CHAPTER 8

Diagnostic endoscopic investigations in lung cancer

N. Navani, S.M. Janes

Centre for Respiratory Research, University College London, London, UK.

Correspondence: N. Navani, Centre for Respiratory Research, University College London, Rayne Building, 5 University Street, London WC1E 6JJ, UK. Fax: 44 2073809476; E-mail: n.navani@ucl.ac.uk

Distinguishing nonsmall cell lung cancer (NSCLC) from small cell lung cancer (SCLC) is of paramount importance, since the treatment and prognosis of the cancers are often significantly different. SCLC is well known to exhibit massive lymphadenopathy, direct mediastinal invasion and paraneoplastic syndromes [1]. However, there is considerable clinical overlap between NSCLC and SCLC such that clinical differentiation is often not possible and pathological diagnosis is essential. A small number of patients who are unfit for any oncological or surgical treatment and are candidates for best supportive care only may not benefit from pathological diagnosis. In these patients, a clinical diagnosis of lung cancer may have to suffice on the basis of imaging alone. The remaining majority of patients undergo various investigations to determine the histological subtype. An initial diagnosis should be pursued from the most distal site of suspected disease in order to provide staging as well as diagnostic information.

Cytology or histology may be provided for pathological analysis, depending on the source and technique employed to generate the sample. Either histology or cytology can discriminate NSCLC from SCLC. Although histology may generally be preferred, cytological samples are also reliable, particularly for NSCLC. Meta-analysis of data from sputum, bronchoscopy and transthoracic needle aspiration compared cytology to histology samples for patients with NSCLC and SCLC [2]. The probability of diagnosing NSCLC in error on the basis of cytology was 0.02 (range 0.01–0.07); however, the converse is less robust. A diagnosis of SCLC had a probability of actually being a NSCLC of 0.09 (range 0–0.33). Therefore, if a diagnosis of SCLC is made on a cytological sample, but the clinical and radiological findings are discordant with the cytological diagnosis, then a histological biopsy should be obtained where possible [2].

In order to achieve a tissue diagnosis of lung cancer, patients may undergo sputum cytology analysis, bronchoscopy, transbronchial needle aspiration (with or without endobronchial ultrasound guidance), endoscopic ultrasound fine needle aspiration, or surgical procedures; these are discussed below. Radiologically guided transthoracic sampling is discussed in chapter 7 in this *European Respiratory Monograph*.

Sputum cytology

Sputum cytology is a noninvasive method of diagnosing lung cancer by detecting exfoliated malignant cells (fig. 1). Sensitivity is higher for central squamous cell and small cell carcinomas, bloody sputum, tumours >2.4 cm in size and in patients with low forced expiratory volume in 1 s values [3]. Yield may be maximised by collecting at least

Eur Respir Mon, 2009, 44, 136–149. Printed in UK - all rights reserved. Copyright ERS Journals Ltd 2009; European Respiratory Monograph; ISSN 1025-448x.

three samples [4]. A meta-analysis of 29,245 patients who underwent sputum cytology analysis demonstrated a pooled sensitivity of 66% and specificity of 99% [2]. The indication for sputum analysis varied considerably and the pooled prevalence of disease was only 15%. One study specifically evaluated sputum cytology in patients with suspected lung cancer and found a sensitivity of 87% and specificity of 90% [5]. However, much of the published data came from centres that have established protocols in sputum analysis. It is likely that sensitivity in routine practice is lower.

Abnormal cells may arise from anywhere in the aero-digestive tract or from pre-invasive lesions, such that a false-positive rate for sputum cytology of ~9% is observed when the disease prevalence is 15% [2]. Furthermore, discordant results have occurred between sputum cytology and histological findings at bronchoscopy. Therefore, sputum analysis as a sole test is reserved for patients who are unable or unwilling to undergo further diagnostic procedures.

Bronchoscopy

Fibreoptic bronchoscopy was first performed in the 1960s in Japan and is now a standard investigation worldwide for the diagnosis and staging of lung cancer. Advances in microtechnology have resulted in fibreoptic bronchoscopes evolving into video-bronchoscopes, which are increasingly used in clinical practice (fig. 2a). The procedure is most commonly performed under conscious sedation with topical anaesthesia in the outpatient setting.

Yield from bronchoscopy is primarily determined by the location of the tumour. Bronchoscopy has a higher sensitivity for the diagnosis of central tumours compared to peripheral tumours and is the primary investigation of choice for centrally located lung cancer. Central lesions (up to a segmental bronchus) may present at bronchoscopy with an exophytic endobronchial mass, tumour infiltration of the bronchial wall or extrinsic

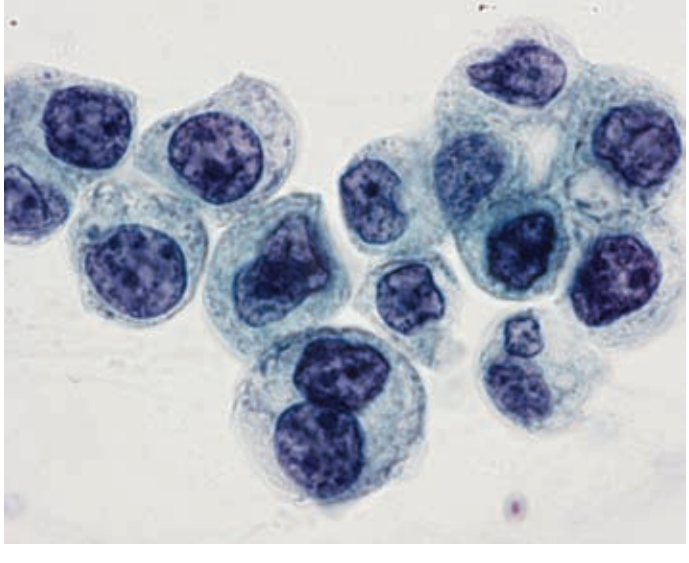

Fig. 1. – Sputum showing adenocarcinoma/alveolar cell carcinoma. A cluster of glandular cells with eccentric nuclei, mild anisonucleosis, prominent nucleoli, irregular nuclear margins and well-defined nonphagocytic cytoplasm. (Papanicoulaou stain; magnification $\times$1,000, using oil immersion).

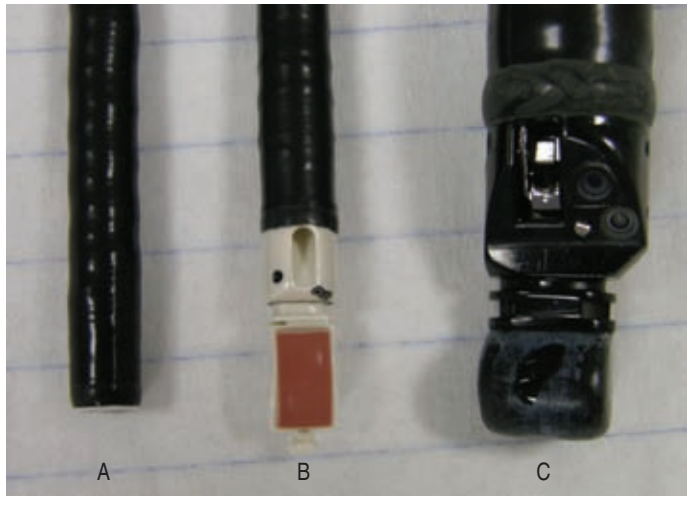

Fig. 2. – A) Standard videobronchoscope. B) Endobronchial ultrasound, which allows real-time ultrasound-guided transbronchial needle aspiration. C) Endoscopic ultrasound, which allows real-time ultrasound guided fine-needle aspiration and biopsy.

compression by a peribronchial mass. Diagnostic yield is highest when the tumour is visible. Meta-analysis of 4,507 patients with central disease from 35 studies has demonstrated a pooled sensitivity of 88% [2].

At bronchoscopy, a combination of biopsy, brush, wash and bronchoalveolar lavage (BAL) is performed. Biopsy of a visible endobronchial lesion is performed by introducing forceps into the working channel of a bronchoscope and carrying out the biopsy under direct vision. Yield for this technique in isolation is reported as 74%, with a range of 50–92% from 20 studies [6]. At least three biopsies of the visible lesion should be performed. Bronchial brushings are achieved by placing a dedicated brush within a sheath into the working channel of the bronchoscope. When the site for sampling is located, the brush is extended beyond the sheath and moved to and fro on the target area. Samples for cytological analysis are obtained and smeared directly onto glass slides. When the lesion is visible, a diagnosis may be obtained by bronchial brushings in ~60% of cases (range 23–92%) [6]. Bronchial washings occasionally add to the diagnostic yield of biopsy and brushings in central tumours. Saline is instilled into the bronchial tree and a sample is collected for cytological (and microbiological) analysis. BAL is performed by obtaining a ''wedge'' of the bronchoscope into the most distal airway. 120–180 mL of saline is then introduced into the distal airway. The saline is returned by suction, allowing evaluation of the distal airways and alveoli.

Bronchoscopy has a more limited role in the diagnosis of peripheral lung lesions, which arise distal to the segmental bronchus. It may retain a place in the diagnosis of lung lesions, which are shown on computed tomography (CT) to have a bronchus extending into them [7]. For peripheral lung lesions, transbronchial biopsies provide the highest sensitivity (57% from 21 studies) [2]. Bronchial brushings and BAL have a pooled sensitivity of 54 and 43%, respectively. Some centres also employ fluoroscopy to direct bronchoscopic procedures, which may improve the diagnostic yield of peripheral lesions [8]. Transbronchial biopsy of lung parenchyma (with or without screening) is useful in the diagnosis of lymphangitis carcinomatosis.

Autofluorescence bronchoscopy

The advent of autofluorescence bronchoscopy (AFB), which uses blue light rather than the standard white light bronchoscopy (WLB), allows identification of pre-invasive lesions that may be missed by usual techniques. Observations in the lung have shown that dysplasia, carcinoma *in situ* (CIS), and microinvasive carcinomas exhibit weaker green fluorescence than normal tissues when illuminated by blue light. Normal endobronchial mucosa therefore appears green while the abnormal areas appear purplish (using the D-Light AF system; Stortz, Tuttlingen, Germany). Several systems are in clinical use. These include light-induced fluorescence endoscopy (LIFE; Xillix Technologies, Vancouver, Canada), as well as integrated AFB and white light bronchoscopes (D-Light AF system and the SAFE 1000 System; Pentax, Tokyo, Japan). The systems appear to be broadly equivalent clinically [9, 10]. Much of the reported data on AFB surrounds the use of the LIFE system and demonstrates the superiority of AFB over WLB for the detection of pre-invasive lesions. A multi-centre randomised study using the D-Light AF device recruited 1,173 participants who were current smokers, >40 yrs of age with at least 20 pack-yrs of smoking and had either symptoms concerning for lung carcinoma (new cough, haemoptysis, or new dyspnoea) or radiological suspicion for carcinoma [11]. Participants were randomised to WLB only, or to WLB plus AFB examination. Only 3.9% of patients had high-grade dysplasia or CIS. Despite the low incidence of detected disease, combined AFB and WLB improved detection of dysplastic lesions by a factor of 2.1 over WLB. However, there was no statistical difference between WLB and combined WLB and AFB in the rate of detection of CIS. The authors concluded that the study confirmed the hypothesis that AFB and WLB are superior to WLB alone for the detection of pre-invasive disease. However, the study did demonstrate a low positive predictive value (PPV) of 25.1% and a low specificity of 58.4% [11]. Similarly low PPVs have been confirmed in other studies.

One explanation for the low specificity of abnormal AF is that inflammation, metaplasia and low-grade dysplasia may display abnormal AF and may be difficult to distinguish from high-grade lesions. Furthermore, the natural history of high-grade lesions remains unclear. One study of 22 patients by GEORGE *et al.* [12] followed pre-invasive lesions with AFB every 4–12 months with CT scan annually. The risk of developing lung cancer in patients with a high-grade lesion was 33% at 1 yr and 54% at 2 yrs [12]. Interestingly, some of the high-grade pre-invasive lesions regressed. Therefore, the best management of high grade pre-invasive lesions remains unresolved and the role of AFB in the early detection of lung cancer requires clarification. Currently AFB may be indicated following the detection of moderate dysplasia, severe dysplasia, CIS, or invasive carcinoma grades in sputum cytology [13], particularly in the context of normal WLB.

Bronchoscopy as a staging tool

In addition to providing pathological information, bronchoscopy also allows assessment of the location and extent of the endobronchial lesion (which may impact significantly on treatment). Careful assessment of the vocal cords is mandatory, as the presence of vocal cord palsy may provide evidence of mediastinal invasion (and inoperability) in a patient with the appropriate radiological features. Bronchoscopy also allows for accurate assessment of the location of an endobronchial tumour within the bronchial tree. NSCLCs involving the carina are staged as T4 disease and are not considered as candidates for surgery. If a tumour is measured to be within 2 cm distal of

the carina, it is currently staged as a T3 lesion. If the NSCLC is in a main bronchus and >2 cm from the carina, it is deemed a T2 lesion.

Transbronchial needle aspiration

Blind transbronchial needle aspiration (TBNA) is a safe but underutilised procedure for mediastinal lymph node staging and was first described in 1978 [14]. It is planned with the aid of CT (and positron emission tomography (PET) if available) to identify the lymph node to be sampled and to note its relationship to bronchial landmarks. During standard bronchoscopy, a TBNA needle is introduced into the working channel of the bronchoscope. The needle punctures the bronchial wall allowing the mediastinal lymph node to be aspirated. This is most commonly performed in the subcarinal lymph node station, but lower paratracheal and hilar lymph nodes can also be sampled. The procedure may be carried out with an 18, 19 or 22 gauge needle.

A meta-analysis of patients undergoing TBNA showed a pooled sensitivity as low as 39% for the technique when the prevalence of mediastinal metastases was 34% [15]. Several modifiable factors have been shown to optimise the diagnostic yield of blind TBNA. First, at least five and up to seven passes in the same area may maximise diagnostic tissue [16]. Secondly, the presence of a cytologist within the endoscopy suite to evaluate aspirates as they are produced, may significantly improve accuracy [17]. Rapid on-site evaluation of samples allows an immediate diagnosis of malignancy or can confirm the adequacy of a specimen by identifying lymphocytes. Thirdly, the use of CT fluoroscopy allows imaging of MLN during TBNA and may improve yield [18]. Finally, since blind TBNA is highly operator dependent, focused education and experience in the technique are invaluable in improving results [19]. The highest yield is seen in lymph nodes >1 cm in the right paratracheal and subcarinal locations [20], and it is this patient group that may benefit most from TBNA.

Assessment of the endobronchial tree is performed at the same sitting as TBNA. In addition, it is a relatively inexpensive and well-tolerated outpatient procedure that can be performed under conscious sedation. A positive result from TBNA may prevent further invasive tests, particularly when combined with PET [21]. However, its generally low diagnostic yield and negative predictive value mean that TBNA has been slow to be embraced by respiratory physicians. Further invasive sampling always remains necessary in the event of a negative or nondiagnostic sample.

Endobronchial ultrasound

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an important new and minimally invasive technique for the diagnosis and staging of NSCLC. A catheter with a radial ultrasound mini-probe at the tip was the first to be developed. The catheter is placed in the biopsy channel of the bronchoscope. When the lymph node to be sampled has been identified using the radial ultrasound scanner, the catheter was withdrawn and replaced with a conventional TBNA needle. The lymph node is then aspirated blindly. Conflicting evidence exists as to whether EBUS-TBNA using the mini-probe is superior to conventional blind TBNA. More recently, an integrated curvilinear ultrasound bronchoscope has been developed (fig. 2b) and allows TBNA under real-time ultrasound guidance. This progress in technology allows the pulmonologist and thoracic surgeon for the first time to sample the mediastinum in a minimally invasive manner under direct vision and with high sensitivity [22].

The integrated scope has a convex ultrasound transducer at the distal end with a 7.5 MHz frequency and allows visualisation of parabronchial structures up to a depth of 5 cm. The outer diameter of the insertion tube is 6.2 mm and that of the tip is 6.9 mm. The distal end of the scope can be adjusted 160° upwards and 90° downward and the endoscope has a biopsy channel of 2 mm. The fibreoptic lens is oblique forward-viewing at 30° and the ultrasound image is in parallel to the scope, with a scanning angle of 50°. After intubation with the EBUS scope, a saline-filled balloon is inflated to maintain contact with the airway wall. Vascular structures are located using power Doppler imaging. Once the target lymph node is identified on the ultrasonography monitor, a dedicated 22 gauge needle is inserted into the working channel. The needle can then be observed to pierce and enter the lymph node under direct ultrasound vision. Suction is applied and the needle is moved to and fro within the lesion. Using this technique, mediastinal lymph nodes as small as 5 mm may be sampled. The procedure is carried out in the ambulatory setting, under conscious sedation or general anaesthesia. Lymph nodes that may represent N3 (contralateral mediastinal or hilar) metastases are sampled first, followed by N2 nodes and finally ipsilateral hilar nodes, so that any contamination will not result in false over-staging. A diagnostic plateau may be reached after three passes per lymph node [23].

EBUS-TBNA affords access to the upper and lower paratracheal nodes, the subcarinal lymph node station and the hilar lymph nodes (fig. 3). Cytological samples are produced, although occasionally histological cores may be obtained. Currently, one single centre trial has compared blind TBNA to EBUS-TBNA and demonstrated that the ultrasound-guided technique has a higher sensitivity for detecting malignant mediastinal nodes [24]. In addition, a growing body of cohort series have illustrated that EBUS-TBNA is a safe and efficacious procedure for the detection of mediastinal metastases. In the largest cohort of 502 patients, the sensitivity of EBUS-TBNA for diagnosing mediastinal disease was 94% in the context of a disease prevalence of 98% [26]. A meta-analysis of the first 918 patients from expert centres revealed a pooled sensitivity of 90%, when the disease prevalence was 68% (table 1) [27].

Importantly, the false negative rate of EBUS-TBNA is currently 20% and therefore negative or benign aspirates should be followed by further invasive mediastinal staging [27]. No complications of the technique have been reported, and the leaning curve may be a short as 10 cases [29]. EBUS-TBNA has several advantages over standard mediastinoscopy. It is less invasive, can be performed without general anaesthetic, enables visualisation of the endobronchial tree and allows access to hilar as well as mediastinal nodes. In the first study to compare EBUS-TBNA with mediastinoscopy, ERNST *et al.* [30] performed both procedures on 66 patients. In this study [30], the diagnostic yield from EBUS-TBNA was 91% compared to 78% from mediastinoscopy. The technique may even be able to detect metastatic disease in mediastinal lymph nodes <1 cm in short axis that are negative on PET scanning [31]. EBUS-TBNA is therefore a safe and efficacious procedure for the diagnosis of mediastinal metastases of NSCLC. However, the relatively low negative predictive value, as well as the lack of randomised controlled trials and healthcare cost data, mean that the precise role of EBUS-TBNA in the diagnostic and staging algorithm for NSCLC requires clarification. Currently, it is most commonly employed as an alternative to mediastinoscopy, with the caveat that negative results are followed by surgical sampling.

In addition to the mediastinal staging of NSCLC, EBUS-TBNA may have an important role in the diagnosis of para-tracheal and para-bronchial lesions. These primary lesions lie extrinsic to the bronchial wall and are not visible at standard bronchoscopy. Two retrospective studies totalling 95 patients have suggested that EBUS-TBNA has a high sensitivity for the diagnosis of these lung lesions, reducing the need for transthoracic or surgical biopsy [32, 33].

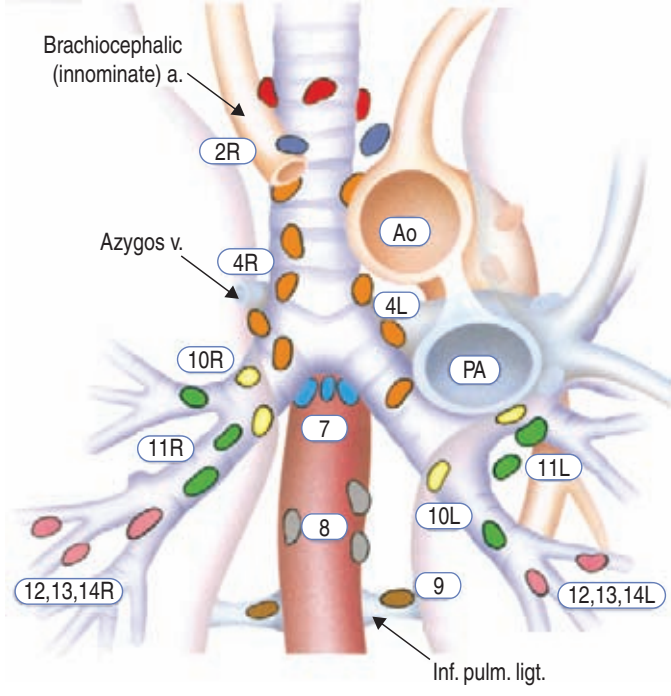

Fig. 3. – Lymph node stations (depicted numerically) that are accessed by endobronchial ultrasound-guided transbronchial needle aspiration and endoscopic ultrasound-guided fine-needle aspiration. Ao: aorta; PA: pulmonary artery; R: right; L: left; a.: artery; v.: vein; inft. pulm. ligt.: inferior pulmonary ligament. Reproduced from [24], with permission from the publisher.

A further important application of linear EBUS-TBNA may be the re-staging of mediastinal disease following neo-adjuvant treatment. Repeat surgical evaluation of the mediastinum is often complicated by adhesions and is performed by few thoracic surgeons. EBUS-TBNA however, may be repeated in the same patient without

Table 1. – Sensitivity, specificity and false negative rates for diagnostic endoscopic investigations in lung cancer

Investigation	Sensitivity	Specificity	False negative rate	Disease prevalence	Comments
Sputum cytology	66	99	6	15	Reserved for patients unable or unwilling to undergo more invasive tests
Bronchoscopy (for central tumours)	88	100	12	100	Standard procedure for the diagnosis of central tumours
TBNA (for mediastinal disease)	78	99	28	75	Highly operator dependent
EBUS-TBNA (for mediastinal disease)	90	100	20	68	Access to para-bronchial mediastinal and hilar lesions
EUS-FNA (for mediastinal disease)	84	99.5	19	61	Access to left-sided and posterior mediastinal lesions

Data are presented as %. TBNA: transbronchial needle aspiration; EBUS-TBNA: endobronchial ultrasound-guided TBNA; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration. Data are taken from [2] and [27]. Table adapted from [28], with permission from the publisher.

difficulty. HERTH *et al.* [34] evaluated 126 consecutive patients with stage IIIA (N2) disease who had undergone induction chemotherapy. EBUS-TBNA had a sensitivity of 76% for detecting residual mediastinal metastases and is therefore a promising tool for mediastinal re-staging, although corroborating data from other centres is required.

Although real-time linear EBUS-TBNA using an integrated scope has largely superseded the radial mini-probe technique for the diagnosis of mediastinal lymph nodes and para-bronchial lesions, the mini-probe may retain a role in the diagnosis of peripheral lung lesions and in the assessment of airway invasion. A mini-probe placed in a distal airway may identify peripheral pulmonary lesions. In one study of 50 patients with peripheral pulmonary lesions inaccessible to standard bronchoscopy, a histological diagnosis was made in 31 patients and was effective in diagnosing lesions >2 cm in diameter [35]. This technique of guiding transbronchial biopsies with the EBUS mini-probe may be particularly useful in patients with peripheral lesions in whom percutaneous transthoracic biopsy is hazardous due to poor respiratory reserve and does not incur the radiation exposure required with fluoroscopy. The radial view provided by the mini-probe may also be employed to assess the depth of invasion of centrally located early stage lung cancer and therefore accurately select those patients who may benefit most from photodynamic therapy [36].

Endoscopic ultrasound

EUS-FNA is an important investigation for the mediastinal staging of NSCLC. The procedure is commonly performed by gastroenterologists and has been increasingly utilised for sampling the mediastinum in the last 10 yrs. A modified endoscope with an ultrasound scanner at its distal end is placed in the oesophagus under conscious sedation. Radial echo-endoscopes provide cross-sectional imaging and may be used in the assessment of mediastinal invasion of primary tumours. One study demonstrated a sensitivity of 88%, but over-staging occurred in 30% of patients limiting its clinical use [37]. Radial echo-endoscopes do not allow tissue samples to be obtained and have been largely replaced by an integrated linear ultrasound probe that allows sampling of the mediastinum under direct vision (fig. 2c). Aspiration with a 22-gauge, adjustable-length needle is performed through the wall of the oesophagus. Due to the anatomical location of the oesophagus, EUS-FNA provides minimally invasive access to left paratracheal, aorto-pulmonary window, subcarinal and para-oesophageal lymph nodes (fig. 3). In addition, EUS-FNA allows aspiration of the celiac axis nodes, left lobe of the liver and left adrenal gland providing crucial further diagnostic and staging information.

Cytology samples are obtained by EUS-FNA with a 22-gauge needle. However, in lymph nodes >2 cm in their short axis, core samples for histopathological analysis may be obtained, using a 19-gauge Trucut needle (Wilson-Cook, Winston-Salem, NC, USA). The availability of rapid on-site evaluation of samples may improve diagnostic yield from the procedure. This involves a cytologist being present in the endoscopy suite and by using rapid staining techniques (*e.g.* modified May–Grunwald–Giemsa stain), the cytologist is able to make an immediate assessment of the sample with high accuracy, eliminating inconclusive or inadequate samples [38]. This arrangement has also been shown to be cost-effective [39]. Diagnostic yield is maximised by performing 3–5 passes.

Studies have demonstrated that EUS-FNA is a safe and efficacious procedure for the mediastinal staging of NSCLC. A meta-analysis of 16 studies, totalling 1,003 patients demonstrated a pooled sensitivity of 84% (range 45–100%) and specificity of 99.5% when the prevalence of mediastinal disease was 61% [28]. The false negative rate from

the pooled data was 19% (table 1). In an important study, SINGH *et al.* [40] employed EUS-FNA as a first test after CT scan in 93 patients. By sampling the mediastinum and extra-thoracic sites, they were able to provide a tissue diagnosis and stage in a single test in 70% of cases. Metastases to coeliac axis nodes were diagnosed in 11% of cases, half of which were in nodes <1 cm in short axis and therefore not suspected on CT scan. The study highlights the improved accuracy of EUS-FNA over CT and PET scanning for the detection of metastases from lung cancer as well as the poor prognosis of coeliac axis nodal involvement [40].

To date, EUS-FNA has been examined in two randomised studies, suggesting that EUS-FNA may reduce the need for mediastinoscopy in the staging of NSCLC [41], and that it may also reduce the number of futile thoracotomies if employed routinely [42]. However, data from these studies on healthcare costs are unavailable. In cohort studies, the high diagnostic accuracy of EUS-FNA has been demonstrated in mediastinal nodes <1 cm as well as PET-positive mediastinal nodes. A study based in the Netherlands evaluated PET-positive mediastinal lesions in 81 patients with proven or suspected lung cancer [43]. A total of 50 patients in this trial had a positive diagnosis of metastatic disease by EUS-FNA. EUS-FNA of PET-positive nodes was a cost-effective strategy, reducing surgical staging procedures by >50% and saving 40% of staging costs. The unreliability of negative EUS-FNA samples, however, means that surgical staging techniques still have an important role.

EUS-FNA therefore represents an important advance in the mediastinal staging of NSCLC. The technique offers a minimally invasive and potentially cost-effective alternative to mediastinoscopy when sampling of left-sided or posterior mediastinal lymph nodes is required. In addition it may diagnose previously unsuspected extra-thoracic disease. Despite these advantages, EUS-FNA has been slow to be incorporated into local diagnostic and staging algorithms. As with other minimally invasive techniques for mediastinal lymph node sampling, negative results must be verified by surgical techniques.

Combining EBUS/EUS

Endobronchial and endoscopic ultrasound provide complimentary access to the mediastinum. Combining EBUS and EUS at the same sitting allows minimally invasive sampling of the entire mediastinum except for the para-aortic nodes which lie anterior and lateral to the ascending aorta and aortic arch. Early results suggest that the combination procedure may be performed safely and have a combined accuracy of approaching 100% [25, 44]. Expertise and availability of the necessary equipment is not universally available and some centres employ the EBUS scope in the oesophagus, having already undertaken EBUS-TBNA. The combination of EBUS and EUS does however, enable more complete access to the mediastinum than standard mediastinoscopy and in the future may be considered the gold standard for mediastinal staging. Results from a European randomised trial comparing combined EBUS/EUS *versus* mediastinoscopy in the mediastinal staging of NSCLC are awaited.

Surgical procedures

Mediastinoscopy is the current gold standard technique for pre-operative mediastinal lymph node (MLN) staging in NSCLC. Performed under general anaesthesia, an incision is made above the suprasternal notch and the mediastinoscope is inserted along

the trachea, allowing visualisation and biopsy of MLNs. The procedure is increasingly performed as a day-case with low morbidity (2%); mortality is rare. Mediastinoscopy affords access to paratracheal nodes, pre-tracheal nodes and anterior subcarinal nodes. However, lymph nodes in the aorto-pulmonary window, anterior mediastinal nodes, posterior subcarinal nodes and inferior mediastinal nodes are not accessible by this technique. The technique allows the surgeon to determine extra-capsular spread (and inoperability) at the time of the operation. Large biopsy samples also allow micro-metastases to be detected, even in normal sized lymph nodes. However, a meta-analysis of 6,505 patients demonstrated a pooled sensitivity of 78% (range 40–97%), and a false negative rate of 11% when the overall prevalence of disease was 39% [27]. This inaccuracy (for the gold standard technique) is in part explained by the limited access of mediastinoscopy to the mediastinum.

Invasive mediastinal sampling (by mediastinoscopy or needle aspiration technique) is currently indicated for the evaluation of any PET positive mediastinal lymph nodes, nodes that are >16 mm in short axis on staging CT scan, central tumours, PET positive hilar disease and in the scenario of low fluorodeoxyglucose uptake of the primary tumour [45]. Surgical mediastinal staging is not currently justified in patients with clinical stage 1 NSCLC with negative CT and PET scan of the mediastinum, on the basis that the prevalence of mediastinal disease in this group of patients is very low. However, mediastinoscopy does appear to be underutilised in clinical practice and when it is carried out, is not uniformly performed to the highest standards. Best practice at mediastinoscopy would require that five nodal stations (upper and lower left and right paratracheal and subcarinal areas) are routinely sampled. SMULDERS *et al.* [46] demonstrated that systematic mediastinal lymph node sampling was performed in only 50% of cases and estimated that 18% of thoracotomies that were subsequently proven futile could have been avoided if gold standard techniques had been observed [46]. Of 39 cases with unexpected N2 disease at thoracotomy, 16 were retrospectively noted to be accessible to mediastinoscopy [46].

The advent of videomediastinoscopy has improved the standard procedure allowing better visualisation and in addition to usual mediastinal lymph node stations, sampling of posterior subcarina lymph nodes. Video-assisted mediastinal lymphadectomy (VAMLA) may also be performed using this technique allowing complete lymph node dissection without the need for thoracotomy. VAMLA offers a standardised approach to surgical MLN sampling and may be superior to standard cervical mediastinoscopy with an accuracy of 88% and negative predictive value of 83% in a recent cohort of 234 patients [47]. Surgical expertise in this technique however is far from universal and further data is required.

Primary NSCLCs of the left upper lobe have a predilection for metastasis to mediastinal lymph nodes in the aorto-pulmonary window (station 5) and para-aortic lymph nodes (station 6), often skipping left hilar (N1) nodes. Although EUS-FNA is able to sample station 5 nodes, the para-aortic area is generally inaccessible to minimally invasive techniques. Few studies have evaluated the best approach for the staging of patients with left upper lobe tumours. A retrospective study of 112 patients with suspected metastases in lymph node stations 5 or 6 suggested that EUS-FNA had an accuracy of 66%, whereas the preferred staging procedure was left video-assisted thorascopic surgery (VATS), with an accuracy of 100% in this group of patients [48]. Nodes in the aorto-pulmonary window (APW), to which left upper lobe cancers commonly spread, can also be accessed by anterior mediastinotomy, also known as the Chamberlain procedure. An incision is made under general anaesthetic in the second or third intercostal space just to the left of the sternum; overnight stay is usually required. Few studies have addressed the accuracy of this procedure, although it is employed as the definitive staging technique for nodes in the APW. Extended cervical mediastino-

scopy is also performed in some centres for the staging of left upper lobe tumours. In one series, this was found to have a sensitivity of 69% and false negative rate of 11% in 100 patients with a prevalence of mediastinal disease of 29% [49].

VATS is performed under general anaesthetic and can directly access one side of the mediastinum, with the right side being technically easier. Few prospective data are available, although the procedure appears to have an acceptable safety and accuracy profile and may be regarded as an adjunct procedure to standard techniques. It may be best suited to the diagnosis of parenchymal lesions inaccessible by other means, assessment of mediastinal invasion (T4 disease) and sampling of APW nodes. In addition, VATS has a key role in the diagnosis and therapeutics of a malignant pleural effusion. The procedure allows the surgeon visual access to the pleural space and biopsy of the pleura, and drainage of the pleural space and pleurodesis is also commonly performed, allowing a tissue diagnosis to be made as well as achieving effective palliation in a single procedure.

Future techniques in diagnostic endoscopy

Progress in technology is resulting in promising advances in diagnostic endoscopy. Medical thoracoscopy is currently performed in many centres for pleural effusions and is analogous to a VATS procedure, but does not require general anaesthesia. Recently an autoclavable semi-rigid thorascope has been introduced into clinical practice. Initial experience with this thorascope in 56 patients has demonstrated a diagnostic yield of over 90% and also allowed talc poudrage [50].

Electromagnetic navigation for peripheral pulmonary lesions is useful for lesions that are not accessible to standard bronchoscopy and is performed under general anaesthesia. Following detailed review of the CT scan, the patient is placed within an electromagnetic field and a sensor probe within a steerable catheter is introduced *via* a bronchoscope. During registration, the probe is touched onto pre-defined anatomical landmarks and data from the CT scan of the thorax are then merged with electromagnetic information using specific computer software. The precise three-dimensional location of the sensor probe can therefore be established and guided precisely towards the target lesion. Once the target lesion has been identified, the sensor probe is withdrawn, leaving the catheter in place. Biopsy forceps or brush may then be inserted into the catheter, which acts as an extended working channel of the bronchoscope. The procedure has been assessed in several series demonstrating diagnostic yields of up to 74% for peripheral lesions and 100% for mediastinal lymph nodes [51]. The addition of a radial EBUS probe to confirm the lesion location may further improve the yield of peripheral lesions to 88% [52].

Confocal laser fluorescent microscopy (alveoloscopy) is at the development stage but is an exciting new technique that allows microscopic tissue views *in vivo* for the first time. When combined with autofluorescence, real-time noninvasive imaging, known as ''optical biopsy'', is possible and may improve yield from conventional biopsy samples. A probe that emits and detects light is inserted into the working channel of the bronchoscopy. The probe is ≤ 1 mm in diameter and therefore may be advanced beyond distal airways. Thin section images of the microscopic autofluorescence structure may be obtained. A French group reported 29 patients who underwent confocal laser fluorescent microscopy. Alterations of the autofluorescence microstructure were seen in 19 out of 22 pre-invasive lesions, all CIS and two (out of two) invasive lesions [53]. The specificity of this technique remains to be defined and image quality can be hindered by endobronchial secretions.

Summary

A tissue diagnosis of lung cancer is crucial to differentiate nonsmall cell lung cancer (NSCLC) from small cell lung cancer. In patients with intra-thoracic disease, bronchoscopy remains a standard, routinely performed procedure that can provide important diagnostic as well as staging information. Surgical biopsy and mediastinoscopy are still considered to be gold standard investigations. However, rapid advances in technology have allowed the bronchoscopist's role to be expanded considerably. Autofluorescence bronchoscopy aids in the diagnosis of pre-invasive lesions and early lung cancers, while endobronchial and endoscopic ultrasound have become established for the mediastinal staging of NSCLC. In the current epidemic of lung cancer, these techniques are at the forefront of establishing a diagnosis and disease stage and are central to the multidisciplinary management of lung cancer.

Keywords: Autofluorescence bronchoscopy, bronchoscopy, endobronchial ultrasound, endoscopic ultrasound, mediastinoscopy, sputum cytology.

Statement of interest
None declared.

References

1. Foster BB. Neuroendocrine carcinomas of the lung: clinical, radiologic and pathologic correlation. *Radiology* 1989; 170: 441–445.
2. Rivera MP, Mehta AC. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132: 131–148.
3. Risse EK, Van't Hof MA, Vooijs GP. Relationship between patient charcteristics and the sputum cytologic diagnosis of lung cancer. *Acta Cytol* 1987; 31: 159–165.
4. Bocking A, Biesterfield S, Chatelain R, *et al.* Diagnosis of bronchial carcinoma on sectinos of paraffin-embedded sputum: sensitivity and specificity of an alternative to routine cytology. *Acta Cytol* 1992; 36: 37–47.
5. Jay SJ, Wehr K, Nicholson DP, *et al.* Diagnostic sensitivity and specificity of pulmonary cytology: comparison of techniques used in conjunction with flexible fiber optic bronchoscopy. *Acta Cytol* 1980; 24: 302–312.
6. Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. *Chest* 2003; 123: 115S–128S.
7. Gaeta M, Pandolfo I, Volta S, *et al.* Bronchus sign on CT in peripheral carcinoma of the lung: value in predicting results of transbronchial biopsy. *Am J Roentgenol* 1991; 157: 1181–1185.
8. Cox ID, Bagg LR, Russell NJ, *et al.* Relationship of radiologic position to the diagnostic yield of fibreoptic bronchoscopy in bronchial carcinoma. *Chest* 1984; 85: 519–522.
9. Herth FJ, Ernst A, Becker HD. Autofluorescence bronchoscopy – a comparison of two systems (LIFE and D-Light). *Respiration* 2003; 70: 395–398.
10. Philippe P, Benoit M, Verdebout JM, *et al.* Flourescence bronchoscopy in high risk patients: a comparison of LIFE and Pentax systems. *J Bronchol* 2001; 8: 251–254.
11. Haussinger K, Becker H, Stanzel F, *et al.* Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomised controlled multicentre trial. *Thorax* 2005; 60: 496–503.

12. George PJ, Banerjee AK, Read CA, *et al.* Surveillance for the detection of early lung cancer in patients with bronchial dysplasia. *Thorax* 2007; 62: 43–50.
13. Kennedy TC, McWilliams A, Edell E, *et al.* Bronchial intraepithelial neoplasia/early central airways: lung cancer ACCP evidence-based clinical practice guidelines (2nd Edition). *Chest* 2007; 132: 221S–233S.
14. Wang KP, Terry P, Marsh B. Bronchoscopic needle aspiration biopsy of paratracheal tumors. *Am Rev Respir Dis* 1978; 118: 17–21.
15. Holty JE, Kuschner WG, Gould MK. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. *Thorax* 2005; 60: 949–955.
16. Chin R, McCain TW, Lucia MA, *et al.* Transbronchial needle aspiration in diagnosing and staging lung cancer: how many aspirates are needed? *Am J Respir Crit Care Med* 2002; 166: 377–381.
17. Diacon AH, Schuurmans MM, Theron J, *et al.* Transbronchial needle aspirates: how many passes per target site? *Eur Respir J* 2007; 29: 112–116.
18. Garpestad E, Goldberg S, Herth F, *et al.* CT fluoroscopy guidance for transbronchial needle aspiration: an experience in 35 patients. *Chest* 2001; 119: 329–332.
19. Hsu LH, Liu CC, Ko JS. Education and experience improve the performance of transbronchial needle aspiration: a learning curve at a cancer center. *Chest* 2004; 125: 532–540.
20. Harrow EM, Abi-Saleh W, Blum J, *et al.* The utility of transbronchial needle aspiration in the staging of bronchogenic carcinoma. *Am J Respir Crit Care Med* 2000; 161: 601–607.
21. Bernasconi M, Chhajed PN, Gambazzi F, *et al.* Combined transbronchial needle aspiration and positron emission tomography for mediastinal staging of NSCLC. *Eur Resp J* 2006; 27: 889–894.
22. Krasnik M, Vilmann P, Larsen SS, *et al.* Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. *Thorax* 2003; 58: 1083–1086.
23. Lee HS, Lee GK, Lee HS, *et al.* Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? *Chest* 2008; 134: 368–374.
24. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997; 111: 1718–1723.
25. Wallace MB, Pascual JM, Raimondo M, *et al.* Minimally invasive endoscopic staging of suspected lung cancer. *JAMA* 2008; 299: 540–546.
26. Herth FJ, Eberhardt R, Vilmann P, *et al.* Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax* 2006; 61: 795–798.
27. Detterbeck FC, Jantz MA, Wallace MB, *et al.* Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132: 202–220.
28. Navani N, Spiro SG, Janes SM, *Advances in mediastinal staging of non-small cell lung cancer. Nature Rev Clin Oncol* 2009; 6: 278–286.
29. Groth SS, Whitson BA, D'Cunha J, *et al.* Endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes: A single institution's early learning curve. *Ann Thorac Surg* 2008; 86: 1104–1110.
30. Ernst A, Anantham D, Eberhardt R, *et al.* Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration *versus* mediastinoscopy. *J Thorac Oncol* 2008; 3: 577–582.
31. Herth FJ, Eberhardt R, Krasnik M, *et al.* 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: 887–891.
32. Tournoy KG, Rintoul RC, van Meerbeeck JP, *et al.* EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. *Lung Cancer* 2009; 63: 45–49.
33. 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: 985–988.

34. Herth FJ, Annema JT, Eberhardt R, *et al.* Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. *J Clin Onc* 2008; 26: 3346–3350.
35. Dooms CA, Verbeken E, Becker H, *et al.* Endobronchial ultrasonography in bronchoscopic occult pulmonary lesions. *J Thorac Onc* 2007; 2: 121–124.
36. Miyazu Y, Miyazawa T, Kurimoto N, *et al.* Endobronchial ultrasonography in the assessment of centrally located early-stage lung cancer before photodynamic therapy. *Am J Respir Crit Care Med* 2002; 165: 832–837.
37. Varadarajulu S, Schmulewitz N, Wildi SM, *et al.* Accuracy of EUS in staging of T4 lung cancer. *Gastrointest Endosc* 2004; 59: 345–348.
38. Tournoy KG, Praet MM, Van Maele G, *et al.* Esophageal endoscopic ultrasound with fine-needle aspiration with an on-site cytopathologist: high accuracy for the diagnosis of mediastinal lymphadenopathy. *Chest* 2005; 128: 3004–3009.
39. Pellisé Urquiza M, Fernández-Esparrach G, Solé M, *et al.* Endoscopic ultrasound-guided fine needle aspiration: predictive factors of accurate diagnosis and cost-minimization analysis of on-site pathologist. *Gastroenterol Hepatol* 2007; 30: 319–324.
40. Singh P, Camazine B, Jadhav Y, *et al.* Endoscopic ultrasound as a first test for diagnosis and staging of lung cancer: a prospective study. *Am J Respir Crit Care Med* 2007; 175: 345–354.
41. Tournoy KG, De Ryck F, Vanwalleghem LR, *et al.* Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. *Am J Respir Crit Care Med* 2008; 177: 531–535.
42. Larsen SS, Vilmann P, Krasnik M, *et al.* Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial. *Lung Cancer* 2005; 49: 377–385.
43. Kramer H, van Putten JW, Post WJ, *et al.* Oesophageal endoscopic ultrasound with fine needle aspiration improves and simplifies the staging of lung cancer. *Thorax* 2004; 59: 596–601.
44. Vilmann P, Krasnik M, Larsen SS, *et al.* Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy* 2005; 37: 833–839.
45. De Leyn P, Lardinois D, Van Schil PE, *et al.* ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 2007; 32: 1–8.
46. Smulders SA, Smeenk FW, Janssen-Heijnen ML, *et al.* Surgical mediastinal staging in daily practice. *Lung Cancer* 2005; 47: 243–251.
47. Leschber G, Sperling D, Klemm W, *et al.* Does video-mediastinoscopy improve the results of conventional mediastinoscopy? *Eur J Cardiothorac Surg* 2008; 33: 289–293.
48. Cerfolio RJ, Bryant AS, Eloubeidi MA. Accessing the aortopulmonary window (#5) and the paraaortic (#6) lymph nodes in patients with non-small cell lung cancer. *Ann Thorac Surg* 2007; 84: 940–945.
49. Ginsberg RJ, Rice TW, Goldberg M, *et al.* Extended cervical mediastinoscopy. A single staging procedure for bronchogenic carcinoma of the left upper lobe. *J Thorac Cardiovasc Surg* 1987; 94: 673–678.
50. Munavvar M, Khan MA, Edwards J, *et al.* The autoclavable semirigid thoracoscope: the way forward in pleural disease? *Eur Respir J* 2007; 29: 571–574.
51. Gildea TR, Mazzone PJ, Karnak D, *et al.* Electromagnetic navigation diagnostic bronchoscopy: a prospective study. *Am J Respir Crit Care Med* 2006; 174: 982–989.
52. Eberhardt R, Anantham D, Ernst A, *et al.* Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 176: 36–41.
53. Thiberville L, Moreno-Swirc S, Vercauteren T, *et al. In vivo* imaging of the bronchial wall microstructure using fibered confocal fluorescence microscopy. *Am J Respir Crit Care Med* 2007; 175: 22–31.