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REVIEW

Effectiveness and safety of endobronchial ultrasound–transbronchial needle aspiration: a systematic review

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ABSTRACT: The aim of the present systematic review was to assess the effectiveness and safety of real time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS–TBNA) in patients with suspected or known bronchopulmonary carcinoma, as well as in other clinical indications presented by lymphatic adenopathies.

A systematic review was carried out in November 2007 and updated in April 2008 using the main databases. Inclusion and exclusion criteria were applied to the papers retrieved.

A total of 20 publications were included. Of these, 14 were original studies that investigated the clinical usefulness of the technique in visualising and staging lymph nodes in patients with suspected or established lung cancer. Sensitivity ranged 85–100% and negative predictive value ranged 11–97.4%. Three studies assessed the clinical usefulness of the technique in the diagnosis of sarcoidosis. EBUS–TBNA was diagnostic in 88–93% of patients. One retrospective study evaluated the use of EBUS–TBNA in the diagnosis of lymphoma. None of the studies included in the present review reported important complications.

Endobronchial ultrasound-guided transbronchial needle aspiration is a safe and highly accurate procedure for the examination and staging of mediastinal and hilar lymph nodes in patients with known or suspected lung malignancy. The evidence is promising for sarcoidosis but is not sufficient for lymphoma.

KEYWORDS: Diagnostic procedures, endobronchial ultrasound-guided transbronchial needle aspiration, endobronchial ultrasound guided transbronchial needle aspiration of lung neoplasms, endobronchial ultrasound real-time transbronchial needle aspiration

Lung cancer is the leading cause of death due to malignant neoplasms worldwide [1]. In European Union (EU) countries, this disease is the leading cause of cancer mortality in men and the fourth-leading cause in women after breast, intestinal and colorectal cancer. Nonsmall cell lung cancer (NSCLC) is the most common form of lung cancer and prognosis and treatment is basically determined by disease stage at diagnosis. Survival at 5 yrs ranges 5–55% depending upon whether patients present lymph node station N3, N2 or N1 disease [2]. The existence of metastatic contralateral adenopathies (N3) contraindicates surgery.

Noninvasive imaging techniques, such as computerised tomography (CT) and, more recently, positron emission tomography (PET), are the standard examinations for the assessment of mediastinal adenopathies. Although these techniques are highly sensitive for detecting enlargement of lymph nodes, their diagnostic accuracy in distinguishing between malignant and benign nodes is often regarded as insufficient for taking clinical decisions [3]. To date, mediastinoscopy has been considered the reference technique for mediastinal staging. Although mean sensitivity stands at ~81%, mediastinoscopy is a highly invasive technique, which requires general anaesthesia, is costly, and has a complication rate in the order of 2–3% [4].

Despite the fact that it has existed for >20 yrs [5], ''blind'' transbronchial needle aspiration (TBNA), guided by static CT images, has been little used, possibly due to the low sensitivity that it has shown in some studies [6]. With the appearance of the radial probe for endobronchial

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ultrasonography (EBUS) in 1999, sensitivity for diagnosing mediastinal nodes appears to have increased, yet results have been very variable [7, 8]. This technique uses a radial scanning ultrasonic miniprobe that is inserted through a conventional bronchofibrescope channel and must be withdrawn for performing needle aspiration, entailing a risk of vascular puncture or sampling the wrong lesion. Recently, a variant of the technique that solves this problem has been developed. It uses an ultrasonic bronchofibrescope with a convex probe (CP–EBUS; XBF-UC160F-OL8/BC-UC260F-OL8; Olympus Medical Systems, Tokyo, Japan) that allows for real-time needle aspiration of mediastinal and hilar lymph nodes guided by ultrasound images [9]. This technique, known as real-time EBUS–TBNA, is minimally invasive and has the potential to replace mediastinoscopy, since it enables the same part of the mediastinum to be accessed. EBUS–TBNA successfully obtained the EU CE marking in July 2004 and US Food and Drug Administration approval in March 2006 [10].

By conducting a systematic review, the present authors sought to compare and assess the effectiveness and safety of EBUS–TBNA in patients with suspected or known bronchopulmonary carcinoma, as well as in other clinical indications presented by lymphatic adenopathies.

METHODS

Bibliographic search

For study purposes, a bibliographic search of the medical literature was conducted in November 2007 and updated in April 2008. No time limits were specified and the following biomedical databases were searched: MEDLINE; EMBASE (Elsevier); ISI Web of Knowledge; Cochrane Library Plus; and National Health Service Centre for Reviews and Dissemination. A common search strategy was used for all databases, employing the terms (''endobronchial ultrasound'' OR ''endobronchial ultrasonography'' OR ''EBUS'' OR ''endobronchial ultrasound-guided'') AND (''TBNA'' OR ''transbronchial needle aspiration''). To complete the search, general information was located *via* the Google search engine, and a manual search was made of all bibliographic references cited in the original papers included.

Selection of papers and classification of scientific evidence

Potentially relevant papers were selected by perusing the abstracts yielded by the search and definitive inclusion was decided based on pre-established selection criteria. Only original papers in English, Spanish, French, Italian or Portuguese published in journals with a peer review process were included. Studies with <10 patients, studies that did not use at least one comparison and/or reference technique and studies that failed to furnish results on effectiveness, safety, or clinical management of patients were excluded. The results of radial endobronchial ultrasonography or EBUS applications other than CP–EBUS were not contemplated. The quality of the evidence was evaluated using the scientific evidence classification scale of the UK National Institute for Health and Clinical Excellence (NICE) [11] for studies of diagnostic validity.

RESULTS

After eliminating duplicates, the primary bibliographic search of biomedical literature databases yielded a total of 102 references. A total of 20 papers were finally selected, including five additional papers found after updating the search on April 2008. In total, 14 papers investigated bronchopulmonary carcinoma.

Effectiveness in bronchopulmonary carcinoma

Two evidence-based clinical practice guidelines on initial diagnosis and mediastinal staging of lung cancer and 14 original studies that examined the usefulness of EBUS–TBNA in the diagnosis and staging of bronchopulmonary cancer were retrieved. Study design was prospective in 12 studies and retrospective in two studies. Sample size ranged 18–502 patients. Seven of the largest-sized prospective studies were conducted by the Japanese group of YASUFUKU and co-workers [9, 12–14] and the multicentre group of HERTH and co-workers [15–17] with main contributions from Germany, Denmark and the USA. Table 1 summarises the characteristics of all original studies along with the main results.

The largest-scale prospective original study published on lung cancer was undertaken by the working group HERTH *et al.* [15] in 2006 and covered 502 patients with mediastinal and hilar adenopathies. The sensitivity and negative predictive value (NPV) of EBUS–TBNA for detecting malignancy were 94% and 11% respectively. This same group carried out another investigation in the same year to investigate the performance of EBUS–TBNA in the staging of patients with suspected tumours of pulmonary origin (tumour stage T1 to T4) as evidenced by CT, but without enlargement of lymph nodes (nodes measuring <1 cm) [16]. In this second study, which included 100 consecutive patients, sensitivity and NPV were 92.3% and 96.3% respectively. In another study undertaken very recently, HERTH *et al.* [17] determined the results of EBUS–TBNA in sampling mediastinal lymph nodes in 100 patients with NSCLC, radiologically normal mediastinum and no PET activity. Comparing all results with those based on surgical staging, the sensitivity for detecting malignancy was 89% and NPV was 98.9%.

WALLACE *et al.* [19] are responsible for the second-largest prospective study published on lung cancer diagnosis and staging. It included 150 patients with known or suspected lung cancer based on a lung or mediastinal abnormality on CT but with no proven extrathoracic metastases. EBUS–TBNA and transoesophageal ultrasonography (EUS)-guided fine needle aspiration (FNA) showed the same sensitivity (69%) and NPV (88%). TBNA alone had lower values (36% and 78%, respectively). The combination of EBUS and EUS obtained a sensitivity of 93% and an NPV 97%. In the subgroup of 60 patients with negative results on CT and PET, the estimated sensitivities of EUS–FNA, EBUS–FNA and EUS plus EBUS were 67%, 50% and 75%, respectively. NPVs were 92%, 89% and 94%, respectively. Another recent study carried out by LEE *et al.* [18] included patients with strongly suspected or histologically confirmed potentially operable NSCLC with lymph nodes of 5–20 mm on chest CT accessible by EBUS. Considering surgical–pathological staging as the gold standard, the sensitivity and NPV of EBUS were 93.8% and 96.9%, respectively.

Recently, BAUWENS *et al.* [20] investigated the value of EBUS–TBNA in 106 patients with suspected or proven lung cancer and fluorodeoxyglucose (FDG)–PET-positive mediastinal adenopathy. In this subset of patients, the sensitivity and NPV for staging mediastinal N1, N2 or N3 lesions were 95% and 91%,

TABLE 1 Results of studies that assess the effectiveness and safety of endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) in bronchopulmonary cancer

First author [ref]	Type of study	Patients/procedures included	Reference/comparison test	Diagnostic performance				P	Adequate sample	Safety
				S	Sp	PPV	NPV			
Lee [18]#	Prospective	91 patients with strongly suspected or histologically confirmed potential NSCLC with lymph nodes accessible to EBUS–TBNA (5–20 mm on CT). Exclusion of M1 disease, inoperable T4 disease, N3 disease with spread to supra-clavicular lymph node, lymph nodes >2 cm or extranodal invasion.	Cytology results in positive cases Surgery (open thoracotomy or video-assisted thoracic surgery) in patients without mediastinal metastasis. No mediastinoscopy performed	93.8%	100%	100%	96.9%	42%	92%	
Wallace [19]¶	Prospective	138 consecutive patients with known or suspected lung cancer on the basis of CT abnormality but no proven extrathoracic metastases Blinded comparison	Pathological confirmation for positive results Surgical sampling by mediastinoscopy or thoracoscopy, open surgical exploration or 6–12 months of follow-up	PET 24% 90% CT 67% 53% TBNA 36% 100% 100% 78% EUS–FNA 69% 100% 100% 88% EBUS–TBNA 69% 100% 100% 88% EUS–FNA + EBUS–TBNA 93% 100% 100% 97%				28%	100%	No complications
Bauwens [20]#	Prospective collection and retrospective assessment	106 patients with proven lung cancer (staging) or suspected lung cancer on FDG–PET (33 combined PET/CT)	Cytology/histology results in positive cases Surgical staging (30 out of 46), diagnostic procedures or follow-up in negative cases Blind retrospective comparison	EBUS–TBNA (n=90 patients) 93% 100% 100% 91% FDG–PET (n=41 patients) 67% 100%				58%	94%	Side-effects, notably cough, seldom encountered
Vincent [21]#	Retrospective	152 procedures carried out in 152 patients with primary lung masses or/and mediastinal adenopathy	Cytology results in positive cases with or without surgical confirmation Mediastinoscopy, lung resection, CT, FDG–PET or metabolic activity	99.1%	100%	100%	97%	74.3%	95.4%	No complications
Herth [17]#	Prospective	97 patients highly suspicious for NSCLC with CT scans showing lymph nodes <1 cm and negative PET in mediastinum	Surgical results in all patients	89%	100%	100%	98.9%	9.2%		
Monsó [22]#	Prospective	67 patients with pulmonary neoplasms and mediastinal and/or lobular lymph nodes >5 mm on ultrasound	Cytology	Diagnostic yield 92.5%				55.2%	87.8%	No complications
Nakajima [14]#	Retrospective	43 patients with suspected metastasis of lung cancer and lymph nodes ⩾5 mm on CT	Cytology or histology results in positive cases Thoracotomy, thoracoscopy or clinical follow-up (⩾6 months)	92%	100%	100%	90%	53.5%	95.3%	No complications

TABLE 1 Continued.

First author [ref]	Type of study	Patients/procedures included	Reference/comparison test	Diagnostic performance				P	Adequate sample	Safety
				S	Sp	PPV	NPV			
HERTH [15]#	Prospective	502 patients with mediastinal or hilar adenopathies (>1 cm; unknown origin or staging of lung cancer, especially exclusion of N3 nodes)	Cytology in positive cases Surgery or clinical follow-up in negative cases	94%	100%		11%	98.2%	93.5%	No complications
HERTH [16]#	Prospective	100 patients with suspected tumour of pulmonary origin evidenced by CT (T1–T4), without enlargement of lymph nodes (measuring <1 cm) or diagnosis of suspected or known NSCLC	Mediastinoscopy (15%) or thoracotomy (85%) with resection of mediastinal nodes in all patients	92.3%	100%		96.3%	17%	100%	No complications
YASUFUKU [13]#	Prospective	102 patients with suspected or anatomopathologically-confirmed lung cancer who were considered candidates for curative thoracic surgery (patients with stage I, II, or clinical minimal IIIa disease). Extensive N2/N3 disease excluded	Thoracotomy performed or diagnosis made from dissection of lymph nodes in potentially operable patients, and follow-up conducted in other patients (N3 or extensive N2 disease).	EBUS–TBNA 92.3%	100%	100%	97.4%	100%	100%	No major complications
				CT 76.9%	55.3%	37%	87.5%			
				FDG–PET 80%	70.1%	46.5%	91.5%			
YASUFUKU [12]#	Prospective	108 patients with suspected NSCLC or proven lung cancer and enlarged mediastinal lymph nodes (>1 cm) or mediastinal lesions suspected of malignancy detected by CT (N2 or N3)	Positive cytologies regarded as final diagnosis Follow-up of the disease and confirmation by thoracic lymphadenopathy in negative cases	94.6%	100%	100%	89.5%	62.9%	97.2%	No complications
RINTOUL [23]#	Prospective	18 patients with suspected or known lung cancer and detection of nodular enlargement or presence of paratracheal or parabronchial masses on CT	Positive cytologies regarded as final diagnosis Benign results confirmed by surgery (n=4) or clinical follow-up (n=1)	85%	100%	100%	71.4%	72.2%	100%	No complications
VILMANN [24]#	Prospective	33 patients for staging of lung cancer (n=20) or diagnosis of mediastinal lesions (n=13)	Thoracotomy (n=9), clinical follow-up (n=19)	EBUS–TBNA 85%	100%		72%	93.9%	95%	No complications
				EUS–FNA 80%	100%		66%			
YASUFUKU [9]#	Prospective	70 patients with hilar and/or mediastinal lymphadenopathies (>1 cm) and with suspected or confirmed lung cancer.	Positive cytologies regarded as final diagnosis In benign results confirmation by thoracotomy or surgery (n=21) and by clinical follow-up (n=3)	95.7%	100%			68.5%	96%	No complications

S: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; P: prevalence of lymph node malignancy; NSCLC: nonsmall cell lung cancer; CT: computerised tomography; M: metastasis; T: tumour; N: lymph node; PET: positron emission tomography; EUS: transoesophageal ultrasonography; FNA: fine-needle aspiration; FDG: fluorodeoxyglucose. #: patient-based analysis; ¶: lesion-based analysis.

respectively. VINCENT *et al.* [21] also carried out a retrospective analysis of 152 patients to determine the additional value of EBUS–TBNA in comparison to staging with CT, PET and CT/PET. The results showed that EBUS–TBNA resulted in nodal status downstaging of 16% of the patients and upstaging in 9.75% of the patients.

The first study conducted by the group of YASUFUKU *et al.* [9] included 70 patients with hilar and/or mediastinal adenopathies measuring >1 cm on CT. EBUS–TBNA avoided thoracotomy in six patients and other invasive procedures, such as mediastinoscopy and thoracotomy, in 17 patients. The second study [12] furnished results on 108 consecutive patients with enlarged mediastinal lymph nodes (measuring >1 cm) or suspected mediastinal malignancy (N2 or N3) detected on CT. The sensitivity and NPV observed were 94.6% and 89.5% respectively. In the opinion of a group of chest surgeons, EBUS–TBNA avoided 29 mediastinoscopies, eight thoracotomies, four thoracoscopies and nine CT-guided percutaneous biopsies. A third study by this group [13] compared the efficacy of EBUS–TBNA against that of CT and FDG–PET. This study included 102 patients with suspected or anatomopathologically confirmed lung cancer who were considered candidates for curative thoracic surgery. The sensitivity and NPV of EBUS–TBNA for predicting the stage of mediastinal lymphatic nodes were 92.3 and 97.4%, respectively. Using CT, these same parameters were 76.9% and 87.5% respectively; FDG–PET produced values of 80%, and 91.5% respectively. The last study of this group [14] was a retrospective analysis of 106 patients with metastasis of lung cancer, in whom CT had shown nodes measuring ⩾5 mm. The sensitivity and NPV in 43 patients who underwent EBUS–TBNA were 92% and 95.3%.

The other two studies that assessed diagnosis or staging of lung cancer presented sensitivity and NPV above 85% and 70%, respectively [23, 24]. VILMANN *et al.* [24] compared the performance of EBUS–TBNA with that of EUS–FNA for assessment of mediastinal lesions. EBUS–TBNA diagnosed 11 cancers unidentified by EUS–FNA, and EUS–FNA diagnosed 12 cancers undetected by EBUS–TBNA. With the combination of the two techniques, diagnostic accuracy was 100%. RINTOUL *et al.* [23] reported the results of 18 patients evaluated by EBUS–TBNA with nodular enlargement or presence of paratracheal or parabronchial masses on the CT scan. EUS–FNA was used in six patients with enlarged lymph nodes in the posterior or inferior mediastinum and provided additional findings of nodular invasion in all cases.

The study of MONSÓ *et al.* [22] assessed the value of EBUS–TBNA exclusively for staging patients with mediastinal or lobular lymph nodes >5 mm found on ultrasound, obtaining a diagnostic yield of 92.5%.

Evidence-based clinical practice guidelines on initial diagnosis of lung cancer, recently published by the American College of Chest Physicians [25] recommend that diagnosis of patients with suspected small cell lung cancer based on clinical and radiological findings must be confirmed by the simplest method (sputum cytology, thoracocentesis, FNA, bronchoscopy including TBNA, EBUS–TBNA or oesophageal EUS–TBNA), as determined by patient presentation (grade of recommendation 1C). The clinical practice guidelines on mediastinal staging [26] conclude that staging by CT or PET is not sufficiently accurate for patients with discrete mediastinal lymph node enlargement. In patients with N2 or N3 node status, invasive techniques are needed for confirmation. The guidelines suggesting as reasonable transthoracic needle aspiration, TBNA, EBUS–TBNA or EUS–TBNA, given the appropriate experience and skills (grade of recommendation 1B). In general, mediastinoscopy is recommended for patients with a central tumour or N1 lymph node enlargement even though EUS–TBNA and EBUS–TBNA can be reasonable alternatives. A nonmalignant result from a needle technique should be further confirmed by mediastinoscopy (grade of recommendation 1B).

Effectiveness in other pathologies

Three prospective studies considered in the present review assessed the usefulness of EBUS–TBNA in patients with suspicion of sarcoidosis [27–29] (table 2). The largest-scale study included 65 patients [27]. EBUS–TBNA was diagnostic in 85–91.8% of patients with a final diagnosis of sarcoidosis. The NPVs found in two of these studies [27, 29] were 11% and 12.5%, respectively. In the investigation carried out by WONG *et al.* [27], 21.6% of the patients (11 out of 51) demonstrated with EBUS–TBNA to have sarcoidosis revealed benign transbronchial lung biopsy results. OKI *et al.* [28] obtained the same performance with EBUS–TBNA and TBNA.

One study has evaluated the usefulness of EBUS–TBNA in the diagnosis of lymphoma: this was a retrospective study that included 25 patients with idiopathic mediastinal adenopathies and suspected lymphomas [30]. EBUS–TBNA enabled a sample of lymph tissue to be obtained in 96% of the patients (24 out of 25). The sensitivity, specificity, positive predictive value (PPV) and NPV observed were 90.0%, 100%, 100% and 92.6%, respectively.

Safety

None of the studies reported serious complications. Only three studies reported having observed agitation [31], cough [20, 31], and presence of blood [9] at the puncture site.

Quality of the evidence

According to the NICE scale, the level of evidence was Ib in two studies carried out by HERTH *et al.* [16, 17] and III in all the remaining studies.

DISCUSSION

The results of the studies retrieved in the present systematic review indicate that the new real-time EBUS with needle aspiration technique is a safe and highly sensitive method for identifying neoplastic invasion of mediastinal and hilar lymph nodes in patients with suspected or known bronchopulmonary neoplasms. Sensitivity values exceeded 85% in all studies. Although EBUS–TBNA could avoid invasive surgery in an important percentage of patients (28–50%), the relatively high false negative rates documented in some studies highlight the need for negative results to be confirmed *via* other surgical techniques or procedures.

Diagnostic performance

EBUS with real-time needle aspiration has shown itself to be extremely useful in assessing nodular metastases. In three of the studies reviewed [13, 19, 20], imaging techniques,

TABLE 2 Results of studies that assess the effectiveness and safety of endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) in sarcoidosis and lymphoma

Author and year	Type of study	Patients included	Reference/comparison test	Diagnostic performance				P	Adequate sample	Safety
				S	Sp	PPV	NPV			
Diagnosis of sarcoidosis										
Wong [27]	Prospective	65 patients with clinical and radiological findings suggestive of sarcoidosis and enlargement of lymph and/or mediastinal nodes (>1 cm)	Positive cytologies taken as final diagnosis In benign results, mediastinoscopy (n=5), thoracoscopy (n=1) and clinical follow-up (n=3)	91.8%		87.5%#	11%#	100%	95.3%	No important complications
Oki [28]	Prospective	15 patients with clinical and radiological findings suggestive of sarcoidosis and enlargement of lymph and/or mediastinal nodes (>1 cm)	TBNA in all patients	Diagnostic performance of EBUS–TBNA 93% Diagnostic performance of TBNA 94%				93.3%		No complications
Garwood [29]	Prospective	50 patients with suspicion of sarcoidosis (90% with clinical symptoms and adenopathy on radiographic imaging)	Positive cytologies taken as final diagnosis In benign results, histology samples (obtained by EBUS–TBNA or transbronchial lung biopsy, endobronchial biopsy or in one case supraclavicular lymph node aspiration) or follow-up	88%	100%	100%	12.5%	98%	88%	No complications
Diagnosis of lymphoma										
Kennedy [30]	Retrospective	25 patients with suspected lymphoma (clinical, radiological data or other previous lymphoma)	Results of the biopsy and clinical and radiological follow-up of patients for 6 months	90.9%	100%	100%	92.6%	44%	96%	No complications

S: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; P: prevalence. #: For this calculation, four cases without definitive diagnosis were deemed positive.

fundamentally CT and FDG-PET, which are frequently used as initial staging methods, displayed a lower sensitivity and specificity than that observed for EBUS–TBNA. The findings of a recent meta-analysis [32] are also in line with the inferiority of imaging techniques in detecting mediastinal involvement: the estimated sensitivity and specificity of FDG–PET and CT were 83% and 92%, and 59% and 78%, respectively. Unlike imaging techniques, EBUS–TBNA enables the identification and sampling of lymph nodes $\leqslant$1 cm in size. Two studies carried out by HERTH *et al.* [16, 17] report sensitivities of 89% and 92%, respectively, among patients with no enlargement of lymph nodes on CT (measuring <1 cm), suggesting that this technique might have a special interest in such patients.

The sensitivity of real-time EBUS–TBNA for assessment of mediastinal and hilar metastasis seems to be equivalent or even superior to that of mediastinoscopy, the reference technique currently used to assess nodular metastases. According to the results of a recent pooled analysis, the sensitivity of mediastinoscopy ranges from 72–89% [33]. EBUS–TBNA could replace mediastinoscopy in an important percentage of cases, though, due to the low NPV observed in some studies, surgical techniques cannot be ruled out in negative cases.

The main limitation of EBUS–TBNA is its inability to visualise posterior nodes (stations 5, 7, 8 and 9) [13]. EUS–FNA is a complementary technique that enables visualisation of posterior nodes not visualised by EBUS–TBNA but does not allow the visualisation of the anterior mediastinum [13, 19]. Two studies [19, 24] support the theory that the combination of EBUS–TBNA and EUS–FNA could dispense with surgical techniques in the great majority of cases, but one of these studies includes only 20 patients [20] and the validity of both is diminished due to the lack of confirmation of all negative results using reference techniques such as mediastinoscopy and/or thoracoscopy. Additionally, WALLACE *et al.* [19] used lymph nodes, instead of patients, as the unit of analysis, so the possibility that study results are inflated cannot be dismissed [34].

Methodological shortcomings of the available literature

The lack of verification of the totality of results using a gold-standard test (surgery procedures) and the absence of adequate follow-up studies to assess the change in the therapeutic management of patients are important drawbacks when it comes to reaching definitive conclusions about the true usefulness of the EBUS–TBNA technique. With the exception of the two studies published by HERTH and co-workers [16, 17], the studies included used the gold standard solely to check negative cases. Although the present authors acknowledge that in usual clinical practice a positive result does not need to be confirmed by additional surgical procedures, which are very invasive, in initial studies assessing the diagnostic performance of EBUS–TBNA all results should have been verified by surgical pathological staging in order to really assess the diagnostic yield of the new procedure. Due to this absence of verification of positive EBUS–TBNA results in these studies, specificities and PPVs have not been reported, assuming that these values are 100%. To confirm negative cases, the studies used a range of reference tests (thoracotomy, thoracoscopy, mediastinoscopy, mediastinotomy or clinical follow-up), such that verification bias can also not be ruled out.

Among the studies presented in the current review, there is great heterogeneity in the size and type of nodes punctured, the method used for puncture and the number of aspirations made to obtain cytology/histology samples, and this too might influence diagnostic accuracy. According to LEE *et al.* [18], sensitivity ranges from 69.8–95.3% when the number of aspirations increases from 1 to 3, but remains constant afterwards.

Generalisability of the published results

There are other important sources of variations that limit the generalisability of these results. Firstly, studies are very heterogeneous in respect to tumour characteristics (suspicion of lung cancer or previously diagnosed patients referred for staging), the types of lung cancer included (small-cell lung cancer or NSCLC) and the location of the lymphadenopathy as evidenced by imaging techniques (N1, N2/N3). The majority of studies do not differentiate between these subgroups and this is an important drawback. Even though the current authors could find no observable differences in studies that exclusively enrolled patients with NSCLC [12, 13, 15, 17] or that primarily analyse mediastinal and hilar metastasis [9, 13, 17, 20] in comparison to those that include only patients with mediastinal metastases [12, 18, 24], additional studies are required to clarify the effectiveness of this test in different clinical situations.

The high prevalence of mediastinal involvement in the reviewed studies and the disease severity are other factors that may limit the extrapolation of results. With the exception of four studies [16–19], prevalence of lymph node malignancy was >50% (table 1) and the patients recruited displayed enlargement of lymph nodes (>1 cm). This might not represent the typical patient population. In a meta-analysis comparing PET with CT scanning for mediastinal staging, the prevalence of malignant lymph nodes was 37% [33]. In another recent meta-analysis comparing PET and CT scanning, the post-test probability for N2 disease was found to be 5% for lymph nodes measuring 10–15 mm on CT and 21% for lymph nodes measuring $\geqslant$16 mm, when patients had a negative FDG–PET [35]. Even though prevalence can be highly dependent on the pre-tests carried out in combination with CT (post-test probability of 62% with FDG–PET), it must be acknowledged that recruiting of patients with a high probability of suffering from the disease, of severe cases or of cases with appreciable enlargement of the lymph glands (>2 cm) can lead to an increase in sensitivity and PPV.

Result generalisability is also hampered by the lack of multicentre studies. Six out of the 14 studies retrieved that assessed the usefulness of EBUS–TBNA in the diagnosis and staging of bronchopulmonary carcinoma were conducted by the same research groups, suggesting that the latter have extensive practical experience in performing the procedure. It is readily acknowledged that EBUS–TBNA calls for in-depth, practical training in the interpretation of ultrasonographic images [36], and a lower degree of effectiveness and a greater proportion of adverse effects may thus be obtained by other, less-experienced teams. In fact, 45% of all the data available comes from the Heidelberg group of HERTH and co-workers [15–17], increasing to 60% if the patients of YASUFUKU and co-workers [9, 12–14] are included.

Conclusion

In summary, real-time endobronchial ultrasound-guided transbronchial needle aspiration is a technique of great interest for the identification and staging of mediastinal and hilar lymph nodes in patients with suspected and/or known bronchopulmonary neoplasm but its real value in clinical practice is still partly unknown. The present authors cite as an important limitation of the present work the absence of a meta-analysis, but felt that this task was at present practically impossible due to the great variability regarding selection criteria (cancer histology, severity of disease, location of the lymphadenopathy), procedure protocol or result interpretation. It is suggested that additional stratified analysis be carried out to establish diagnostic accuracy for different subgroups, especially for patients with nonsmall cell carcinoma and lymph node stations N2/N3, where staging is clinically relevant. Despite this device's apparent superiority over other existing procedures used for the same purpose, the present authors did not find suitably designed studies that compare these techniques against other alternative new techniques such as positron emission tomography–computed tomography, and this is needed in order to clarify the place that endobronchial ultrasound-guided transbronchial needle aspiration can occupy in the diagnostic algorithm. Appropriate follow-up studies are also called for to ascertain its usefulness in patient prognosis and therapeutic management. There is insufficient evidence, in terms of both -quality and quantity, to determine its usefulness in clinical indications other than that of lung cancer, although the published studies on sarcoidosis point to the effectiveness of endobronchial ultrasonography in diagnosing this disease.

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