EUS-FNA and FDG-PET are complementary procedures in the diagnosis of enlarged mediastinal lymph nodes

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Abstract

Background and Study aims : **Transoesophageal endosonography with fine needle aspiration (EUS-FNA) and 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (FDG-PET) are now standard diagnostic procedures of the mediastinum. Our aim was to compare their value in the assessment of enlarged mediastinal lymph nodes detected by computed tomography.**

Patients and methods : **Forty consecutive patients with a suspicion of cancer or a history of pulmonary, digestive, urogenital or mammary neoplasia and presenting with supracentimetric lymph nodes on computed tomography underwent whole body FDG-PET and EUS-FNA. Final diagnosis of malignancy was obtained by cytology, surgery or long-term follow-up.**

Results : **EUS-FNA showed a sensitivity, specificity and accuracy for detection of malignancy of 79.3, 100 and 85%, respectively. The biopsy material was adequate for cytological examination in 37 patients. Sensitivity, specificity and accuracy of PET were 100, 54.5 and 87.5%, respectively. FDG-PET correctly diagnosed the primary site in 27 patients, and showed additional unknown extrathoracic metastatic sites in 15 patients. The five false positive results observed with FDG-PET consisted in a final diagnosis of sarcoidosis, tuberculosis, anthracosilicosis and reactive lymph nodes, respectively. The association of FDG-PET and EUS-FNA avoided more invasive procedures (mediastinoscopies or staging surgery) in 34 patients.**

Conclusions : **EUS-FNA and FDG-PET are complementary diagnostic procedures combining the high sensitivity of FDG-PET and the high specificity of EUS-FNA to accurately diagnose malignancy in enlarged mediastinal lymph nodes identified by CTscan. The combination of the two procedures in selected cases with pulmonary cancer or extra-thoracic tumours avoided more invasive diagnostic and surgical procedures.** (Acta gastroenterol. belg., **2008**, 71, **219-229**).

Introduction

Mediastinal lymphadenopathy is a frequent observation in patients with benign and malignant conditions (1-2). The advent of diagnostic tools such as endoscopic ultrasonography (EUS) and 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (FDG-PET) has increased the detection rate of mediastinal lymph nodes even in healthy control volunteers, where EUS was able to detect enlarged lymph nodes in 86% of cases (3-4). The differential diagnosis includes a wide variety of benign and malignant lesions. Benign lymph nodes are usually reactive to infectious broncho-pulmonary disease, but can be related to anthracosis, silicosis, tuberculosis, histoplasmosis, and sarcoidosis. The common primary sites of malignancy associated with mediastinal lymph nodes are the lung and the oesophagus, as well as extrathoracic tumours sites (5-7). In patients without a known cancer history, malignant lymph nodes originate from the lung in more than 80% of cases whereas in those with previous malignancy, metastases of extra-thoracic tumours in the mediastinum are often observed, especially in patients with head and neck, breast, proximal stomach, colon, renal or prostate cancer (2,8-12).

The value of computed tomography (CT) and magnetic resonance imaging (MRI) for imaging the mediastinum has been evaluated extensively. Although mediastinal lesions can be visualized with CT and MRI, a definite diagnosis is generally not obtained solely on the basis of morphological characteristics. Enlargement of lymph nodes may be hyperplastic, whereas normal-sized lymph nodes may be malignant. Tissue confirmation is therefore recommended either by transbronchial fine needle aspiration (TBNA), or EUS-FNA, or more recently by EBUS-TBNA (endobronchial ultrasound guided transbronchial needle aspiration) (13-15), or even transthoracic FNA, mediastinoscopy or thoracoscopy with varying diagnostic yields and complication rates (16). None of these modalities can reliably evaluate the inferior and posterior mediastinum. Transoesophageal EUS-guided fine needle aspiration (EUS-FNA) has been compared with these techniques. It has been shown to be a safe (< 1% complication rate), sensitive (> 80% in experienced hands) and cost-effective procedure in the diagnosis of malignant mediastinal tumours or lymph nodes (17-19).

The need for tissue diagnosis has however been questioned by provocative data in lung cancer staging suggesting that the prognostic information obtained with metabolic imaging modalities such as FDG-PET could be sufficient to diagnose malignancy and reduce the need

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for invasive diagnostic procedures including cytology and histologic sampling (3). The FDG-PET is now used in many oncological centres to stage malignant diseases (20). The FDG-PET exploits increased glucose metabolism by malignant tumours but increased glucose uptake has also been demonstrated in benign inflammatory and infectious diseases (21-22). In the assessment of mediastinal lymph nodes, positron emission tomography with F18-fluorodeoxyglucose (FDG-PET) is more accurate than CT scan (22). A recent consensus recommends that, in patients who are potential candidates for surgery, a whole-body FDG-PET scan should be performed to evaluate the mediastinum (23). PET scan also provides significant additional information in the search for distant metastasis of lung cancer and is cost-effective (24). Positive PET mediastinal lymph nodes nevertheless require histological confirmation because of possible increased FDG uptake related to non-neoplastic (mainly inflammatory) processes.

The aim of our study was to evaluate the respective diagnostic accuracy of EUS, EUS-FNA and FDG-PET for the diagnosis of malignancy in patients with enlarged mediastinal lymph nodes detected by spiral CT.

Methods

Study design

Forty consecutive patients (32 men and 8 women) were prospectively enrolled in FDG-PET evaluation and mediastinal EUS-FNA in the work-up of enlarged mediastinal lymph nodes detected by spiral CT in the setting of current or previous neoplasia. Spiral CT evaluation (MX 8000, Philips Medical Systems, The Netherlands) was performed from the adrenal glands to the supraclavicular region with a slice thickness of 5 mm. All diagnostic procedures (CT, FDG-PET, EUS-FNA) were performed within a 4 weeks interval. The study was approved by the local Ethical Committee.

EUS and EUS-FNA

EUS was performed by two experienced physicians (DP and SD). All examinations were done under conscious sedation using 2 to 5 mg of diazepam and 25 to 75 mg of pethidine, intravenously. The patient's clinical information, as well as CT scan results, was available to the endosonographers at the time of EUS, but they were blinded to the results of PET-FDG. The instrument used was a Pentax FGUX 36 echoendoscope (Pentax Ltd, Hamburg, Germany) equipped with a bi-focal curved linear-assay transducer (5 and 7.5 Mhz). This instrument was connected to the Hitachi EUB525 ultrasound console (Ecoscan Gmbh, Wiesbaden, Germany). Four ultrasonography features were chosen to suggest malignancy in the lymph nodes : a size greater than 1 cm, a hypoechoic pattern, well-delineated margins and a round shape. Diagnosis of malignancy can commonly be predicted with high accuracy when all four features are present, but this is rarely the case (25). Pulse-wave Doppler was used to ensure absence of major vascular structures between the oesophageal wall and the mediastinal lesions. EUS-FNA was performed using a 22 Gauge Cook needle (Wilson-Cook, Winston-Salem, NC), introduced through the echoendoscope's 2.4 mm biopsy channel. Two to five passes were done under continuous suction applied with a 20 ml syringe while the needle was advanced and withdrawn a minimum of ten times each, and stopped before the needle was withdrawn in order to prevent seeding of malignant cells along the needle tract. There were no complications and all patients were discharged one hour after the procedure, without any antibiotic prophylaxis.

Cytology

The material obtained by FNA was spread on 2 glass slides and immediately immersed in methanol. The syringe containing the rest of the material was rinsed in 50% alcohol. This material was then centrifuged and cytocentrifuged. All slides were stained with the Papanicolaou method and ancillary were used if necessary, such as immunochemistry. Presence of hormonal receptors was also evaluated in cases of breast carcinoma.

FDG-PET imaging

All FDG-PET examinations were interpreted by the same nuclear physician (ML). Patients were asked to fast for six hours prior to their arrival in the PET facility. Blood glucose was checked before examination and FDG-PET was postponed in case of hyperglycaemia. Sixty minutes after iv injection of 370 MBq (10 mCi) 2-(fluorine-18)fluoro-2-deoxy-D-glucose (FDG), patients were positioned on the PET camera (ECAT EXACT HR, CTI, Knoxville, USA) and whole body emission scan was obtained followed by a transmission scan for subsequent attenuation correction. Total scanning time was 40 min. Images were reconstructed by means of iterative processing of both emission and transmission data, following the procedure previously described (21). Images were interpreted on colour monitors with simultaneous display of non-attenuated and attenuated images in the transaxial, coronal and sagital planes. PET images were interpreted by experienced specialists in nuclear medicine and PET imaging. Results from other imaging modalities were not available at the time of image interpretation. A hot spot was considered as positive for cancer if the intensity of uptake was above that of the mediastinal blood pool. No uptake quantification was performed, i.e. no SUV values were calculated.

Data analysis

The sensitivity, specificity, accuracy and predictive values were calculated using the standard definition for both methods in detecting neoplastic tissue. A

cytological diagnosis of malignancy was accepted as sufficient evidence of true positive, as false-positive results on cytology are extremely rare and regarded as equivalent to those in pathology (8). Diagnosis of true-negative, false-negative and false-positive patients for both methods was established according to comparison with additional diagnostic procedures (mediastinoscopy, surgery or autopsy) or long-term follow-up (> 12 months). The sensitivity of each technique for the diagnosis of malignant lymph nodes was compared by Student t test. Significance was defined as $p < 0.05$.

The impact of EUS-FNA and PET results on clinical management was evaluated by comparing theoretical vs. actual planning of investigation and treatment. A change in management was defined as the difference between the "theoretical" planning (based on CTscan and mediastinoscopy when indicated) and the "actual" plan (after EUS and FDG-PET). By definition, if these differed, the management was considered to have been altered by the EUS-FNA and PET results.

Results

Mean age of patients was 60 years with a range from 38 to 79 years. Three groups of patients were studied. Seven patients had a history of previous cancer (cervix squamous carcinoma, n = 1 ; breast carcinoma n = 1 ; head and neck carcinoma, n = 2 ; prostatic carcinoma, n = 2 and B cell lymphoma, n = 1) with a time interval from the previous malignancy ranging from 6 months to 6 years (group 1). Fourteen patients had a cytological or histological proven neoplasm with a suspicion of mediastinal metastasis (2 pancreatic adenocarcinomas, 1 breast, 1 gastric, 8 lung carcinomas and 2 oesophageal carcinomas) (group 2). Nineteen patients had a suspicion of malignancy without any cytological or histological confirmation, including 3 patients with a suspicion of lymphoma (group 3).

Individual patient data, PET and EUS results are shown in Table 1. Final diagnosis of a mediastinal malignant lesion (n = 29) was established for all patients by EUS-FNA in 23 patients, surgery in 5 patients (2 lung resections, 1 head and neck surgery, 1 mediastinoscopy and 1 surgical biopsy of an inguinal lymphadenopathy), and transbronchial biopsy in 1 patient. Final diagnosis of a benign mediastinal lesion (n = 11) was obtained by EUS-FNA in 2 cases (anthracosilicosis, sarcoidosis), mediastinoscopy in 1 patient (tuberculosis), pulmonary lobectomy in 3 cases and follow-up in 5 cases. These results are summarized in Table 2.

In group 1 (history of previous cancer), 6/7 patients had tumoral conditions, corresponding to a relapse of the previous neoplasm in 5 of them (head and neck carcinoma in 2 patients and cervix squamous carcinoma, B-cell non Hodgkin lymphoma (B-cell NHL), breast carcinoma in 1 patient) and to a second cancer unrelated to the previous one in the last patient.

In group 2 (staging of proven neoplasm), 10/14 patients were affected with a malignant mediastinal extension, corresponding to the histologically proven neoplasm in all 10 patients.

In group 3 (suspicion of malignancy), 13 neoplastic malignant spreading were detected, corresponding to 10 bronchogenic malignancies and 3 extrathoracic malignancies (B-cell lymphoma, breast carcinoma and neurofibrosarcoma).

EUS

Assessment of malignancy in mediastinal lymph nodes was based on the classical four EUS criteria of malignancy (Table 3). Sensitivity, specificity and accuracy were calculated with a cut-off level of 4 criteria vs. less than 4 criteria. The 4 criteria were found in 4/40 patients (10%), corresponding to true positive (TP) patients. Three criteria were found in 6/40 patients (15%), two criteria were found in 14/40 patients (35%) and 12/40 patients (30%) had only one criteria of malignancy, corresponding to 25 false negative (FN) patients and 7 true negative (TN) patients. No criteria were found in the remaining four patients (10%), corresponding to TN patients. The mean number of malignancy features for malignant lymph node was 2.1 ± 0.5 compared to 1.4 ± 0.3 for benign lymph nodes (difference not statistically significant, $p = 0.1$). The lymph node size varied from 7.8 to 80 mm (Table 4). Size on its own was not discriminant since size of benign lymph nodes was 24.8 ± 5.7 mm (median and SD) in comparison with 32.7 ± 14.1 mm for malignant lymph nodes ($p = 0.2$).

EUS-FNA

Overall sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of EUS-FNA for diagnosing malignancy in mediastinal lesions are shown in Table 3. Sensitivity of EUS-FNA (79.3%) was statistically significant ($p < 0.001$) in comparison with EUS based on the 4 morphological criteria (13.8%). EUS-FNA allowed a primary cytological diagnosis of malignancy in 23 patients (13 thoracic and 10 extrathoracic origins). Eleven true negative patients were identified, consisting in 7 benign conditions, 3 lung neoplasms without mediastinal spread proven by the histological analysis of surgical specimens and 1 pancreatic neoplasm without mediastinal metastases.

In the 6 false-negative EUS-FNA cases, including 3 patients with inadequate specimens (subcarinal area), final diagnosis of malignancy was obtained by surgery in 5 patients and mediastinoscopy in 1 patient. The lymph node size varied in these patients from 6 to 35 mm and they were punctured with a 22 G Cook fine needle without any technical difficulty (2 to 5 needle passes).

Immunohistochemistry was performed on 9 selected cases when the results of routine staining were inconclusive, allowing a diagnosis of mixed squamous/adenocarcinoma lung (n = 2), breast (n = 2), bronchial (n = 2)

Table 1. — **Clinical data, FDG-PET, EUS-FNA results and final diagnosis in all 40 patients**

Cases	Age/sex	Primary neoplasm	LN location	PET	EUS-FNA	Final diagnosis	Method of diagnosis
MALIGNANCIES							
1.	45/F	Cervix squamous	Subcarinal	+	+	Cervix squamous carcinoma	EUS-FNA
2.	61/M	Neck carcinoma	Aortopulmonary	+	-	Neck carcinoma	Surgery
3.	76/F	Breast carcinoma	Subcarinal	+	+	Breast carcinoma	EUS-FNA
4.	70/M	Neck squam carcin	Paratracheal	+	+	Neck carcinoma	EUS-FNA
5.	68/M	SCLC	Subcarinal	+	+	SCLC	EUS-FNA
6.	75/M	B-cell lymphoma	Subcarinal	+	Acellular	B-cell NHL, large cell	Surgery
7.	72/M	MCLC	Posterior med.	+	+	MCLC	EUS-FNA
8.	61/M	Br adenocarcinoma	Aortopulmonary	+	+	Br adenocarcinoma	EUS-FNA
9.	79/M	Br squamous carc	Paraaortic	+	+	Br squamous cell carcinoma	EUS-FNA
10.	57/M	Br squamous carc	Subcarinal	+	+	Br squamous cell carcinoma	EUS-FNA
11.	74/F	Br squamous carc	Subcarinal	+	-	Br squamous cell carcinoma	Surgery
12.	51/M	Metastat adenocarc	Paraesophageal	+	+	Adenocarcinoma	EUS-FNA
13.	78/F	Pancreatic adenoc	Superior med.	+	+	Pancreatic carcinoma	EUS-FNA
14.	44/M	Oesophagus carc	Paraoesophageal	+	+	Oesophageal carcinoma	EUS-FNA
15.	76/M	Br squamous carc	Subcarinal	+	Acellular	Br squamous cell carcinoma	Tr Br biopsy
16.	64/M	Oesophagus carc	Paraoesophageal	+	+	Oesophageal carcinoma	EUS-FNA
17.	58/M	Br squamous carc	Subcarinal	+	+	Br squamous cell carcinoma	EUS-FNA
18.	44/M	Br adenocarcinoma	Subcarinal	+	+	Br adenocarcinoma	EUS-FNA
19.	59/F	B-cell lymphoma	Paraoesophageal	+	+	B-cell NHL, large cell	EUS-FNA
20.	52/M	Br adenocarcinoma	Subcarinal	+	+	Br adenocarcinoma	EUS-FNA
21.	67/M	Br squamous carc	Paraaortic	+	-	Br squamous cell carcinoma	Mediastinoscopy
22.	50/F	Br adenocarcinoma	Subcarinal	+	+	Br adenocarcinoma	EUS-FNA
23.	52/F	Br adenocarcinoma	Aortopulmonary	+	-	Br adenocarcinoma	Surgery
24.	64/M	Br adenocarcinoma	Subcarinal	+	+	Br adenocarcinoma	EUS-FNA
25.	46/F	Breast carcinoma	Aortopulmonary	+	+	Breast carcinoma	EUS-FNA
26.	67/M	Neurofibrosarcoma	Aortopulmonary	+	+	Neurofibrosarcoma	EUS-FNA
27.	38/M	MCLC	Subcarinal	+	+	MCLC	EUS-FNA
28.	71/M	SCLC	Subcarinal	+	+	SCLC	EUS-FNA
29.	62/M	SCLC	Subcarinal	+	+	SCLC	EUS-FNA
BENIGN CONDITIONS							
1.	54/M	None	Superior mediast	+	-	Tuberculosis	Mediastinoscopy
2.	67/M	None	Subcarinal	+	-	Anthracosilicosis	EUS-FNA
3.	73/M	Pancreatic adenoc	Subcarinal	-	-	Benign lymph node	Clinical FU
4.	56/M	Br squamous carc	Subcarinal	-	-	Benign lymph node	Surgery
5.	66/M	SCLC	Subcarinal	-	-	Benign lymph node	Surgery
6.	40/M	None	Subcarinal	+	-	Sarcoidosis	EUS-FNA
7.	68/M	None	Subcarinal	-	-	Reactive lymph nodes	Clinical FU
8.	68/M	Br squamous carc	Subcarinal	-	-	Benign lymph node	Surgery
9.	41/F	None	Paraaortic	+	-	Reactive lymph nodes	Clinical FU
10.	43/M	None	Subcarinal	-	Acellular	Reactive lymph nodes	Clinical FU
11.	53/M	None	Subcarinal	+	-	Reactive lymph nodes	Clinical FU

Abbreviations : Neck squam carcin : Neck squamous carcinoma ; SCLC : small cell lung carcinoma ; B- cell NHL : B- cell non Hodgkin carcinoma ; MSCLC : Mixed cell lung carcinoma (squamous/adenocarcinoma) ; Br adenocarcinoma : Bronchial adenocarcinoma ; Br squamous carc : Bronchial squamous cell carcinoma ; Metastat adenocarc : metastatic adenocarcinoma ; Oesophagus carc : oesophagus carcinoma ; Clinical FU : Clinical Follow-Up ; Tr Br biopsy : transbronchial biopsy.
PET + : hypermetabolic mediastinal lymph nodes ; PET - : no FDG uptake in mediastinal lymph nodes.
EUS-FNA + : neoplastic tissue ; EUS-FNA - : benign tissue ; Acellular : acellular sample.

carcinomas, neurofibrosarcoma (n = 1), adenocarcinoma of unknown origin (n = 1) and small cell carcinoma (n = 1).

Cultures for mycobacterium tuberculosis were performed in 5 cases on the EUS-FNA sampling. In case of suspicion of a lymphoma, additional aspirates were placed in a cytological preservative solution for flow cytometry and immunochemistry. Additional procedures included bronchoscopic biopsy in 14 patients, transbronchial biopsy in one patient, percutaneous biopsy of a lung mass in 4 patients and both procedures in 3 patients. Correlation of EUS-guided cytology and immunocytochemistry with surgical specimen was obtained in 13 patients [mediastinoscopy (n = 4), surgical lobectomy (n = 7), oesophagectomy (n = 1), head and neck surgery (n = 1)], and with autopsy in 1 patient. Five patients with negative EUS-FNA and PET-FDG results were followed clinically and by computed tomography. No malignancy could be detected after a mean follow-up of 18 months (range : 9-30).

FDG-PET imaging

Overall sensitivity, specificity, accuracy, PPV and NPV of FDG-PET imaging are shown in Table 3. The sensitivity for detecting malignant lymph nodes reached 100%, statistically significant (p = 0.034) in comparison with EUS-FNA (79.3%). There were no false negative FDG-PET studies, i.e. no patient with a negative FDG-PET for whom other imaging modality or follow-up identified a malignant lesion in the mediastinum.

Table 2. — **Final diagnosis of malignant and benign mediastinal lymph nodes**

Malignant disease (n = 29)		
Lung (n = 17)		
	Squamous cell carcinoma	n = 6
	Adenocarcinoma	n = 6
	SCLC	n = 3
	Mixed squamous/adenocarcinoma	n = 2
Digestive tract		n = 6
Urogenital tract		n = 3
Lymphoma		n = 2
Mediastinal neurofibrosarcoma		n = 1
Benign disease (n = 11)		
	Tuberculosis	n = 1
	Sarcoidosis	n = 1
	Infectious diseases	n = 4
	Anthracosilicosis	n = 1
	Carcinomas without malignant lymph nodes	n = 4

Table 3. — **Comparative results of FDG-PET, EUS and EUS-FNA in the diagnosis of malignant mediastinal lymph nodes**

Results	**FDG-PET**	**EUS**	**EUS-FNA**
Sensitivity	100% (29/29)	13.8% (4/29)	79.3% (23/29)
Specificity	54.5 (6/11)	100% (11/11)	100% (11/11)
Diagnostic accuracy	87.5% (35/40)	37.5% (15/40)	85% (34/40)
Positive predictive value	85.2% (29/34)	100% (4/4)	100% (23/23)
Negative predictive value	100% (6/6)	30.5% (11/36)	64.7% (11/17)

Table 4. — **Size of lymph nodes punctured by EUS-FNA**

Size	**Benign lesions (n = 11)**	**Malignant lesions (n = 29)**
< 1 cm	2	1
1-2 cm	3	8
2-3 cm	2	6
> 3 cm	4	14

Table 5. — **Efficacy of FDG-PET in detecting malignant mediastinal adenopathy**

Variables	**Sensitivity**	**Specificity**	**Accuracy**
1-3 cm (n = 19)	100% (12/12)	57.1% (4/7)	84.2% (16/19)
> 3 cm (n = 21)	100% (17/17)	50% (2/4)	90.5% (19/21)

However, 5 false positive (FP) FDG-PET were observed, resulting in a 54.5% specificity : sarcoidosis (n = 1), tuberculosis (n = 1), anthracosilicosis (n = 1), infectious and reactive lymph nodes (n = 2). Analysis of results according to the size of the lymph nodes is shown in Table 5.

The primary site was FDG-PET positive in 27/29 patients and concerned 20 patients with a bronchogenic neoplasm, 2 patients with an oesophageal tumour, 2 patients with a pancreatic neoplasm and 1 patient with a gastric carcinoma, head and neck carcinoma and mediastinal sarcoma, respectively.

FDG-PET found additional unknown metastatic sites in 15 patients, mainly in bones (n = 7), the adrenal glands (n = 6) and abdominopelvic lymph nodes (n = 2). These sites were confirmed by cytology in 3 patients (peritoneal carcinomatosis, lymphomatous inguinal lymph node and bone metastases), by CT in 4 patients (abdominal lymph nodes, tumoral adrenal glands) and by conventional X-ray in 1 patient with bone metastases. A splenomegaly corresponding to a B-cell NHL was also identified.

Impact of EUS-FNA and FDG-PET on diagnosis and therapy

FDG-PET affected the diagnostic work-up and the subsequent therapeutic choice in 17 patients by correctly staging 7 patients with a bronchogenic neoplasm as TN2M1 due to distant metastases or by diagnosing a distant metastatic extension in 10 patients with a non-bronchogenic neoplasm (Table 6). FDG-PET findings in the mediastinum were confirmed by EUS-FNA in 29/40 patients. Illustrations of comparative CT, EUS and FDG-PET results are shown in Figure 1.

The association of FDG-PET and EUS-FNA altered the subsequent diagnostic evaluation by avoiding

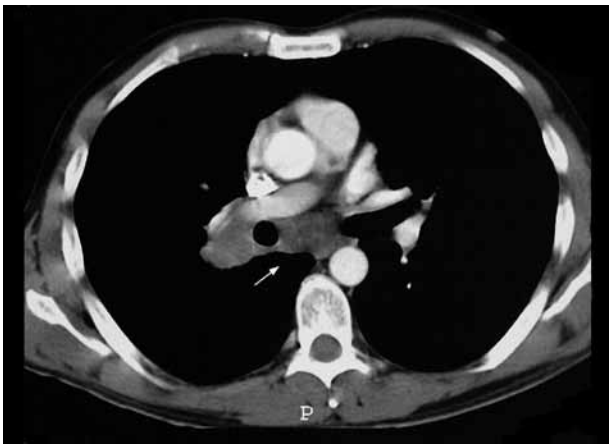

Fig. 1a. — Thoracic computed tomography with mediastinal involvement in the subcarinal area of a bronchogenic carcinoma.

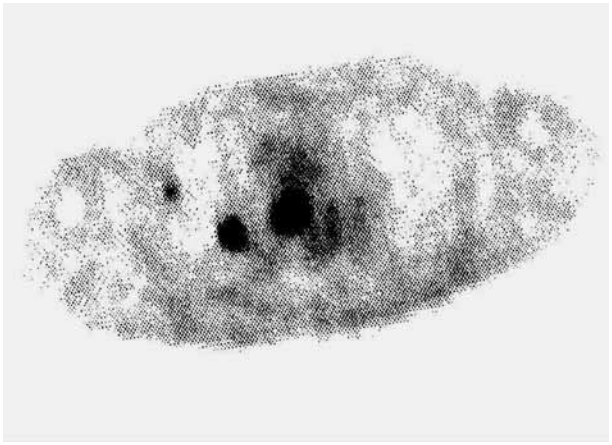

Fig. 1b. — FDG-PET examinations with a mediastinal spot consistent with a malignant mediastinal lymph node.

possibly more invasive procedures (mediastinoscopy, transbronchial biopsy, CT-guided fine needle aspiration and others) in 34/40 patients (85%) (Table 7). Six patients however underwent further invasive procedures : 1 patient with a TN2M0 bronchial squamous cell carcinoma underwent a mediastinoscopy after an induction chemotherapy to perform a pre-surgical staging ; 1 patient TN for EUS and FP for FDG-PET underwent a mediastinoscopy to achieve the diagnosis of tuberculosis ; 3 patients, respectively FN for EUS and TP for FDG-PET, underwent transbronchic biopsy and mediastinoscopy, with final diagnoses of TN2M1 bronchial carcinomas. Finally, 1 patient FN for EUS and TP for FDG-PET underwent a surgical inguinal lymph node biopsy (detected by FDG-PET) diagnostic for a B-cell lymphoma.

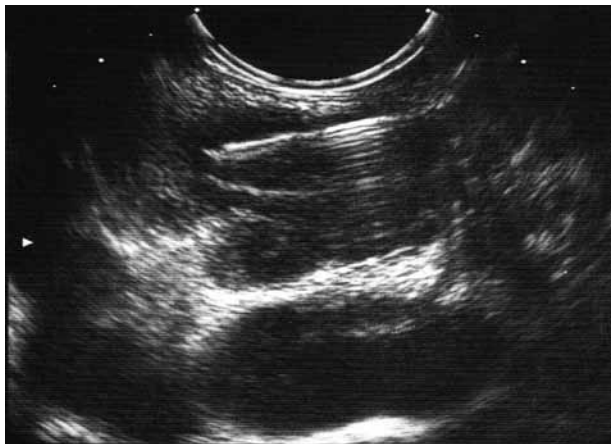

Fig. 1c. — EUS-FNA of the suspected mediastinal lymph node on basis of FDG-PET. Cytological examination revealed a squamous cell carcinoma.

Cytological diagnosis by EUS-FNA was of crucial importance in 21/23 patients (91.3%) for the choice of a complementary treatment : chemotherapy in 16 patients (12 lung carcinomas, 1 cervix squamous carcinoma, 1 metastatic adenocarcinoma, 1 B-cell NHL and 1 breast carcinoma), radiotherapy in 1 patient (1 head and neck carcinoma), combined therapy in 3 patients (2 oesophageal carcinomas and 1 SCLC) and hormonotherapy in 1 patient with metastatic breast carcinoma. The other patients (2/23) were treated palliatively.

Finally, EUS-FNA had an important role to play by rectifying the diagnosis of malignancy in 4/5 FDG-PET false positives and by providing a correct cytological diagnosis. Mediastinoscopy was however necessary in the fifth false positive FDG- PET to diagnose tuberculosis.

Table 6. — **Impact of FDG-PET on final diagnosis**

Bronchogenic neoplasms		
	Staging TN2M1 (distant metastases)	**N = 7**
Non bronchogenic neoplasms spreading in the :		**N = 10**
Mediastinum	squamous carcinoma of the cervix	n = 1
	pancreatic adenocarcinoma	n = 1
	B-cell lymphoma	n = 2
	breast carcinoma	n = 2
	neck carcinoma	n = 1
	adenocarcinoma of unknown origin	n = 1
Peritoneum	gastric neoplasm with peritoneal carcinomatosis	n = 1
Bones	mediastinal sarcoma	n = 1

Table 7. — **Impact of EUS-FNA and FDG-PET results on clinical management**

No further invasive procedures		**34/40 pts (85%)**
Invasive procedures :	**6/40 pts (15%)**	
Mediastinoscopy	TN2M0 bronchial squamous cell carcinoma	n = 1
	Tuberculosis	n = 1
	Benign lymph nodes	n = 1
	Bronchial adenocarcinoma	n = 1
Transbronchial biopsy	Bronchial squamous cell carcinoma	n = 1
Surgical LN biopsy	B-cell NHL	n = 1

Discussion

Mediastinal enlarged lymph nodes can be detected by CT in various clinical conditions including incidental findings in patients with no history of cancer, during staging of various pulmonary or extra-thoracic tumours or during follow-up surveillance of previous cancer (26-28). Our study compared the accuracy of EUS-FNA and FDG- PET in patients in whom CT detected mediastinal lymph nodes exceeding 1 cm of size. Our results showed similar accuracies between the two methods, a significantly higher sensitivity of FDG-PET and a higher specificity of EUS-FNA. From these results, both methods appear complementary in the work-up of newly detected mediastinal lymph nodes. Indeed, no single imaging method alone was fully conclusive in evaluating enlarged mediastinal lymph nodes. Similar conclusions were also recently reported in studies comparing the role of thoracic CT, FDG-PET and EUS with and without FNA for the mediastinal lymph node involvement in potentially resectable lung cancer (29). With respect to the correct prediction of mediastinal lymph node stage, the sensitivities of CT, FDG-PET and EUS were 57, 73 and 94%. Specificities were 74, 83 and 71%. Accuracies were 67, 79 and 82%, respectively (30).

Some recent studies showed that EUS had a higher sensitivity and predictive value than PET for posterior mediastinal lymph nodes (31-32).

All lymph nodes evaluated in our study were detected on CT scan primarily and had a size exceeding one centimetre. This could lead to a positive bias for PET scan and a negative on EUS as PET scan is less sensitive in nodes less than 1.5 cm and EUS is especially sensitive in nodes not detected with other techniques. EUS was indeed shown by Wallace *et al.* to be of clinical importance even when no adenopathy could be found on CT imaging (33). It avoided unnecessary surgical exploration in almost one of four patients with no evidence of mediastinal disease on CT (33).

EUS on its own should be considered of limited value (sensitivity of 13.8% and specificity of 100%) when all 4 criteria of malignancy were searched for. Lymph node size could not discriminate benign from malignant nodes. No statistically significant difference could be shown between the numbers of criteria in benign vs. malignant nodes. These results can be explained by the rather subjective evaluation of these features (echogenicity and distinction through sharp and indistinct margins) and the variation between observers (34,35). These shortcomings can be obviated by the use of FNA, improving the clinical workup by providing a tissue diagnosis including tumour type, as previously described (30,36-37).

Sensitivity of EUS-FNA in our series was similar to the results shown in the literature (sensitivity 82-96%) (8,38-39). Although more than 200 transoesophageal EUS-guided FNA are performed by two experienced endosonographers each year in our institution, we were unable to reach a 96% sensitivity. These results could be explained to the variety of pathologies encountered in our series, the limited number of passes performed (mean 2.6 ± 0.2) and the absence of an attendant pathologist in the examination room shown to improve the results (40). Our EUS-FNA procedure allows our patients to leave the endoscopy unit within one hour after the investigation, without antibiotics and without any complications in this series. Very low complications rates of EUS-FNA have indeed been reported in the literature (41,42).

Alternative methods to EUS-FNA for cytological diagnosis are CT-guided transthoracic fine-needle aspiration, mediastinoscopy and thoracoscopy, and more recently transbronchial EBUS-TBNA (13-15). Particularly, CT-guided transthoracic fine-needle aspiration was established as an accurate diagnostic method with a sensitivity of 87-98% and an accuracy of 78-89% for mediastinal lesions (43-46). However, these are more invasive procedures with minor complication rates up to 10% and major complication rates of 1.4%-2.3% (46-50). In addition, mediastinoscopy and thoracoscopy require hospitalisation and general anaesthesia. The regions accessed by these techniques (anterior and paratracheal lymph nodes) are different from those reached by EUS-FNA (posterior regions, including the subcarinal node stations and the inferior mediastinum) (51).

More recently the combination of EBUS and EUS-FNA has been recommended as a new complete "medical" mediastinoscopy with a proposed sensitivity and specificity of 100% when EUS-FNA and EBUS-TBNA are used in combination for staging of the mediastinum (13-15,52-55).

Given the high sensitivity and negative predictive value of FDG-PET, we would propose FDG-PET as the

first-line imaging procedure for patients with enlarged mediastinal lymph nodes and suspicion of metastatic carcinoma. This procedure also detected the primary lesion in 93% of our cases and showed additional metastatic sites in 52% of our patients. The detection of the primary and additional sites dramatically changed the staging and treatment for both pulmonary and extra-thoracic cancers. FDG-PET could also provide an easier access for histological sampling (i.e. inguinal lymph node in our case of B-cell lymphoma) and detect unsuspected distant metastasis (30).

Such a high sensitivity and NPV have not been shown in all series in the literature (3,30,56-57). One could argue that some nodal stations remained unexplored since our patients did not undergo complete mediastinal surgical staging. In a recent study of potentially resectable NSCLC patients, FDG-PET imaging was compared to systematic surgical staging and its sensitivity and specificity was 67% and 85%, respectively (57). However, when it comes to studies about lung cancer staging, one must keep in mind that infracentimetric lymph nodes can harbour metastatic tissue (58). This malignant tissue can be missed by FDG-PET because of the partial volume effect (transaxial resolution of 6 to 7 mm for standard cameras). Indeed, it is known that the sensitivity of FDG-PET is reduced when the size of lesions falls below 1 cm, reaching 80% (56). In our study, patients were referred to FDG-PET evaluation for enlarged lymph nodes seen on CT, i.e. lymph node above 1 cm. Our FDG-PET results were comparable to the literature data concerning lymph nodes with a size greater than one centimetre (56). Nowadays, FDG-PET can be combined with CT into PET-CT, allowing a better anatomical localisation of lesions (59). The impact on sensitivity and specificity related to the introduction of integrated PET-CT scans still needs further evaluation. Fusion of PET and CT images, provided they confirm that the uptake is located within a lymph node, may indeed lead to the decision to consider the lymph node as a suspicious one, even if the visual analysis suggest moderate FDG uptake (14).

The FDG-PET false positive results (12.5%) confirmed previously published results on increased FDG uptake encountered in lymph nodes related to benign conditions such as histoplasmosis, tuberculosis or inflammatory conditions. Inflammatory cells (i.e. activated macrophages) can indeed concentrate FDG at similar levels to neoplasms (60-61). We observed, as others, a high FDG uptake in lymph nodes of patients with sarcoidosis, tuberculosis, anthracosilicosis and pulmonary infection (62-65).

The addition of a standardized uptake value (SUV, a semi-quantitative estimation of FDG uptake) may allow further refinement in patient selection but needs validation (64). SUV (standardized uptake values) is a semi-quantitative index that "normalizes" the measured uptake to the patient's weight and injected dose. It has been shown that this index is highly variable, especially when the time interval between tracer injection and the start of imaging varies. Moreover, uptake quantification is hampered by the partial volume effect, which results in a dramatic underestimation of the uptake in small structures, typically below 1.5 cm, which is often the case of metastatic mediastinal lymph nodes. Several studies have compared visual interpretation and SUV in terms of sensitivity and specificity. These studies were performed in lung cancer but their conclusions can be applied for the present study. Using ROC analysis, it has been shown that visual analysis yielded the best diagnostic performance, better than SUV using any threshold (22,24). Usually, it is recommended (e.g. for lung cancer staging) to consider every lymph node (or hot spot) as positive for cancer if its uptake is higher than the mediastinal blood pool. The gold standard for image interpretation in PET is thus the visual comparison between the mediastinal hot spot and the surrounding blood pool. Using SUV might also be problematic. Firstly, what is the optimal threshold to discriminate benign from malignant node ? This issue is not solved. Secondly, due to the partial volume effect, the uptake in small lymph nodes (< 1.5 cm) would be greatly underestimated, therefore yielding to a possible misclassification as "benign". This has been shown in multiple studies. For those reasons, we preferred to stick to international guidelines for image interpretation in PET, and use the visual analysis.

In case of negative FDG-PET activity in the mediastinum, the guidelines recommend surgical management in patients with a proven NSCLC, even with a 7-9% false negative rate of PET scan in the diagnosis of malignant lymph nodes (64,66). These guidelines may however be confronted by reports describing positive EUS-FNA after a negative PET study (31,32,67) or positive EBUS-TBNA (55).

Interestingly, the combination of EUS-FNA and FDG-PET results influenced subsequent management and therapy in 85% of our patients. Such a major impact on patient management had already been shown with EUS-FNA with avoidance of thoracotomy/thoracoscopy and mediastinoscopy in 49% and 68% of patients, respectively (68). Although other studies showed interesting results with a subsequent influence for workup (77-87%) and therapy (73-87%), respectively (68-70), it is surprising that some centres of respiratory disease still do not include EUS and EUS-FNA in their diagnostic approach or that publications did not even quote EUS-FNA as an alternative to mediastinoscopy or surgical staging (57, 64,72). EUS-FNA however should be considered as a safe and sensitive minimally invasive procedure for evaluating patients with mediastinal lymph nodes or solid masses (73-78). FDG-PET imaging was also shown to significantly reduce the number of mediastinoscopies in patients with non-small cell lung cancer, given its high negative predictive value (57,64,79-80). Combination of the 2 procedures is very rarely proposed even in centres with a high expertise in both FDG-PET and EUS-FNA. Some authors do however support the combination

which might qualify as a minimally invasive staging strategy for NSCLC (81), now in combination with EBUS-TBNA (14-15,52-55).

In summary, our study demonstrated that EUS-FNA and FDG-PET were complementary diagnostic procedures combining the high sensitivity of FDG-PET and the high specificity of EUS-FNA to accurately diagnose malignancy in mediastinal supracentimetric lymph nodes identified by CT. The combination of the two procedures in selected cases with pulmonary cancer or extrathoracic tumours avoided invasive diagnostic procedures, such as mediastinoscopy or thoracoscopy/thoracotomy. Should they be used together in all patients presenting with enlarged lymph nodes ? Even with the high negative predictive value of FDG-PET, we suggest that both techniques should be used to combine with FDG-PET as whole body first examination and EUS-FNA for cytological confirmation or detection of additional small lesions. These results will surely be improved by the calculations of SUVmax during PET-CT and by the additional information given by EBUS-FNA, which should be nowadays part of the work-up of mediastinal masses and lymph nodes.

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