ORIGINAL ARTICLE

Relationship between endobronchial ultrasound-guided (EBUS)-transbronchial needle aspiration utility and computed tomography staging, node size at EBUS, and positron emission tomography scan node standard uptake values: A retrospective analysis

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Abstract

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) diagnoses and stages mediastinal lymph node pathology. This retrospective study determined the relationship between EBUS-TBNA utility and non-small cell lung cancer (NSCLC) stage, lymph node size, and positron emission tomography (PET) standard uptake values (SUV), and the utility of neck ultrasound in bulky mediastinal disease.

Methods: Data of 284 consecutive patients who had undergone EBUS-TBNA was collected. Two hundred patients had suspected NSCLC, with 148 confirmed NSCLC cases. The diagnostic utility of EBUS-TBNA was determined according to NSCLC stage, EBUS lymph node size, PET SUV, use in distal metastases, and mutation testing. The utility of neck ultrasound for N3 disease was calculated in patients with bulky mediastinal disease.

Results: EBUS-TBNA was well tolerated with 97% sensitivity in distant metastatic disease, avoiding the need for distal metastases biopsy in 81% of cases. It had equivalent diagnostic accuracy in all NSCLC stages and in lymph nodes <10 mm, <20 mm or >20 mm (sensitivity >92% in all cases), with no mutation testing failures. EBUS-TBNA had 33% sensitivity in PET indolent (SUV < 4) nodes and 79% sensitivity in PET active nodes (SUV > 4). EBUS-TBNA diagnosed 12 cases of lymphoma without flow cytometry.

Conclusions: The use of EBUS-TBNA meant that distant metastatic biopsy was avoided in 81% of cases, performing well irrespective of cancer stage, node size, and facilitating mutation testing. Neck ultrasound failed to detect N3 disease in patients with bulky mediastinal disease. EBUS-TBNA had a sensitivity of 33% for metastases in PET negative nodes, highlighting PET limitations.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is commonly used as a single initial investigation for both the staging and diagnosis of suspected malignant mediastinal lesions, as well as for investigation of benign mediastinal lesions.[1,2] The diagnostic utility of EBUS-TBNA for the detection of mediastinal malignancy has a reported sensitivity between 88% and 93%.[3] However, few pragmatic studies have examined the relationship between EBUS-TBNA and computed tomography (CT) staging, node size at EBUS, positron emission tomography (PET) node standard uptake values (SUV), and the utility of neck ultrasound in bulky N2 disease.

Kumaran et al. demonstrated high utility of neck ultrasound in bulky N2 disease, detecting malignancy in 46% of patients with N2 or N3 disease on CT; however, EBUS-TBNA was not used at the time of that study.[4] Shingyoji et al. detected occult N2 disease in 17.6% of patients using

EBUS-TBNA with normal mediastinal PET and CT scans.[5] EBUS had a sensitivity of 35%, negative predictive value of 88%, and accuracy of 88% in nodes of ≤10 mm, although lymph node size has been shown to be an independent predictor of lymph node metastases.[5,6] This is also in keeping with the fact that PET scanning (although superior to CT scanning in performance) still only has 74% sensitivity and 85% specificity for mediastinal staging of lung cancer.[7]

The aim of this pragmatic study was to undertake a retrospective analysis of EBUS-TBNA performance in a real world setting in patients referred with suspected malignancy to an English tertiary EBUS center between November 2009 and January 2015. We analyzed the diagnostic utility of EBUS-TBNA by lung cancer radiological stage, the use of EBUS-TBNA in patients with distal metastases compared to biopsy of distal metastases, the utility of EBUS-TBNA according to node size at ultrasound and according to PET SUV, and the utility of neck ultrasound biopsy in high volume N2 disease.

Methods

Retrospective analysis of 284 consecutive EBUS-TBNA cases referred to a tertiary EBUS center in South West England between November 2009 and January 2015 was conducted. Cases were referred for the diagnosis and/or staging of enlarged mediastinal/hilar nodes detected on either CT scanning or nodes with an elevated SUV on PET scanning in which there was a clinical suspicion of malignancy based on clinico-radiological assessment. All cases of non-small cell lung cancer (NSCLC), including carcinoid tumors and large cell neuroendocrine tumors, were included. Small cell lung cancer (SCLC), non-lung cancers, lymphoproliferative malignancies, and benign conditions, such as sarcoidosis and tuberculosis, were excluded from analysis. As this study was part of the ongoing standard of care for patients undergoing EBUS-TBNA and evaluation of our service, no specific ethical approval was required after consultation with our local Research and Ethics Committee.

Our EBUS center serves a local population of 550 000 in Bristol, as well as the regional Cancer Network. All biopsy results were reviewed at multidisciplinary team meetings after verification by two independent lung histopathologists.

Three trained primary operators in an endoscopy unit performed EBUS-TBNA with patients under conscious sedation (midazolam and fentanyl), using a dedicated convex probe ultrasound bronchoscope (Olympus BF-UC260FW, Olympus, Tokyo, Japan), as previously described.[8,9] The same operator measured the nodes in millimeters, taking the longest measurement of the short axis diameter from the same orientation for each node. Dedicated 21-G or 22-G EBUS-TBNA needles (Olympus

ViziShot, NA-201SX-4021 and NA-201SX-4022) were used for sampling at the discretion of the operator.[10] The operator determined the number of stations sampled, but for staging EBUS procedures, at least three nodal stations (7, 4R, and 4L) were undertaken. The needle was passed 10 times per sample and two samples were taken per lymph node. EBUS-TBNA samples were transferred from the microcassettes in which they were placed at the time of the procedure into a tissue cassette for later fixing in formalin, paraffin-embedding, staining with hematoxylin and eosin, and further immunostaining, rather than liquid cytology preparation.[10,11] Neck ultrasound +/− biopsy was undertaken as previously described by a team of two thoracic radiologists, both very experienced in neck ultrasound biopsy.[4]

Contingency table statistical analysis using Wilson's method was performed using GraphPad Prism version 5 - (GraphPad Software Inc., La Jolla, CA, USA) to calculate the diagnostic performance of EBUS-TBNA in NSCLC. A false negatives was defined as a negative EBUS-TBNA followed by either a positive repeat EBUS-TBNA, positive mediastinoscopy or positive biopsy elsewhere from either the primary lesion (e.g. CT-guided lung biopsy); or a distant metastatic lesion (e.g. bone biopsy) in the context of enlarged mediastinal nodes on CT or enlarged nodes with high SUV on PET. A true negative was defined as a negative EBUS-TBNA followed by negative nodes on resection or mediastinoscopy, PET with a low SUV and no nodal enlargement, or clinico-radiological stability of the mediastinum on CT scan for a minimum of 12 months. A true positive was defined as a positive EBUS-TBNA from an identified nodal target on CT and was not confirmed by mediastinoscopy, as this was a pragmatic real world study.

Information was gathered using the Trust PACS System, hospital records, and an anonymized interventional database on Microsoft Excel, crosschecked with the regional cancer network database. Data included patient demographics, indication for EBUS-TBNA, radiological stage (on CT and PET), PET SUV, lymph node size and location, number of lymph node stations sampled, histology, epidermal growth factor receptor mutation status, treatment outcome, and neck ultrasound results for cases with bulky N2 disease. The "high SUV group" PET SUV was defined as SUV > 4; the "low SUV group" was defined as PET SUV between undetected and <4. Although a PET SUV > 2.5 has often been used as a cut-off point for malignancy for nodal metastases, two studies have reported more accurate cut-offs at >4.5 and 5.3, respectively.[12,13] In addition, the cut-off for malignancy is more specific to local PET imaging. Because of these factors and local knowledge of the more accurate SUV cut-off, and the fact that our data were evenly divided below and above an SUV of 4, an SUV > 4 was selected as our cut-off point.

Table 1 Breakdown of study cohort

Non-small cell lung cancer†	148
SCLC	39
Suspected extrathoracic cancer	45
Lymphoma	12
Genito-urinary (renal, prostate, endometrial) cancer	7
Breast cancer	6
Carcinoma of unknown primary (non-lung)	6
Colorectal cancer	3
Malignant mesothelioma	1
Laryngeal cancer	1
True negative	7
False negative	1
True negative	43
Surgical resection – nodes clear	1
Negative mediastinoscopy	19
PET negative nodes with low SUV	5
Clinical and radiological stability over 12 month period on CT	18
False negative	9
Positive mediastinoscopy	1
Repeat positive EBUS-TBNA	1
Positive EUS-FNA	1
Positive CT-guided lung biopsy with enlarged nodes on CT	3
Positive bone biopsy with enlarged nodes on CT	2
PET scan with nodes with high SUV	1
Total	284 (200 suspected NSCLC)

†Included 80 adenocarcinoma, 47 squamous, 15 undifferentiated, 4 large cell, and 2 neuroendocrine cases. CT, computed tomography; EBUS-TNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, endoscopic ultrasound-guided-fine needle aspiration; PET, positron emission tomography; SCLC, small cell lung cancer; SUV, standard uptake value.

Bulky N2 or multistation N2 disease was defined as one N2 node >2 cm in short axis diameter or two or more N2 nodes >1 cm in short axis diameter. As the data were evenly distributed above and below a cut-off of 20 mm nodal size, this cut-off was used for analysis; however, separate analysis of the 30 patients with nodes <10 mm was also performed. All data were analyzed per patient except for node size and PET data, which were analyzed per node.

Results

In the study period, 284 patients underwent EBUS-TBNA for suspected malignancy (239, 84% lung cancer, 45 extra-thoracic cancer) (Table 1). Of the 239 patients referred with suspected lung cancer, 187 were subsequently diagnosed with lung cancer (78%): 39 SCLC and 148 NSCLC (of which 44 underwent EBUS-TBNA for staging alone and the remainder for both diagnosis and staging). The

only complication was that one patient developed atrial fibrillation with a fast ventricular rate post procedure requiring overnight admission for monitoring alone, which was alleviated without pharmacological intervention. There was a male preponderance (164, 58%), with an average age of 66 years (range 30–87).

There were nine false negative EBUS-TBNA results (Table 1). In three cases, mediastinal metastases were proven via mediastinoscopy, repeat EBUS-TBNA or endoscopic ultrasound-guided-fine needle aspiration; and in six cases (assumed false negative because of a positive metastatic biopsy elsewhere), with CT demonstrable mediastinal adenopathy in five of the cases and a high SUV on PET with enlarged nodes but no biopsy in one case. Forty-three true negative EBUS-TBNA results were confirmed. In 20 cases, the absence of mediastinal metastasis was proven by negative mediastinal pathological analysis, and in the remaining 23 this was assumed by either low PET activity or the absence of clinico-radiological progression over 12 months. All 43 of these cases had suspected NSCLC with no evidence of hilar or mediastinal metastases, with confirmed NSCLC in 27 cases and assumed in the other 16.

A total of 485 nodal stations were sampled in these 284 patients. The nodal stations sampled were 2R, 2L, 3, 4R, 4L, precarinal, 7, 10R, 10L, 11R, and 11L. The mean node size was 23.7 mm (standard deviation 8.4 mm). Of the 80 lung adenocarcinomas, epidermal growth factor receptor mutation testing was undertaken in 65 (81%) patients (mutation positive in 5, mutation negative in 60) and there were no mutation testing failures (Table 1). The treatment outcomes for the 148 NSCLC patients are shown in Table 2. Active cancer treatment was administered to 116 patients (78%) and radical treatment to 20 patients (14%).

Diagnostic utility of EBUS-TBNA for malignancy according to NSCLC stage, nodal size, and PET node SUV

Table 3 shows the diagnostic utility of EBUS-TBNA for the whole study cohort, lung cancer cohort, NSCLC cases, and individual NSCLC stage. Table 4 shows the diagnostic utility for nodes at EBUS < 10 mm, <20 mm or >20 mm, and PET node SUV < 4 or >4 in the lung cancer cohort. The majority of the stage I/II group comprised patients with N1 hilar adenopathy, accounting for the mean node size of 17.4 mm (Table 3). Fifty-one patients referred with suspected NSCLC had PET scans. Thirteen PET reports were unavailable, three node PET SUVs were not reported, and two PET SUVs were for masses sampled rather than nodes, leaving a total of 33 patients with nodal PET SUV data, as shown in Table 4 (an additional 5 patients had PET scans for either SCLC or extra-thoracic cancer, thus were excluded from analysis).

Table 2 Treatment outcomes in 148 confirmed NSCLC patients

						Total
Radical treatment	20	Palliative treatment	96	No specific anticancer treatment/unknown	32	148
Surgery	3	Palliative chemo-RT	24	Best supportive care (including 3 who declined treatment)	18	
Radical RT	10	Palliative chemo	55	Died	1	
Radical Chemo-RT	7	Palliative RT (9 local, 5 brain, 3 spine – includes 1 stent)	17	Not known/referred back to original center	13	

NSCLC, non-small cell lung cancer; RT, radiotherapy.

Table 3 Diagnostic utility of EBUS-TBNA (per patient analysis) in study cohort (extrathoracic cancers and all lung cancers), all NSCLC cases and stages

Cohort	Number of patients	Number of nodes	PET	Mean EBUS node size (mm)	Sensitivity (%)	Accuracy (%)	NPV (%)	Prevalence (%)
Whole study cohort	284	503	56	21.2	95.7	96.5	83.3	82.4
NSCLC only (combined)	200[†]	349	51	20.3	94.3	95.7	85.5	74.8
NSCLC Stage I & II	28 (14%)	42	17	17.4	93.8	96.4	92.3	57.1
NSCLC Stage IIIa	65 (32.5%)	119	18	19.3	94.1	95.4	82.4	78.5
NSCLC Stage IIIb	33 (16.5%)	73	8	22.0	96.8	97	66.7	93.9
NSCLC Stage IV	74 (37%)	125	8	20.9	93.2	94.6	79.0	79.7

[†]Includes all non-small cell lung cancer (NSCLC) cases, including true negative and false negative cases. EBUS-TNA, endobronchial ultrasound-guided transbronchial needle aspiration; NPV, negative predictive value; PET, positron emission tomography.

Table 4 Diagnostic utility of EBUS-TBNA (per nodal analysis) according to EBUS node size < or >20 mm and PET node SUV < or >4

Cohort	Number of patients	Number of nodes	Mean node size (mm)	Sensitivity (%)	Accuracy (%)	NPV (%)	Prevalence (%)
EBUS node size <10 mm	30	38	8.9	92.3	96.7	94.4	40.0
EBUS node size <20 mm	94	165	15.6	93.4	95.7	89.2	64.9
EBUS node size >20 mm	106	184	24.6	94.8	95.3	66.7	90.6
PET node SUV <4	16	20	15.8	33.3	90.0	89.5	15.0
PET node SUV >4	17	20	17.7	78.6	85.0	66.7	70.0

EBUS-TNA, endobronchial ultrasound-guided transbronchial needle aspiration; NPV, negative predictive value; PET, positron emission tomography; SUV, standard uptake value.

Performance was maintained for all stage groups with sensitivity above 92% and accuracy above 94.5%. Sensitivity fell slightly to 92% for smaller nodes (<10 mm) compared to over 95% for larger nodes (>20 mm). In patients with a PET SUV of <4, the sensitivity of EBUS-TBNA for malignancy was still 33% and <80% in those with a PET SUV > 4.

Diagnostic utility and impact of EBUS-TBNA in distant metastatic disease

Ninety-three patients were referred with radiological stage IV lung cancer (including SCLC cases before diagnosis available). Of these 93 patients, 75 (81%) had a clinically relevant alternative site of distal metastatic disease suitable for biopsy (including adrenal, bone and brain, liver and pleural metastases, but excluding metastatic lung nodules). EBUS-TBNA had 97% sensitivity and 81.8% negative predictive value in these patients.

Neck ultrasound

In 239 patients with suspected lung cancer (NSCLC and SCLC), bulky or multi-station mediastinal nodal disease (>2 cm) was present in 123 cases. Nineteen of these 123 patients received neck ultrasound before EBUS with a view to potentially confirming N3 disease and avoiding the need for further investigation. In 14 of these 19 cases, no nodes were observed on neck ultrasound, and in the remaining five cases the biopsied nodes were negative. Ninety patients did not have a neck ultrasound and data were unavailable in 14 cases.

Discussion

This pragmatic study has demonstrated that EBUS-TBNA is often used to confirm diagnosis in patients with distant metastatic disease, avoiding the need for more invasive techniques in 81% of cases that may require radiological or surgical expertise, although left adrenal biopsy is possible via endoscopic ultrasound-guided-fine needle aspiration or even endoscopic ultrasound-guided-fine needle aspiration with bronchoscope, subject to available expertise.[14–16] EBUS-TBNA is generally selected for out-patients unsuitable for radical treatment but where palliative oncological therapy is appropriate. In our study, EBUS-TBNA was followed by oncological therapy in 78% of patients and radical treatment in 14% of NSCLC patients. Only one patient required overnight admission, supporting previous reports that EBUS-TBNA is well tolerated under conscious sedation.[9]

We hypothesized that smaller EBUS nodal sizes are observed in lung cancers detected at earlier stages. Although the mean nodal size was lower in the stage I and II NSCLC cohort in our study (17.4 mm compared to 19.3 mm in stage 3A cohort), the performance of EBUS-TBNA did not significantly differ between NSCLC lung cancer stage, supporting its utility in both the diagnosis and staging of bulky N2 disease and staging for radical treatment and diagnosis in small volume disease/single station N2 disease. Moreover, the accuracy of EBUS-TBNA in nodes sampled <10 mm (96.7% vs. 95.7% and 95.3% accuracy, compared with <20 mm and >20 mm, respectively) did not differ significantly.

This study also highlights the limitations of PET in radiological staging.[7] In nodes with low PET activity (SUV < 4), EBUS-TBNA still had 33% sensitivity with a 15% prevalence of malignancy. This is in keeping with Shingyoji *et al.* who noted 35% sensitivity for EBUS in PET negative nodes, albeit of smaller size.[5] In high PET active nodes (SUV > 4), EBUS-TBNA only had 79% sensitivity, with a prevalence of malignancy of only 70%. Therefore, sampling of nodes with low PET avidity is recommended, as malignancy may sometimes be present despite the lack of PET avidity.[7] Further studies are needed to explore the prognosis and clinical implications of PET negative mediastinal metastases. Sampling of PET active nodes is also advisable to confirm N stage as mediastinal metastases are not always present in PET avid nodes and some cases will be downstaged.[7]

In contrast to published data, neck ultrasound biopsy had no positive utility to diagnose N3 disease in this study and was performed in only 15% of cases with bulky mediastinal disease.[4] The reasons for our contradictory findings compared to Kumaran *et al.*'s are difficult to explain, although 18% of the malignant cases in Kumaran *et al.*'s study resulted from SCLC, which may be more readily detected and/or accessible by neck ultrasound biopsy (Medford AR, 2007, unpublished data).[4] In addition, there was no evidence of neck nodes in 39% of the patients in Kumaran *et al.*'s study, despite N2 and N3 mediastinal disease on CT.[4]

We have confirmed a high mutation testing success rate (no failures) consistent with our previous work,[11] and a high diagnostic utility of EBUS-TBNA without the need for rapid on-site evaluation for cytology, traditionally used for conventional TBNA but also for EBUS.[17,18] Using formalin baskets rather than liquid cytology bottles more commonly used in most centers by cytopathologists,[5–8] we have demonstrated that immunohistochemical techniques can achieve a high success rate in specimen analysis without the need for cytospins to create a cell block.[9–11] We have confirmed the utility of EBUS-TBNA, including for the diagnosis of lymphoma (12 cases), without the use of flow cytometry and obviating the need for larger samples via mediastinoscopy. The utility in lymphoma may partly result from developments in larger EBUS-TBNA needle gauges, specifically the 21-gauge needle and a recent 19-gauge needle (Medford AR, 2016, unpublished data).[10]

The strength of this study is in its real world design. The same three trained operators made all EBUS nodal measurements in the same manner. We were rigorous in assuming PET positive nodes negative at EBUS to be false negatives, as not all PET positive nodes were malignant in our study and all true negative cases underwent careful clinical follow-up for 12 months. The same two lung pathologists with experience in EBUS-TBNA pathology analyzed all EBUS-TBNA samples and all primary EBUS-TBNA operators were experienced, minimizing any operator-related factors.[19,20]

We acknowledge the limitations of this retrospective, observational, single center study. True positive cases of malignancy at EBUS-TBNA were not confirmed by surgical sampling and we acknowledge that false positives have occasionally been observed following TBNA and EBUS-TBNA in the literature.[21–23] The number of PET nodal SUV data were limited by incomplete reporting and lack of availability of all PET scans. Nodal size calculation at EBUS may be subject to variation, depending on the quality of ultrasound imaging.

In summary, EBUS-TBNA is increasingly used to avoid invasive metastatic biopsies. Diagnostic accuracy of EBUS-TBNA was not affected by NSCLC cancer stage or nodal size. In nodes with lower PET SUV, EBUS has sensitivity of 33% and in high SUV nodes, sensitivity of only 79%, indicating the limitations of radiological staging and the need for tissue sampling. Neck ultrasound may not be as useful as first thought when CT evidence of mediastinal N2 or N3 disease exists. The clinical implications of PET negative EBUS positive nodes require further study.

Disclosure

No authors report any conflict of interest.

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