Endobronchial ultrasound-guided transbronchial needle aspiration in routine care – plenty of benign results and follow-up tests

T. J. Lange, F. Kunzendorf, M. Pfeifer, M. Arzt, C. Schulz

SUMMARY
Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a widespread technique for tissue sampling from hilar and mediastinal lymph nodes (LN). The diagnostic yield of this method is reported to be very high even outside clinical trials. We aimed to assess the diagnostic accuracy of EBUS-TBNA after its implementation at a University hospital. Methods: We analysed the first 100 consecutive patients who underwent an EBUS-TBNA procedure at our institution with respect to indication and cytological results. Sensitivity and negative predictive value (NPV) were calculated on the basis of histological confirmation or follow-up. Results: From 03/2007 to 03/2008, EBUS-TBNA of 218 LNs was performed on the basis of chest computed tomography. The primary indication for EBUS-TBNA was lymphadenopathy of unknown cause with (44%) or without (37%) pulmonary nodule(s). Only 19% of patients had known cancer and underwent the procedure for (re-)staging. In 73% of patients a non-diagnostic cytology was reported. A diagnosis could be established in only 27% by EBUS-TBNA including four patients with sarcoidosis. Sensitivity and NPV were low with 61.4% and 76.7%, respectively. Diagnostic yield increased over time and was better in cancer patients than in patients with incidental lymphadenopathy. Conclusion: Although EBUS-TBNA is reported to have a very high diagnostic yield in selected patients, the predominant finding in routine care, depending on the patient population, can be a non-diagnostic cytology result with the need for surgical procedures or follow-up studies. This should be considered in the approach to patients with mediastinal or hilar lymphadenopathy.

What’s known
Endobronchial ultrasound-guided transbronchial needle aspiration is commonly used for mediastinal staging of lung cancer and as diagnostic procedure in patients with mediastinal or hilar lymphadenopathy of other causes. The diagnostic yield of this procedure is reported to be very high even outside clinical trials.

What’s new
In patients with CT-diagnosed mediastinal or hilar lymphadenopathy and a low prevalence of malignancy, EBUS-TBNA can be markedly less often diagnostic than reported. The consequent need for surgical procedures and follow-up studies can therefore be substantial. This should be considered when approaching patients with mediastinal or hilar lymphadenopathy.

Introduction
Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a bronchoscopy-technique for tissue sampling from hilar and mediastinal lymph nodes (LN). Since its introduction in 2004, it has been investigated primarily in clinical trials of LN staging of lung cancer (1,2), but also sarcoidosis (3), metastases from other solid tumours (4) and lymphoma (5) can be detected. Therefore, EBUS-TBNA has become a widespread technique commonly used by pulmonologists and thoracic surgeons.

The diagnostic yield of EBUS-TBNA in clinical trials is usually very high with reported sensitivities well above 90%. However, patients investigated in these trials are usually preselected, which can obviously influence the results, e.g. higher rates of malignant LNs in patients with known lung cancer. Even in seemingly unselected patients referred for TBNA to two large bronchoscopy reference centres, the rate of malignancy was 98% and the reported sensitivity was 94% (6). Furthermore, clinical trials in the field are usually carried out by experienced centres and investigators, probably leading to better results.

The value of EBUS-TBNA in daily clinical practice is less clear. There are only few reports available describing the diagnostic accuracy of mediastinal and hilar LN sampling after implementation of EBUS-TBNA outside clinical trials (7–9) or in unselected patients.

Therefore, we sought to assess the diagnostic yield of cytological specimens from mediastinal or hilar LNs sampled by EBUS-TBNA in unselected consecu-
tive patients after the implementation of this technique at a University hospital. Secondary objectives were to test whether diagnostic accuracy was different with respect to indication or increases with the number of performed EBUS-TBNAs.

Methods

The first 100 consecutive patients who underwent EBUS-TBNA at our institution were retrospectively identified in the computerised bronchoscopy database. The following information was extracted from patient medical records: age, gender, indication for EBUS-TBNA including results of computed tomography (CT) and positron emission tomography (PET), LNs sampled according to the Mountain classification system (10), cytology results, results of surgical procedures (histology) and complications. The study protocol was approved by the local ethics committee.

CT and PET-CT

In patients who received a CT at our hospital, images were retrospectively reviewed and the short axis diameter of LNs sampled by EBUS-TBNA was measured. LNs with a short axis diameter of more than 10 mm were classified as 'enlarged'. The largest LN on each patient’s CT is referred to as ‘index LN’. In patients in whom a PET-CT was available, the reports were reviewed and classified to be 'positive' or 'negative' with respect to the hilar and mediastinal LNs on a patient basis.

Bronchoscopy

Patients were examined under general anaesthesia via a laryngeal mask by two experienced investigators (TJL and CS) who had previously performed conventional TBNA on a regular basis and completed a 1-day training programme at an EBUS-TBNA expert centre. A conventional flexible video-bronchoscopy was performed followed by EBUS-TBNA (BF-UC160F, Olympus, Tokyo, Japan). Accessible LNs were systematically visualised and punctured when enlarged, otherwise suspicious, or appeared significant for staging in patients with known or suspected cancer. Most LNs were measured in two dimensions.

Cytology

Lymph node aspirates were smeared onto glass slides, air dried and sent to an experienced cytologist for analysis. A short description of the EBUS-TBNA-indication was enclosed. The results were reported within days based on the Papanicolau (PAP) classification system. PAP I, II and III were classified as 'benign', PAP IV and V were classified as 'malignant'. The presence of non-caseating granulomas together with a corresponding clinical presentation led to the diagnosis of sarcoidosis. Aspirates not containing lymphocytes were reported as 'not representative' (PAP 0).

Confirmation of diagnosis

Histological confirmation of EBUS-TBNA results by either thoracotomy or mediastinoscopy served as the gold standard. In patients who did not undergo subsequent surgical procedures, results of follow-up CT scans, out-patient department visits and telephone contact were used as a substitute to the invasive gold standard. Patients with a non-diagnostic cytology who were either lost to follow-up, died, or in whom a final judgment on the LN-status ('positive' or 'negative') could not be made were assumed to have a ‘false negative’ EBUS-TBNA. Positive cytology results (malignant or sarcoidosis) were assumed to be ‘true positive’ without surgical confirmation.

Statistical analysis

Patient demographics, number and size of punctured LNs, and results are given as mean, standard deviation (SD), and range where appropriate. Sensitivity, specificity, and negative and positive predictive values (NPV, PPV) were calculated by comparing results from cytology, CT and PET-CT with the gold standard (surgical confirmation or follow-up). Non-representative cytology results (PAP 0) together with benign cytologies were regarded as ‘negative’ (non-diagnostic) EBUS-TBNA. Malignant cytologies and non-caseating granulomas were regarded as a ‘positive’ result if not stated otherwise. For comparison of LN sizes, t-statistics were used after testing for normal distribution. For non-parametric comparisons, the chi-square test was used. SPSS statistic package (version 18.0; IBM corporation, New York, NY, USA) was used for all calculations. A two-sided p-value of < 0.05 was considered statistically significant.

Results

Patient demographics

Between March 2007 and March 2008 an EBUS-TBNA procedure was performed in 29 women and 71 men. Their mean age was 58 ± 14 years and ranged from 18 to 80 years.

Indications for EBUS-TBNA

Symptoms which prompted further diagnostic evaluation are displayed in Figure 1. Indication for EBUS-TBNA was based on chest CT (n = 99) or additional PET-CT (n = 48) with exception of a 20 year-old woman with suspected sarcoidosis and marked lymphadenopathy on chest x-ray. In 57 patients in whom CT images were electronically available, 52
(91%) had at least one LN with a short axis diameter of more than 10 mm. The mean short axis diameter of the index LNs on CT was 15.0 ± 5.6 mm (8.1–45.0). Four out of five patients without radiologically suspicious LNs (all ≤ 10 mm) had a positive PET-CT.

Patients were grouped according to CT findings and indication for TBNA as follows:

- Hilar or mediastinal lymphadenopathy only, \( n = 37 \) (group A).
- Suspicious pulmonary nodule(s) together with enlarged LNs, \( n = 44 \) (group B).
- Lymphadenopathy with known extrapulmonary malignant disease, \( n = 13 \) (group C).
- Known non-small cell lung cancer (NSCLC) for (re-)staging, \( n = 6 \) (group D).

**EBUS-TBNA procedure**

All patients were examined under general anaesthesia via a laryngeal mask. Procedure times were not recorded. No major procedural complications were reported.

**Punctured lymph nodes**

Overall 218 LNs were sampled. The mean short axis diameter was 13.3 ± 4.8 mm on CT and 12.2 ± 4.2 mm on EBUS with two-thirds measuring 10 mm or above. There were no significant differences in LN size between indication groups or between EBUS and CT (Figure 2). The distribution of sampled LNs according to the Mountain classification system is shown in Figure 3. The cytology results are presented in Table 1. The mean frequency of punctured LNs was 2.2 per patient (range 1–6). Two or more LNs were sampled in 73 patients. One third (33) had TBNA of at least three LN positions. More than four and five LNs were punctured in eight and three patients respectively. In one patient six LNs were sampled.

**Cytology results of EBUS-TBNA**

The reported cytology results are given in Figure 4. Sarcoidosis was established as final diagnosis in seven patients. In two of these patients the EBUS-TBNA specimen did not contain lymphatic cells, and in another patient lymphatic hyperplasia (PAP II) was described. In all three cases, LN in position 7 according to the Mountain classification system was sampled. Finally, sarcoidosis was diagnosed histologically in specimens from transbronchial lung biopsy (two patients) or surgical sampling (one patient).

**Malignant cytology**

Endobronchial ultrasound-guided transbronchial needle aspiration revealed malignancy in 23 patients. The primary cancer site in eight cases of metastatic LN involvement was kidney \( (n = 2) \), rectum \( (n = 2) \), thyroid gland \( (n = 2) \), pancreas \( (n = 1) \) and prostate \( (n = 1) \). The cytological diagnosis of M. Hodgkin in one patient was confirmed based on histology.

**Benign cytology**

Representative specimens without tumour cells or other specific cells (only ‘lymphatic hyperplasia’, usually PAP II) were obtained in 161 LNs of 71 patients. The 16 patients (23%) with histological confirmation of their ‘true negative’ EBUS-TBNA result were mainly lung cancer patients who underwent tumour resection with radical LN dissection \( (n = 12) \). In 40 patients, the benign EBUS-TBNA result was assumed to be ‘true negative’ on the basis of follow-up visits (with a CT-scan in 11 patients). The mean follow-up time was 22.3 ± 7.0 months (range 8.3–33.6).
In one patient each the diagnosis of lymphoma and sarcoidosis was missed on EBUS-TBNA. The remaining 13 patients were assumed to be ‘false negative’ on EBUS-TBNA as they were lost to follow-up, died or had malignant disease without surgical confirmation of the LN status (e.g. SCLC, diagnosed by CT-guided transthoracic biopsy).

### Diagnostic accuracy of EBUS-TBNA

For the entire group of patients, sensitivity of cytology results obtained by EBUS-TBNA was 61.4% with a NPV of 76.7%. In patients with a ‘positive’ PET-CT \((n = 40)\), sensitivity and NPV were 62.5% and 64.0% respectively. As all positive cytology results were assumed to be ‘true positive’, specificity and PPV were all 100% (see contingency table, Table 2). With respect to indication group, the highest sensitivity of 81.8% was obtained in patients with known cancer (calculation with numbers of group C and D together) compared with group A (sensitivity 38.5%) and group B (sensitivity 65.0%). The rate of malig-
nancy (final results) in patients from group C and D was 57.9% compared with 35.1% and 45.5% in group A and B respectively. Regarding development over time, sensitivity increased from 54.2% in the first 50 patients to 70.0% in the second half, whereas the rate of malignancy in the respective patient groups were 48% and 40% respectively. Sensitivity and NPV for various quartiles of patients are shown in Table 3.

### Diagnostic accuracy of CT and PET-CT

Computed tomography images were available in 57 patients. The mean difference between CT and EBUS-TBNA was 11 ± 14 (0–62) days (median 6 days). Distribution according to indication groups A–D (not shown) and mean short axis LN diameter on EBUS (12.4 ± 3.9 vs. 11.8 ± 4.4, p = 0.282) were not significantly different compared with the group of patients without CT images available. Using a cut-off for the short axis index LN diameter on CT of > 10 mm, CT had sensitivity, specificity, NPV and PPV of 91.3%, 8.8%, 60.0% and 40.4% respectively. Raising the cut-off to > 14 mm (median of the group), CT had sensitivity, specificity, NPV and PPV of 65.2%, 61.8%, 72.4% and 53.6% respectively.

Computed tomography images were available in 23 of 37 patients (62%) from group A. Excluding one patient with sarcoidosis, mean short index LN diameter was 17.8 ± 4.4 (13.8–25.7) mm in malignant LNs compared with 14.9 ± 3.5 (9.0–20.2) mm in benign LNs (p = 0.88). The smallest short axis diameter of malignant index LNs in groups A, B, C and D was 13.8, 13.3, 8.6 and 17.3 mm respectively.

A PET-CT report was available in 48 patients and classified as ‘positive’ in 40 (83%). Sensitivity and NPV were 100% each whereas specificity and PPV were low with 33.3% and 60.0% respectively.

### Discussion

In this analysis of the first 100 EBUS-TBNA examinations in unselected consecutive patients at a University bronchoscopy unit, we found a very high rate of 73% negative cytologies. The diagnostic accuracy was much lower than expected with a sensitivity of only 61.4% and an NPV of 76.7%. However, sensitivity seemed to be dependent on TBNA indication and respective prevalence of malignancy within the different patient groups, with the highest sensitivity of 81.8% in patients with known cancer. Furthermore, sensitivity increased over time from 54.2% in the first 50 patients to 70.0% in the second half.

We observed a negative, non-diagnostic EBUS-TBNA result in 73% of our patients. This proportion is very high compared with other published case series who described a definitive diagnosis with EBUS-TBNA in 63–83% of their patients (9,11). In a large...
series from two bronchoscopy reference centres, a definitive diagnosis was achieved in even 94% by EBUS-TBNA (6). Although the consecutive patients in this study were seemingly unselected, over 98% had lung cancer and the mean LN size was 16 mm. These factors could have contributed to the high diagnostic yield reported. In our patients, only 37% had a malignant disease as final diagnosis (including patients lost to follow-up), reducing the possibility of obtaining a positive cytology result. Furthermore, given the small number of available reports describing results of EBUS-TBNA in a routine clinical care setting, a possible publication bias has to be taken into account when comparing our results to the literature.

When a cytological specimen from EBUS-TBNA is reported to be negative (but with lymphatic cells present), there are three possible scenarios: (i) The LN is free from tumour cells (‘true negative’ result). (ii) The LN contains tumour cells which have been missed by EBUS-TBNA sampling (‘false negative’ result). (iii) The specimen contains tumour cells, but the diagnosis is missed by the cytologist (‘false negative’ result). The latter two scenarios are indistinguishable in routine practice, but false negative results are usually ascribed to a sampling error of EBUS-TBNA (12). However, given the excellent reproducibility of diagnosis in EBUS-TBNA-derived samples by experienced pathologists (13), this approach seems to be justified. As we sent our specimens to an experienced cytologist, misdiagnosis is unlikely to contribute to the high number of negative cytology results.

We found a sensitivity of only 61.4% for consecutive EBUS-TBNA examinations in unselected patients in our study. This number is low compared with other retrospective case series who reported sensitivities for EBUS-TBNA between 85% and 92% (9,11,14). A recent systematic review including mainly prospective clinical trials in the field of lung cancer staging, reported sensitivities between 85% and 100% (15). This obvious difference could again be explained by a higher proportion of cancer patients within these studies leading to more malignant cytology results and therefore to a higher sensitivity of EBUS-TBNA. In prospective clinical trials of lung cancer staging, the negative EBUS-TBNA results are usually confirmed by a surgical procedure revealing the true number of ‘false negative’ cytologies. Furthermore, patients in clinical trials are less frequently lost to follow-up. We counted 13 patients who were lost to follow-up, died, or had an unclear LN status, but cancer diagnosed from another biopsy site as a ‘false negative’ EBUS-TBNA, leading to a marked decrease in sensitivity. Our numbers are comparable to a retrospective analysis of the first 100 EBUS-TBNA examinations of five different operators in the UK, who reported a pooled sensitivity of 67.4% ranging from 59.7% to 80.3% (16). The authors applied similar rigorous statistical criteria counting patients who were lost to follow-up, died or were diagnosed with malignancy on follow-up as a ‘false negative’ EBUS-TBNA result. The above-mentioned factors are likely to explain the lower rate of false negative cytologies in reported trials compared with our analysis.

Sensitivity and NPV were found to be the lowest in our group of patients with solely enlarged LNs (group A), followed by patients with additional pulmonary nodule(s) (group B), whereas sensitivity was 81.8% with an NPV of 80% in patients with known malignancy. This finding can most probably be explained by a different prevalence of malignancy within the different groups. As shown in a meta-analysis of TBNA-studies in NSCLC, sensitivity of TBNA depends critically on the prevalence of mediastinal metastasis (17). However, this seems not to be true for prospective clinical trials with well-selected patients and a mandatory surgical gold standard as in a lung cancer staging trial by Herth and colleagues (18). In their patients with radiologically and PET-normal mediastinum, they reported a sensitivity of EBUS-TBNA staging of 89%, although only 10 of 97 included patients with NSCLC had mediastinal metastasis, resulting in a corresponding prevalence of malignancy of 10%. However, assuming that EBUS-TBNA would have missed just one more mediastinal metastasis in these patients, sensitivity would have dropped to 82%, demonstrating the great influence of malignancy prevalence on sensitivity. An additional explanation for the different sensitivities with respect to indication groups as observed in our study could be investigator bias, with more thorough examination (e.g. more passes per LN) in patients with known or expected cancer.

In published clinical trials of this subject, the examinations are usually carried out by experienced investigators familiar with EBUS-TBNA over a long period of time, or in centres with a high volume of procedures, which could also influence sensitivity and NPV. The two investigators at our site (TJL and CS), who are experienced bronchoscopists performing TBNA on a regular basis, completed a 1-day training programme at an expert center before starting EBUS-TBNA. We found an increase in sensitivity from 54.2 to 70% and in NPV from 70.3% to 83.3% comparing the first and second half of procedures, suggesting the existence of a certain learning curve. Steinfort and colleagues have reported improvements in diagnostic performance of EBUS-TBNA after 20
and even 50 examinations (9), others described the learning curve to be at only about 10 procedures (19). The retrospective analysis by Kemp and colleagues, who reported similar sensitivities compared with our study, found a wide variability in the learning curves for EBUS-TBNA but showed a steady increase in diagnostic performance over 100 procedures in three of five operators (16). Therefore, the relatively small number of procedures analysed in our study could have contributed to the low sensitivity.

The EBUS-TBNA indication was based on chest CT in almost all of our patients. Using the generally accepted definition of a LN with a short axis diameter of more than 10 mm to be ‘enlarged’, CT showed a markedly low specificity for diagnosis of a ‘positive’ result. Raising the cut-off to a short axis index LN diameter of 14 mm (median of the group) on CT, specificity increased from 8.8% to 61.8% at the cost of a decrease in sensitivity from 91.3% to 65.2%. As a result of the overlap in size between malignant and benign LNs, a clear cut-off could not be identified for the entire group. As demonstrated by others (18), there is no ‘save’ cut-off for the short axis LN diameter on CT in patients with suspected lung cancer. This is reflected by a malignant index LN size down to 8.6 mm in our patients with known malignancy. However, in patients from group A, the smallest malignant index LN diameter was 13.8 mm. Although this finding has to be interpreted cautiously, a non-invasive follow-up without EBUS-TBNA could be justified in patients with an incidental finding of hilar or mediastinal lymphadenopathy with a short axis LN diameter of < 13 mm, unless further clinical or radiological suspicion of malignancy exists.

A PET-CT was performed in 48 patients and was ‘positive’ in 40 (83%). The sensitivity of EBUS-TBNA in these patients was only slightly higher compared with the whole group of patients (62.5% vs. 61.4%) and apparently lower compared with a retrospective multicenter study of EBUS-TBNA in lung cancer patients with PET-positive LNs, where a sensitivity of 91% was reported (20). However, even if only eight patients with a negative PET-CT result have been included in our analysis (again, most probably because of selection bias), all of them were found to be ‘true negative’. The very high sensitivity and NPV of PET-CT in NSCLC-staging could also be demonstrated in a recent study and a meta-analysis (21,22). The authors of the latter study found a sensitivity of even 100% in patients with radiologically enlarged LNs. Therefore, in patients with enlarged hilar or mediastinal LNs, a negative PET-CT together with a low probability of malignancy could help to avoid invasive procedures in favour of follow-up.

Admittedly, our study has potential limitations. As a result of the retrospective nature, important issues which are known to influence EBUS-TBNA results were neither standardised nor systematically recorded, e.g. the frequency of passes per LN. Furthermore, we performed the procedures primarily under general anaesthesia which presumably increased accuracy. A major problem is also the deficiency of histological (surgical) confirmation of negative cytologies, which is only inadequately substituted for by clinical follow-up as used in the majority of our patients. On the other hand, the mean duration of our follow-up of almost 2 years makes the potential of missing a malignant diagnosis very unlikely. Furthermore, the routine clinical care setting represents a strength of our study by examining a patient population with a low prevalence of malignancy which has not been systematically investigated in the field of EBUS-TBNA so far.

In our study, we found a very high rate of 73% non-diagnostic cytologies sampled by EBUS-TBNA in unselected consecutive patients and a lower than expected sensitivity of 61.4%. These findings are most likely explained by the relatively low prevalence of malignancy within our patient population. Our study reveals the common medical problem of a high rate of negative diagnostic tests without having an easily available gold standard to verify the results. Yet the uncertainty of diagnosis is counterbalanced by possible morbidity through invasive procedures, cost of follow-up examinations, and potential harm caused by radiation exposure associated with follow-up CT scans.

In conclusion, although EBUS-TBNA is reported to have a very high diagnostic yield in selected patients, the predominant finding in routine care, depending on the patient population, can be a non-diagnostic cytology result with the need for surgical procedures or follow-up examinations. This highlights the need for development of an algorithm incorporating clinical probability of malignancy, (PET-)CT, EBUS-TBNA and surgery and should be considered in the approach to patients with mediastinal or hilar lymphadenopathy in routine care.

Acknowledgements
None.

Author contributions
Tobias J. Lange: concept of the study, performing EBUS-TBNA, acquisition of data, analysis and interpretation of data, drafting of the manuscript,
approval of the final manuscript version. Frederike Kunzendorf: acquisition, analysis and interpretation of data, critical revision of the manuscript, approval of the final manuscript version. Michael Pfeifer: interpretation of data, critical revision of the manuscript, approval of the final manuscript version. Michael Arzt: interpretation of data, critical revision of the manuscript, approval of the final manuscript version. Christian Schulz: concept of the study, performing EBUS-TBNA, interpretation of data, critical revision of the manuscript, approval of the final manuscript version.

References
1 Rintoul RC, Skwarski KM, Murchison JT, Wallace WA, Walker WS, Penman ID. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. *Eur Respir J* 2005; 25: 416–21.
2 Yasufuku K, Chiyo M, Koh E et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 2005; 50: 347–54.
3 Wong M, Yasufuku K, Nakajima T et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Respir J* 2007; 29: 1182–6.
4 Nakajima T, Yasufuku K, Fujiwara T et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. *J Thorac Oncol* 2008; 3: 985–8.
5 Kennedy MP, Jimenez CA, Bruzzi JF et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Thorax* 2008; 63: 360–5.
6 Herth FJF, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax* 2006; 61: 795–8.
7 Alsharif M, Andrade RS, Groth SS, Stelow EB, Pambuccian SE. Endobronchial ultrasound-guided transbronchial fine-needle aspiration: the University of minnesota experience, with emphasis on usefulness, adequacy assessment, and diagnostic difficulties. *Am J Clin Pathol* 2008; 130: 434–43.
8 Jacob-Ampuero M, Haas AR, Ciocca V, Bibbo M. Cytologic accuracy of samples obtained by endobronchial ultrasound-guided transbronchial needle aspiration at thomas jefferson University hospital. *Acta Cytol* 2008; 52: 687–90.
9 Steinfort DP, Hew MJ, Irving LB. Bronchoscopic evaluation of the mediastinum using endobronchial ultrasound - a description of the first 216 cases performed at an australian tertiary hospital. *Intern Med J* 2011; 41: 815–24.
10 Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997; 111: 1718–23.
11 Tian Q, Chen L, Wang H et al. Endobronchial ultrasound-guided transbronchial needle aspiration of undiagnosed mediastinal lymphadenopathy. *Chin Med J (Engl)* 2010; 123: 2211–4.
12 Herth FJF, Ernst A, Eberhardt R, Vilmann P, Diemenmann H, Krasnik M. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J* 2006; 28: 910–4.
13 Skov BG, Baandrup U, Jakobsen GK et al. Cytopathologic diagnoses of fine-needle aspirations from endoscopic ultrasound of the mediastinum: reproducibility of the diagnoses and representativeness of aspirates from lymph nodes. *Cancer* 2007; 111: 234–41.
14 Tournoy KG, Rintoul RC, van MeerbeeckJP et al. Ebus-tbna for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. *Lung Cancer* 2009; 63: 45–9.
15 Varela-Lema L, Fernández-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *Eur Respir J* 2009; 33: 1156–64.
16 Kemp SV, El BatawySH, Harrison RN et al. Learning curves for endobronchial ultrasound using cusum analysis. *Thorax* 2010; 65: 534–8.
17 Holty JC, Kuscher WG, Gould MK. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. *Thorax* 2008; 63: 949–55.
18 Herth FJF, Eberhardt R, Krasnik M, Ernst A. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. *Chest* 2008; 133: 887–91.
19 Groth SS, Whitson BA, D’Cunha J, Maddaus MA, Alsharif M, Andrade RS. Endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes: a single institution’s early learning curve. *Ann Thorac Surg* 2008; 86: 1104–9 discussion 1109–10.
20 Rintoul RC, Tournoy KG, El DalyH et al. Ebustbna for the clarification of pet positive intra-thoracic lymph nodes-an international multi-centre experience. *J Thorac Oncol* 2009; 4: 44–8.
21 Darling GE, Mazakia DE, Inculet RI et al. Positron emission tomography-computed tomography compared with invasive mediastinal staging in non-small cell lung cancer: results of mediastinal staging in the early lung positron emission tomography trial. *J Thorac Oncol* 2011; 6: 1367–72.
22 Gould MK, Kuscher WG, Rydzak CE et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003; 139: 879–92.

Paper received November 2011, accepted February 2012