table 2. Pathologic results of US-guided aspirations and biopsies from PET-CT-observed lesions

Location	n	Inadequate biopsies ¹	Benign diagnosis	Malignant diagnosis	Stage-defining lesions ²
Local thoracic lesions	24	5 (21)	2 (8)	17 (71)	9 (53)
Supraclavicular nodes	74	3 (4)	7 (9)	64 (86)	32 (50)
Distant lesions	36	1 (3)	10 (28)	25 (69)	20 (80)
Total	134	9 (7)	19 (14)	106 (80) ³	61 (58)

Figures in parentheses are percentages.

¹ Inadequate biopsies are failures to find PET-CT-observed lesions by US and biopsies without adequate material as assessed by the pathologist. ² Percentage of malignant lesions that determine the tumour stage. ³ 106 lesions containing malignant tissue were biopsied in 102 patients. In 4 patients, 2 malignant lesions were biopsied.

Table 3. US-guided aspirations and biopsies from 106 PET-CT-observed lesions in 102 patients that lead to pathologically confirmed malignant diagnoses

	Local thoracic lesions	Supraclavicular nodes	Distant lesions
NSCLC	7	45	16
SCLC	0	13	2
LCNEC	1	2	1
Sarcoma	1	2	0
Mesothelioma	5	0	1
Non-pulmonary metastasis	1	1	0
Malignant lymphoma	0	1	5
Thymoma	2	0	0
Total	17	64	25

SCLC = Small cell lung cancer; LCNEC = large cell neuroendocrine cancer.

Table 4. Subtyping results of NSCLC in FNA and TCB based on morphologic and immunohistochemical analysis

Subtypes	FNA	TCB
Local thoracic lesions		
Adenocarcinoma	2	0
Squamous cell carcinoma	2	1
Not differentiated	1	1
Subtotal	5	2
Supraclavicular lesions		
Adenocarcinoma	30	0
Squamous cell carcinoma	11	0
Large cell carcinoma	1	0
Not differentiated	1	0
Not applicable ¹	2	0
Subtotal	45	0
Distant lesions		
Adenocarcinoma	10	2
Squamous cell carcinoma	3	0
Not differentiated	1	0
Subtotal	14	2
Total	64	4

¹ One patient was known with a pulmonary adenocarcinoma 2 years before, and in 1 patient, bronchial biopsies already showed a primary adenocarcinoma.

cal thoracic, supraclavicular and distant lesions (distant lesions are metastatic lesions other than mediastinal or supraclavicular lesions).

Successful US-guided biopsies were performed in 93% (125/134) of lesions.

Seven percent (9/134) of US-guided biopsies were considered inadequate either because PET-CT-observed lesions could not be detected by US (n = 5) or because biopsies contained inadequate material (n = 4) (table 2).

Palpation

At physical examination (performed after PET-CT), palpation of lesions was recorded in 92% (68/74) of patients with supraclavicular lesions and in 94% (34/36) of patients with distant lesions. Table 1 shows that 54% of examined supraclavicular and 51% of examined distant lesions were not palpable (as expected, local thoracic disease was not palpable in any of the patients).

Malignancy by US-Guided Biopsies

Overall, malignancy was confirmed in 80% (106/134) of US-guided biopsies in PET-CT-positive lesions with a predominant representation of non-small cell lung cancer (NSCLC; 51%, 68/134) as shown in table 3. Subtypes of NSCLC in FNA and TCB are shown in table 4. In 3 FNA and 1 TCB, subtyping was not possible, and in 2 FNA, subtyping was not carried out because a histological diagnosis was already available. Local thoracic US-guided biopsies were positive for malignancy in 71% (17/24) of lesions, supraclavicular US-guided biopsies in 86% (64/74) of lesions and distant US-guided biopsies in 69% (25/36) of lesions (table 2). Positive predictive values to find malignancy by US-guided punctures in thoracic, supraclavicular and distant lesions observed with PET-CT were 77, 90 and 69%, respectively.

Benign Disease

Benign diagnoses were obtained in 14% (19/134) of PET-CT-positive lesions. In 8% (2/24) of local thoracic lesions, a benign diagnosis was derived. Supraclavicular US-guided biopsies showed benign disease in 10% (7/74) of biopsied lesions, and distant US-guided biopsies showed benign disease in 28% (10/36) of lesions. Benign diagnoses are listed in table 5.

Inadequate Biopsies

The overall rate of inadequate US-guided biopsies was 7% (9/134), as demonstrated in table 2. Inadequate US-guided biopsies were performed in 21% (5/24) of local lesions. One patient had a clinical follow-up of local pleural

Table 5. US-guided aspirations and biopsies from PET-CT-observed lesions that lead to pathologically confirmed benign diagnoses

	Local thoracic lesions	Supraclavicular nodes	Distant lesions
Non-specific reactive lymph nodes	0	6	7
Organizing pneumonia	2	0	2
Whartin's tumour	0	0	3
Sarcoidosis	0	1	0
Total	2	7	10

broadening after pneumonectomy during 18 months without any sign of progression. Two lesions were biopsied subsequently by surgery (1 mesothelioma and 1 malignant lymphoma), and 1 lesion was biopsied under CT guidance (bronchoalveolar carcinoma). In 1 patient, a thoracic tumour could not be detected with percutaneous US, but a diagnosis was obtained by a US-guided biopsy of the left adrenal gland (NSCLC).

Inadequate US-guided biopsies were performed in supraclavicular regions in 4% (3/74) of lesions and in 3% (1/36) of distant lesions. During a median clinical follow-up of 1 year (range 7–41 months) of the 3 supraclavicular non-successfully biopsied lesions, no tumour appeared. The distant non-successfully biopsied lesion was lost to follow-up.

Staging of Disease

In 58% (61/106) of lesions with a malignant diagnosis, this result confirmed the tumour stage. For local thoracic malignant lesions, supraclavicular malignant lesions and distant malignant lesions, these rates were 53% (9/17), 50% (32/64) and 80% (20/25), respectively (table 2).

A total number of 106 lesions with malignancy was found in 102 patients (2 different malignant lesions were biopsied in 4 patients). A pathological confirmation of tumour stage was achieved in 55% (56/102) of patients with malignancy. In 45% (46/102) of patients, the biopsy provided a diagnosis, but the lesions were not confirmative for disease stage. Ten percent (10/102) of patients with malignancy needed additional invasive investigations to confirm disease stage or subtyping of the tumour. The procedures were lymph node excisions and thoracoscopy by surgery ($n = 4$) and endoscopic US with histologic biopsies for immunohistochemical subtyping of malignant lymphomas ($n = 1$), endobronchial US for mediastinal

node metastasis ($n = 1$) and 4 FNAs (in the left adrenal gland, in a coeliac and axillar lymph node, and a cutaneous metastasis, respectively).

For the other 36 patients, additional biopsies were not required. In 26 patients (25%), PET-CT showed obvious extensive metastatic disease, where confirmation of malignancy seemed not appropriate, 5 patients had mesothelioma, 4 patients had brain metastases, and for 1 patient, the biopsy was obtained to differentiate between progression of 2 different recurrent malignant diseases.

Complications

There were 2 (1.5%) complications registered. Both occurred after TCB of a local thoracic lesion. One of the histologic biopsies was complicated by a severe haemoptysis leading to intubation. One of the TCB also contained spleen tissue on pathologic examination without adverse events after the biopsy. No other significant adverse events were noticed.

Discussion

This study shows that percutaneous US-guided biopsies in the diagnosis and staging of thoracic tumours have a high diagnostic success rate after localization with PET-CT. The quality and quantity of cytologic specimen allowed pathologists to specify subtypes of NSCLC in almost all patients.

The high resolution of US for lesions within about 5–10 cm distance from the skin brings many lesions within the scope of US-guided biopsies. For intrapulmonary lesions, this may not be the case due to positional alterations by gravity when CT images in the prone position are used to select lesions for the US-guided approach in the supine position (fig. 2). Other failures of US-guided punctures were due to inaccurate interpretations of PET-CT like brown fatty tissue located at supraclavicular locations and inaccurate pathologic sampling.

Thoracic Lesions

Although US is a relatively underused diagnostic modality, it provides an accurate localization of chest abnormalities if not surrounded by aerated lung [9]. In this study, the most prominent reason for test failure in local thoracic disease was indeed the inability to image lesions through aerated lung by US. Former studies already demonstrated the benefit of US-guided biopsies after CT imaging. Percutaneous biopsies of pulmonary, pleural or mediastinal lesions in contact with the chest wall under

Fig. 2. Effect of body position on US visibility of an intrathoracic lesion. Example of problems encountered with the use of US. **a** Patient in prone position. Lesion in the dorsal left lung adjacent to the thoracic wall. **b** Same patient lying in supine position for biopsy. The lesion is no longer adjacent to the thoracic wall and becomes invisible for US.

US guidance yielded a diagnosis in 90% of patients with a malignancy and in 67% of patients with benign lesions in a study of 124 patients [10]. A high efficacy of US-guided biopsies was reported in 31 out of 34 lesions in the analysis of thoracic tumours [11]. Recently, a diagnostic yield of >93% was reported in a single-session sequential approach of mediastinal masses with US-assisted trans-thoracic FNA (with rapid on-site evaluation) eventually followed by TCB [12].

Even centrally located tumours with post-obstructive collapse or pneumonitis can be safely biopsied with deep passes and an acceptable diagnostic yield of 74% [13].

Evaluation of local thoracic disease with PET scans has the important advantage to discriminate between active metabolic diseases (inflammatory and malignant) and diseases without increased metabolic activity such as atelectasis, loculated fluid or scar tissue. Lesions without FDG uptake are probably benign and justify a wait and see attitude. Lung cancer is generally characterized by high FDG uptake, but for assessment of the T stage, PET scans have limited value [14]. The variety of possible alternative diagnoses of PET-CT-positive solitary thoracic tumours accounts for the need for tissue. This is demonstrated by the high number of benign and non-primarily pulmonary malignancies found in this study (11 out of 19 diagnoses).

Supraclavicular Lymph Nodes

Supraclavicular nodes are frequently involved in lung cancer and define stage IIIB disease. In this study, we focused on PET-CT-positive supraclavicular findings and demonstrated malignancy in the majority of patients suspected to have a thoracic neoplasm, especially NSCLC.

PET-CT has a diagnostic accuracy of 71% in detecting non-palpable supraclavicular lymph node metastasis as was demonstrated in a group of 32 patients with NSCLC [15]. In our study, accuracy was 85%. The sensitivity of palpation of supraclavicular node metastasis in lung cancer is significantly lower than with US or CT. This was illustrated by a study that demonstrated malignancy with US-guided FNA in 8% of patients with suspected and potentially operable lung cancer without palpable lymph nodes [16]. A study of 117 patients analysed for lung cancer confirmed this low sensitivity of palpation compared to US or CT and demonstrated that only markedly enlarged metastases were palpable [17].

In patients with proven N2 or N3 disease, enlarged but non-palpable supraclavicular lymph nodes (on CT) contained metastatic disease in even 45.5% of patients [18]. This study confirms the added value of US in detecting enlarged but non-palpable supraclavicular lymph nodes.

Distant Metastatic Disease

An important feature of FDG-PET is the ability to detect distant metastatic disease.

In about 8–10% of resectable patients with NSCLC and in 18 and 24% of stage II and III patients who were staged conventionally (with CT scan, bone scans and ultrasonography), PET scan detected distant metastatic disease [19–21].

With US, many metastatic sites can be reached percutaneously if lesions are not surrounded by air or covered by bony structures. The ability to visualize lesions is furthermore dependent on the size of lesions, tissue characteristics and interfaces, distance to transducer and sensitivity of equipment.

In this study, US-guided biopsies were performed in axillary, retromandibular, retroauricular, intercostal, soft tissue, skin and osseous lesions. Half the patients (51%) had non-palpable lesions. The value of US guidance to obtain material for pathologic verification of PET-CT-positive lesions is emphasized in this study.

Staging with US-Guided Biopsies

For more than half of the patients with malignancy in this study, the minimally invasive approach with an US approach confirmed diagnosis and disease stage at one time. Endoscopic investigations, often performed as a routine practice in the analysis of thoracic tumours, are generally considered unpleasant and can be omitted if percutaneous US-guided biopsies confirm malignancy.

Diagnostic tests to obtain pathologic specimen should be chosen with a minimal burden to the patient but with maintenance of high-quality diagnostic characteristics [5]. US-guided biopsies match these qualities, as demonstrated in this study.

Palpation of Lesions

A careful physical examination is one of the first parts of the diagnostic workup of patients with a suspected thoracic malignancy. In this study, more than half the lesions were not palpable, although the physician was aware of the results of the PET-CT. With the use of US guidance, the lesions could be detected and biopsied very effectively. On the contrary, when lesions are palpable, the use of US guidance diminishes the chance of inadequate biopsies in thyroid nodules when compared with palpation-guided biopsies [22]. Therefore, the use of US is recommended in both situations.

Limitations

Although the study is a prospective analysis of US-guided biopsy results, there was no well-defined selection of patients according to protocol criteria. Patients were selected on clinical criteria that work sufficiently in daily practice but influence the outcome of results unequivocally. At the start of a new technique, there is a tendency to select lesions with high pretest probability for successful biopsies. When experience increases, biopsies of more difficult lesions will be attempted but will also lead to increasing failure rates.

A criterion to select lesions for percutaneous US-guided biopsies was the uptake of FDG. Small lesions, which do not have enough tracer to be seen on PET-CT were not selected for US-guided biopsies and could therefore be missed for staging.

In conclusion, this study demonstrates that US-guided percutaneous biopsies increase the pathological outcome in the workup of thoracic tumours after PET-CT. PET-CT in combination with subsequent US-guided biopsy provides a definitive diagnosis and tumour stage in the majority of patients and can be performed safely.

Percutaneous US-guided biopsies expand the diagnostic capability of pulmonologists in diagnosing and staging thoracic tumours.

Financial Disclosure and Conflicts of Interest

The authors declare no conflict of interest.

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