Endoscopic ultrasound guided fine-needle aspiration and \textsuperscript{18}FDG-positron emission tomography in the evaluation of patients with non-small cell lung cancer

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Abstract

The accuracy of mediastinal staging is of paramount importance in the management of patients with non-small cell lung cancer (NSCLC) to select only those patients who might benefit from upfront resection or multimodality treatment. Although CT is the imaging technique of first choice, its performance characteristics have led to an increased use of both EUS-FNA and \textsuperscript{18}FDG-PET to improve (mediastinal) staging. In view of the relatively few studies employing both techniques simultaneously, we evaluated 20 consecutive patients (median age 70 years, range 48\textendash{}83 years) with NSCLC in whom CT suggested N2 and/or N3 involvement. The sensitivity, specificity, PPV and NPV of EUS-FNA and \textsuperscript{18}FDG-PET was 86\%, 100\%, 90\%, and 100\%, 89\%, 88\% and 100\%, respectively. EUS-FNA confirmed the absence of malignancy in all patients with a negative \textsuperscript{18}FDG-PET scan. Similarly, in the PET-positive patients, EUS-FNA confirmed malignancy in seven out of nine (78\%) sites. Unnecessary surgery was prevented in six out of 16 patients otherwise considered as surgical candidates (37\%). We conclude that both EUS-FNA and \textsuperscript{18}FDG-PET have excellent operating characteristics. However, initial \textsuperscript{18}FDG-PET findings should guide the complementary use of EUS-FNA to define treatment options and to prevent unnecessary surgery in selected patients.

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1. Introduction

To assess mediastinal lymph node involvement in patients with (suspected) non-small cell lung cancer (NSCLC), CT is the imaging technique of first choice, although its sensitivity, specificity and accuracy rarely exceed 80\%\textendash{}85\% [1]. Not surprisingly, a retrospective analysis reported that 36\% of thoracotomies performed were considered futile [2].

To improve the diagnostic work-up, \textsuperscript{18}Fluoro-deoxyglucose positron emission tomography (\textsuperscript{18}FDG-PET) has been increasingly used. Not only does \textsuperscript{18}FDG-PET have a higher sensitivity, specificity and diagnostic accuracy than CT in mediastinal staging, incorporating \textsuperscript{18}FDG-PET in the routine diagnostic work-up was shown to prevent unnecessary surgery in up to 20\% of patients [3]. However, the positive predictive value (PPV) may vary from 72\%\textendash{}90\% [4]. Hence, tissue confirmation is mandatory in \textsuperscript{18}FDG-PET-positive lesions. Tissue confirmation has long been obtained solely by means of surgical techniques. However, advances in linear endoscopic ultrasound (EUS) have enabled fine needle aspiration (FNA) of lymph node stations and/or lesions that defy sampling by means of mediastinoscopy, particularly the aortopulmonary nodes, posterior subcarinal nodes and lower para-esophageal nodes, stations 5, 7, 8 and 9, respectively [5]. Since most EUS-FNA studies have been performed in a time period prior to the routine implementation of \textsuperscript{18}FDG-PET, we assessed its role \textendash; with particular emphasis on concomitant PET findings \textendash; in the diagnostic work-up of patients with (suspected) NSCLC, in whom CT and/or \textsuperscript{18}FDG-PET suggested N2 or N3 involvement.

2. Patients and methods

2.1. Patients

During the period June 2004 \textendash; December 2005, 20 consecutive patients with suspected (n=2) or biopsy-proven NSCLC (n=18) were referred for EUS-FNA after CT and/or \textsuperscript{18}FDG-PET scan indicated possible N2 or N3 involvement at stations 5 and/or 7. Moreover, in two patients, CT demonstrated an enlarged left adrenal gland.

2.2. Methods

2.2.1. \textsuperscript{18}FDG-PET

PET scans were performed with an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) at the clinical PET center of the VU University Medical Center (n=12) or...
at the referring community hospital (n=8). All patients were normoglycemic. Patients fasted 6 h prior to the scan. Hereafter, 370MBq 18Fluoro-deoxyglucose (18FDG) was injected intravenously. One hour after injection, a whole body acquisition was performed. The mid-femur-skull trajectory was imaged with emission scans for 5 min. Images were reconstructed using ordered subset expectation maximization (OSEM) with two iterations and 16 subsets following post-smoothing of the reconstructed image using a 5-mm fwhm Gaussian filter.

2.2.2. **EUS-FNA**

EUS-FNA was performed using a linear GF-UMT140 (Olympus Optical Co, Tokyo, Japan) in combination with a DSS 4000 ProSound ultrasound scanner (Aloka, USA) and a 22G needle (Cook Medical, USA). Patients were consciously sedated, using 5–7.5 mg midazolam intravenously. No cytopathologist was present on-site. The gastroenterologist, performing EUS-FNA, was familiar with the results of the CT and PET scans. Hence, EUS-FNA was focused at the subcarinal (station 7) and aortopulmonary lymph nodes (station 5). In two patients, the concomitant enlarged left adrenal gland was needled first. Hereafter, the needle was changed and the mediastinal nodes were needled as well. After EUS-FNA, patients were monitored for two to three hours and discharged after having been advised to contact the hospital in case of complaints.

2.2.3. **Gold standard**

Postoperative histology after systematic mediastinal lymph node dissection was considered the gold standard. However, a positive FNA result was considered a true positive result without additional investigations since false-positive FNA results have not been described. Patients fulfilling either one of these two criteria were included in the calculation of EUS-FNA and 18FDG-PET results.

2.2.4. **Statistics**

Descriptive statistics and an unpaired Student t-test were used, when appropriate. A P < 0.05 was considered significant.

3. **Results**

Overall, a male preponderance was present in the group of patients with a M/F ratio of 4:1. The median age of the patients was 70 years (range 48–83 years).

3.1. **EUS-FNA**

EUS-FNA diagnosed mediastinal lymph node metastasis in six patients with a median short axis diameter of 21 mm (range 20–29 mm) and reactive nodal changes in 10 patients with a median short axis diameter of 11 mm (range 6–17 mm), P < 0.0001. Inconclusive findings were reported in four patients (20%) due to a poor quality of the FNA (Fig. 1). Only one out of four patients with a poor quality FNA was considered a good surgical candidate. This patient underwent mediastinoscopy with additional sampling of stations 3, 4, and 7 and was diagnosed as T1N2M0. After induction chemotherapy, surgical resection was performed demonstrating metastatic spread in station 5. Nine out of ten patients with reactive nodal changes underwent surgery including systematic mediastinal lymph node dissection. Postoperative histological examination confirmed the absence of malignancy in all nine patients. Based on a total number of 16 patients – six patients with a positive FNA and 10 patients with postoperative histology (nine patients with a negative FNA and one patient with a poor quality FNA (considered as negative) – the sensitivity, specificity, PPV and NPV of EUS-FNA was 86%, 100%, 100%, and 90%, respectively. Finally, EUS-FNA confirmed metastasis in one out of two patients with a CT enlarged left adrenal gland. No adverse events were observed/reported after EUS-FNA.

3.2. **18FDG-PET scan**

A positive 18FDG-PET scan was found in 10 patients and a negative 18FDG-PET scan in 10 patients as well. The median short axis diameter of the lymph nodes – assessed by EUS-in PET-positive and negative patients – was 18 mm (range 10–29 mm) and 11 mm (range 6–17 mm), P = 0.029. In the 10 patients undergoing surgery (eight with a negative PET scan, two with a positive PET scan), malignancy was found absent in eight out of eight patients with a negative PET scan, and in one out of two patients with a positive PET scan. Based on a total number of 16 patients (six patients with a positive FNA and 10 patients undergoing surgery with postoperative histology), the sensitivity, specificity, PPV and NPV of 18FDG-PET was 100%, 89%, 88%, and 100%, respectively. Finally, 18FDG-PET was positive in one out of two patients with a CT enlarged left adrenal gland.
3.3. Correlation between EUS-FNA and \(^{18}\)FDG-PET

FNA was of good quality in 16 patients, i.e. in eight out of 10 patients with a positive PET scan and in eight out of 10 patients with a negative PET scan. In the group of PET-positive patients with a good quality FNA, EUS-FNA yielded malignancy in six out of eight (75%) patients and reactive changes in two patients (25%). One of the two patients with reactive changes was operated, confirming the absence of malignancy. The other patient was considered a poor surgical candidate. Similarly, one of the two patients with a poor quality FNA was operated as well after mediastinoscopy and subsequent induction chemotherapy, confirming the presence of malignant aortopulmonary nodes. The other patient was considered a poor surgical candidate. Finally, EUS-FNA confirmed the presence of distant metastatic spread in one patient with a concomitant PET-positive, enlarged left adrenal gland.

In the group of PET-negative patients, EUS-FNA confirmed the absence of malignancy in all eight patients with a good quality FNA (100%). In the remaining two patients with a poor quality FNA, surgery was not performed because of high age and co-morbidity. Finally, no malignancy was found in the patient with a concomitant CT enlarged, PET-negative adrenal gland. Summarizing in terms of clinical relevance, four patients were considered poor surgical candidates due to high age and the presence of (severe) comorbidity (COPD, ischemic heart disease, renal insufficiency), six patients were upstaged and eight patients were downstaged due to concordant results of EUS-FNA and \(^{18}\)FDG-PET. Moreover, in the remaining two patients with discordant results, one patient was downstaged (negative EUS-FNA, positive PET scan) and one patient was upstaged (poor quality EUS-FNA considered negative, positive PET scan). In view of the above, unnecessary surgery was prevented in six out of 16 patients otherwise considered surgical candidates (37%).

4. Discussion

At present, it is generally accepted that imaging techniques relying solely on lymph node size are unreliable in mediastinal staging. Whereas the likelihood of metastasis increased with size, 37% of the lymph nodes measuring 2–4 cm in short-axis diameter on CT proved hyperplastic. Moreover, normal-sized nodes contained metastases in up to 7% of cases [6, 7]. Similarly, a review by Toloza et al. including 3438 lung cancer patients, reported false-positive CT findings in 44% and false-negative findings in 17% of patients [8]. Hence, \(^{18}\)FDG-PET is routinely employed in our work-up. The results of \(^{18}\)FDG-PET in our series compare favorably with the results of other studies [2–4]. We found an NPV of 100% suggesting that PET-negative nodes do not need further tissue confirmation. The largest study to date on the prognostic significance of PET in NSCLC patients \((n=266)\) reported almost similar findings, with a false-negative rate of 0.7%, but did not specifically analyze lymph node size in relation to PET findings [9]. However, the issue of lymph node size in relation to PET findings is of particular importance in view of a recent meta-analysis, reporting a 5% and 21% post-test probability for N2 disease, respectively, in PET-negative patients with lymph nodes of 10–15 mm and \(\geq 16\) mm [10]. Our series demonstrates a significant difference in size between PET-positive and negative nodes. Moreover, all PET-negative patients with postoperative confirmation were shown to be true-negatives, corroborating the suggestion that patients with lymph nodes \(< 16\) mm in diameter should be planned for thoracotomy without additional investigations [10]. However, our study fails to address the issue of whether or not PET-negative lymph nodes \(\geq 16\) mm should be sampled. PET-negative findings in these larger nodes might, for example, result from an inability of \(^{18}\)FDG-PET to discriminate between the centrally located primary tumor and adjacent mediastinal lymph nodes and/or from small deposits of metastatic tumor cells evading detection by means of PET [11].

We considered all EUS-FNA-positives as true-positives despite the absence of post-surgical histological confirmation. The reasons for doing so were two-fold. First of all, to the best of our knowledge, no false-positive EUS-FNAs have ever been reported in the literature. Secondly, in line with other investigators, we found it unethical to subject patients to additional invasive interventions to verify a true-positive result [12]. Overall, the operating characteristics of EUS-FNA were comparable with the results of other investigators, as reviewed elsewhere [4]. However, twenty percent of FNAs were of poor quality in our series frustrating straightforward clinical decision making, underscoring the necessity of an on-site cytopathologist for optimal results [13]. To date, relatively few studies have addressed the combined use of EUS-FNA and \(^{18}\)FDG-PET findings [12–15]. Combining EUS-FNA and \(^{18}\)FDG-PET proved highly instrumental in defining treatment options in the majority of our patients and prevented unnecessary surgery in 37% of patients considered as surgical candidates. Despite two potential drawbacks, namely twenty percent of FNAs being of poor quality and twenty percent of patients not being operated preventing postoperative histological confirmation, a 100% concordance between EUS-FNA, negative \(^{18}\)FDG-PET and postoperative histology was observed. Moreover, EUS-FNA confirmed malignancy in 77% of PET-positive sites. Hence, our study corroborates the proposed minimally invasive staging strategy, i.e. refraining from EUS-FNA in PET-negative cases and restricting EUS-FNA to PET-positive cases [15], provided that on-site cytopathological examination is available to optimize FNA results. Whether this strategy holds true in PET-negative nodes 16 mm [10] remains to be established, since the median diameter of PET-negative nodes was 11 mm (range 6–17 mm) in our series. In conclusion, EUS-FNA is a safe, minimally invasive technique with excellent sensitivity, specificity, PPV and NPV. However, initial \(^{18}\)FDG-PET findings should guide the complementary use of EUS-FNA to define treatment options and to prevent unnecessary surgery in selected patients.

References


