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Endobronchial ultrasound and value of PET for prediction of pathological results of mediastinal hot spots in lung cancer patients

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Summary In the staging of lung cancer with positron emission tomography (PET) positive mediastinal lymph nodes, tissue sampling is required. The performance of transbronchial needle aspiration (TBNA) using linear endobronchial ultrasound (real-time EBUS-TBNA) under local anaesthesia and the value of PET for prediction of pathological results were assessed in that setting. The number of eluded surgical procedures was evaluated. All consecutive patients with suspected/proven lung cancers and FDG-PET positive mediastinal adenopathy were included. If no diagnosis was reached, further surgical sampling was required. Lymph node SUVmax (maximum standardized uptake value) was assessed in patients whose PET was performed in the leading centre. One hundred and six patients were included. The average number of TBNA samples per patient was 4.9 ± 1.1. The prevalence of lymph node metastasis was 58%. Sensitivity, accuracy and negative predictive value of EBUS-TBNA in the staging of mediastinal hot spots were 95, 97 and 91%. Patients without malignant lymph node involvement showed lower SUVmax (respective median values of 3.7 and 10.0; $p < 0.0001$). Surgical procedures were eluded in 56% of the patients. Real-time EBUS-TBNA should be preferred over mediastinoscopy as the first step procedure in the staging of PET mediastinal hot spots in lung cancer patients. In case of negative EBUS, surgical staging procedure should be undertaken. The addition of SUVmax cut-off may allow further refinement but needs validation.

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1. Introduction

Staging before surgical resection of lung cancer is of paramount importance to limit the number of futile thoracotomies. In particular, patients with N2 mediastinal lymph node involvement remain poor candidates for initial surgical resection even if neoplastic invasion is limited to a single mediastinal station [1].

In the assessment of mediastinal lymph nodes, positron emission tomography with F^{18}-fluorodeoxyglucose (FDG-PET) is more accurate than CT scan [2]. 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 [3]. PET scan also provides significant additional information in the search for distant metastasis of lung cancer and is cost-effective [4]. Positive PET mediastinal lymph nodes nevertheless require histological confirmation because of possible increased FDG uptake related to non-neoplastic (mainly inflammatory) processes [2,3]. For that purpose, mediastinoscopy still remains the ''gold-standard'' [5]. However, this procedure has a mortality rate of 0.2% and a morbidity rate of 0.5—2.5%, and requires general anaesthesia; in addition, even if it can be performed on an ambulatory basis, many patients still stay at least one night in the hospital [6].

In this study, the diagnostic yield of a new tool, endobronchial ultrasound (EBUS) examination with real-time guided TBNA under local anaesthesia [7—9] was assessed in the staging of PET positive lymph nodes. The number of avoided surgical staging/diagnostic procedures was also evaluated. All the patients with suspected or proven lung cancers from Hôpital Saint-Pierre/Institut Bordet or referred from other hospitals to Hôpital Saint-Pierre/Institut Bordet endoscopic unit for this indication were included. As secondary aims, we also tried to assess whether the addition of a standardized uptake value (SUV, a semi-quantitative estimation of FDG uptake) cut-off to the usual simple visual (subjective) interpretation of FDG uptake in lymph nodes may allow further refinement in patient selection [10].

2. Materials and methods

All the patients with suspected/proven lung cancer and FDG-PET positive lymph nodes referred to Hôpital Saint-Pierre/Institut Bordet endoscopic unit were considered. Data were prospectively collected and retrospectively assessed. Patients had two different initial clinical presentations. In the first group (staging), the procedure was performed to stage the mediastinum in a proven lung cancer without any evidence for distant metastasis. In the second group (diagnosis and staging), patients had suspected lung cancer but the initial bronchoscopy was not contributive, and FDG-PET was abnormal on the tumour and on the mediastinum. Patients with previous chemotherapy induction treatment were excluded. Sixty-nine (65% of the study population) were referred from 26 other hospitals. All patients underwent EBUS for localization of the FDG-PET abnormal lymph nodes followed by real-time guided TBNA using the same standardized equipment and technique throughout the study period.

Forty-three patients (all the 37 patients from Hôpital Saint-Pierre/Institut Bordet and six referred patients) underwent FDG-PET scanning using the same combined PET/CT system in the leading centre (GE Discovery LS, GE Medical systems, Milwaukee, WI). Time of fasting before injection was at least 6 h. Pre-injection serum glucose was normal (range 78—122 mg/dL). A fixed FDG dose of 296 MBq (8 mCi) was administered 60 min before acquisition that included the trajectory from mid-thigh to mid-skull. Acquisition time was 4 min at each table position. Attenuation correction used the tomodensitometry data. Image reconstruction using ordered subset expectation maximization (OSEM) was obtained with two iterations and 28 subsets after images were smoothed by a 5.45 mm FWHM Gaussian filter.

Bronchoscopy was performed using a linear-array ultrasound bronchoscope (BF TYPE-UC160F-OL8; Olympus Ltd., Tokyo, Japan) while patients were comfortably seated in a 30° recumbent position. Oxygen (2 L/min) was administered with nasal prongs, and transcutaneous hemoglobin saturation and cardiac rhythm (Ohmeda Biox 3740; Louisville, CO) were continuously monitored. Anaesthesia of the airways was performed as previously described [11] with conscious sedation using intravenous midazolam and patients were managed on an outpatient basis. The technical description of ultrasound examination and real-time guided needle aspiration of lymph nodes using 22-gauge needle has previously been described [7—9]. Colour Doppler was used as needed to avoid main vessel puncture. Identification of lymph nodes levels was performed according to the international staging system [12] and lymph nodes dimensions were also recorded. For positive PET lymph nodes areas, assessment was concentrated on N2 and/or N3 lymph nodes in case of proven lung cancer but also on positive PET N1 lymph node in case of suspected lung cancer. If accessible PET negative lymph nodes of higher staging were seen during EBUS, (e.g. N3 PET negative areas in case of N2 PET positive areas), we sampled these first in order to detect FDG-PET occult metastases. Two to seven punctures were performed in each patient, beginning with the highest staging node level if several areas were hypermetabolic on PET-scan. The aspirated material was smeared onto glass slides that were air-dried and also fixed in 70% alcohol. In addition, the catheter and needle were flushed with one millilitre of NaCl 0.9% and the material was collected for cytological examination. No rapid on-site cytological examination was used.

3. Data analysis

For the purpose of EBUS lymph node size analysis, we considered the sampled lymph node with the largest short-axis in each patient. TBNA was considered contributive whenever a clear definite cytological or histological diagnosis was obtained. It was not contributive if no diagnosis could be reached. In these latter cases, surgical staging/diagnostic procedures (mediastinoscopy or thoracotomy with mediastinal lymph node dissection) were recommended. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated using the standard definitions, excluding patients in whom surgery was not undertaken to verify non contributive TBNA results. False-positive aspirations were considered unlikely and no