Review

Tools used in the diagnosis and staging of lung cancer: what’s old and what’s new?

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Introduction

Lung cancer is the most common cause of cancer related death in the world. In the UK in 2005, there were around 39 000 new cases of lung cancer and 34 000 deaths due to the condition (http://info.cancerresearchuk.org). Moreover, within the UK, rates of lung cancer in Scotland—especially within urban areas—are far higher than in other areas. While lung cancer incidence in men is falling in the UK, more women are being diagnosed due to increased cigarette smoking.

Over the years, new tools such as positron emission tomography/computed tomography (PET/CT), transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS), oesophageal ultrasound and medical thoracoscopy have been introduced and many studies have evaluated where they may become suitably placed in lung cancer diagnostic and staging algorithms. This evidence-based review provides the reader with an update of current and recently developed strategies in the diagnosis and staging of lung cancer. All authors performed a comprehensive search of articles published up to September 2008 using Pubmed and Medline. Keywords and phrases used were lung cancer, diagnosis, staging, investigations, endobronchial ultrasound, lymph node metastasis, positron emission tomography, PET/CT, transbronchial needle aspiration, mediastinum, mediastinal lymphadenopathy, survival rates, computerized tomography, bronchoscopy, pleural biopsy.

How is lung cancer classified and staged?

Lung cancer is divided histologically into non-small cell (NSCLC) and small cell (SCLC). NSCLC accounts for ~80% of all lung cancer and includes a number of pathological subtypes (mostly adenocarcinoma, squamous cell and large cell); SCLC accounts for the remainder. Currently, NSCLC is staged using the TNM system (revised in 1997), based on tumour size (T1-4), lymph node involvement (N1–3) and presence of metastasis (M0–1). Compared with NSCLC, SCLC has a greater tendency to be widely disseminated at the time of presentation and a two-stage system is employed. Limited stage SCLC means tumour is confined to the hemithorax of origin including the mediastinum and supraclavicular nodes, and which can be encompassed within a tolerable radiotherapy field. Extensive stage SCLC means tumour is too widespread to be included within the definition of limited disease. An updated staging system for all lung cancer based on large numbers of pathologically and clinically staged patients is scheduled.
to be disseminated in 2009, but is outwith the scope of this article.\(^1\)

**Why is accurate diagnosis and staging important?**

As with most cancers, early diagnosis and staging of lung cancer is important in terms of management and prognosis (Table 1; http://www.sign.ac.uk and http://www.nice.org.uk). The median survival of limited and extensive disease in SCLC is \(\sim 12–18\) and \(6–8\) months, respectively, with treatment. However, in some individuals with significant co-morbidities and poor performance status, it may be inappropriate to pursue a tissue diagnosis. These patients should be offered palliative treatment following discussion in a multidisciplinary team setting.

**What are the conventional imaging methods used to diagnose and stage lung cancer?**

The chest radiograph is the most important first-line imaging test in suspected lung cancer (Figure 1). Indeed, lung cancer uncommonly presents with a normal chest radiograph, although a normal examination should not preclude further investigations. Unlike a chest radiograph, computerized tomography (CT) provides anatomical characterisation of abnormalities, and often indicates the best approach for sampling tissue (Figure 2). In the mediastinum, most studies measuring CT imaging accuracy have used a short-axis diameter of \(\geq 1\) cm as the threshold for abnormal lymph node size, based on a retrospective review \((n=56)\) of patients.\(^2\) However, in patients with NSCLC, a systematic review of 5111 patients \((n=35\) studies\) found that 40% of nodes considered malignant by CT size criteria are benign, while 20% of nodes considered benign are malignant.\(^3\)

Ultrasound can be used to assess indeterminate liver lesions found on CT; it can also guide biopsy of accessible suspected metastatic lesions (neck nodes and solid liver masses). Magnetic resonance imaging is the preferred technique for evaluating suspected tumour involvement of the spinal canal or brachial plexus. Clinical assessment is generally unreliable in predicting the presence of bone metastases. For example, in a well-conducted prospective study \((n=100)\) of individuals with NSCLC, 27% judged not to warrant isotope bone scans, were found to have metastatic bone lesions.\(^4\) False positive abnormalities (rib fractures) are often found, and the pooled sensitivity and specificity of bone scintigraphy is \(\sim 87\%\) and \(67\\%\), respectively.\(^5\)

![Figure 1. Chest radiograph showing a right upper zone mass.](image)
What are the conventional sampling methods used to diagnose and stage lung cancer?

Confirmation of the diagnosis with tissue is important in most patients. Cytological examination of sputum has a sub-optimal diagnostic yield unless the tumour is large and centrally located; bronchoscopy is therefore the usual way by which to sample endobronchial lesions. Using a combination of biopsy, bronchial washings and brushings, the diagnostic yield is between 80% and 90% of proximal tumours (http://www.sign.ac.uk). Percutaneous fine needle aspiration or biopsy is usually more appropriate in peripheral lung lesions, although a multivariate analysis of 660 lung biopsies found complication risks of pneumothorax (25%), haemothorax (4%) and chest tube placement (1%). Fine needle aspiration can also diagnose and stage lung cancer in those found to have palpable supraclavicular lymph nodes and skin metastasis, in turn indicating that a thorough clinical examination is necessary in all patients.

Some patients are diagnosed with lung cancer following investigation of a unilateral pleural effusion. Pleural fluid analysis has a sensitivity of ~60% for malignancy while performing a concomitant blind biopsy using an Abrams needle can increase the diagnostic yield by up to 10%. However, CT guided pleural biopsy is now considered a far more reliable diagnostic test in an undiagnosed unilateral pleural effusion and helps overcome some of the problems associated with blind biopsy.

Mediastinoscopy requires administration of a general anaesthetic and a short in-patient stay. It is usually performed once lung cancer has been diagnosed and staging of mediastinal lymphadenopathy is necessary. Mediastinoscopy is well established in the staging algorithm of patients with NSCLC, but not all hilar and mediastinal nodes are accessible and its sensitivity, specificity and sampling strategy can be variable. Although generally safe, it does carry a small but appreciable complication rate of up to 2.5%, and cannot be easily repeated in the same individual.

What new techniques are there in the diagnosis and staging of lung cancer?

Positron emission tomography/computed tomography

Positron emission tomography (PET) imaging provides a metabolic map of living tissue. Lung cancer cells require greater amounts of glucose relative to non-malignant cells and the uptake of a radiolabelled glucose analogue 18F-fluoro-2-deoxy-D-glucose (FDG) parallels that of glucose. The location of FDG uptake can be assessed with integrated PET/CT systems (Figure 3). A recent National Institute of Clinical Excellence guideline reported that in 1515 patients with NSCLC, 15%...
had unsuspected metastases identified by PET which led to a change in management in 25%. In the mediastinum, PET is more sensitive than conventional CT for assessing lymph node status. A meta-analysis of 39 studies reported sensitivity and specificity of PET scans of 100% and 78% in patients with enlarged nodes. The negative predictive value of PET for mediastinal metastasis is influenced by numerous factors including the avidity for FDG, tumour location and presence of hilar nodal involvement. Moreover, non-malignant processes that involve increases in glucose transport may cause false positive FDG uptake (Table 2). Consequently, patients with PET-positive lymph nodes (with potentially curable disease) should have nodal sampling to exclude benign causes for uptake. In patients with peripheral clinical stage I tumours, invasive staging of the mediastinum is not routine and not cost-effective. A retrospective study of 248 patients with stage I disease found that mediastinoscopy added 0.008 years of life expectancy at a cost of $250,989 per life-year gained, with a false negative PET rate in the mediastinum of 5%. PET studies are useful in identifying unsuspected distant metastases, which may preclude curative treatment. Two separate analyses on the identification of distant metastases concluded that PET had a sensitivity of 93% and specificity of 96%, with unsuspected metastases identified in 15% of patients.

The use of PET/CT in SCLC has been studied in much smaller numbers than NSCLC, with less than 400 patients in three prospective trials of varying quality. However, PET has sensitivity and specificity exceeding 90% for brain and nodal metastases, although clear evidence of improved patient outcomes is lacking, and it is not routinely used.

Transbronchial needle aspiration

Transbronchial needle aspiration (TBNA) is usually performed using a retractable beveled needle passed through a channel in a fibreoptic bronchoscopy. The end of the needle is inserted through the endobronchial wall into a lymph node with suction applied at the proximal port of the bronchoscope. It is useful for patients to have a CT scan prior to the procedure enabling enlarged lymph nodes to be preferentially sampled. However, the diagnostic yield is variable and influenced by lymph node size and site, operator experience, tumour type, needle used and speed of cytological examination. A recent well-conducted meta-analysis (n=13 trials) indicated that the procedure was highly specific although sensitivity was as low as 39% and depended upon the patient population. TBNA is considered safe although adverse effects such as pneumothorax, pneumomediastinum and bleeding have been reported.

Endobronchial ultrasound needle aspiration

To overcome blind sampling of TBNA, needle aspiration using real time ultrasound has been developed (endobronchial ultrasound guided transbronchial needle aspiration; EBUS). An ultrasound transducer is integrated into the bronchoscope and comes into contact with the endobronchial mucosa; the biopsy needle is then introduced and passed into the lymph node under direct vision. This technique can provide a safe and potentially cost effective alternative to surgical staging with mediastinoscopy. As well as enabling mediastinal and hilar nodes to be sampled, EBUS can also permit biopsy of intra-pulmonary tumours adjacent to main bronchi.

In one of the largest studies published, 572 enlarged lymph nodes (mean diameter 1.6 cm) in 502 patients were sampled of which 535 (94%) resulted in a diagnosis. In the same study, the sensitivity and specificity for mediastinal staging was 94 and 100%, respectively. In a further study, the accuracy of EBUS in sampling lymph nodes ≤1 cm in diameter (n=119) in patients with non-small cell lung cancer (n=100) was assessed. Malignancy was detected in 19 patients but missed in two; all
diagnoses were confirmed by surgical findings. The sensitivity of this approach for detecting malignancy was 93%, specificity was 100%, with a negative predictive value of 96%. Moreover, in a well-conducted prospective crossover study, EBUS was superior to mediastinoscopy (91% vs. 78%, respectively, \(P = 0.007\)) in detecting paratracheal and subcarinal tumour invasion.27

**Transoesophageal ultrasound needle aspiration**

EBUS is unable to sample all mediastinal and hilar lymph node stations; inaccessible nodes include those located in the paraoesophageal and subaortic areas. Transoesophageal ultrasound needle aspiration helps provide complementary information to EBUS by way of ability to sample these particular areas. During this technique, the biopsy needle is passed through a channel in an endoscope and guided ultrasonically through the oesophageal wall into the mediastinal node under investigation. In patients with enlarged lymph nodes on CT (>1 cm), the sensitivity has varied between 72% and 100% and specificity between 88% and 100%. In the only published prospective randomized controlled trial (\(n = 40\) patients), endoscopic ultrasound was compared with mediastinoscopy. The former technique was more sensitive (although the difference was non-significant) but did result in fewer complications and obviated the need for in-patient stay. Thus, by combining EBUS and transoesophageal ultrasound needle aspiration, the vast majority of lymph node stations can be safely sampled with a high degree of sensitivity and specificity. Moreover, these procedures can be performed under light sedation and on an outpatient basis.

**Medical thoracoscopy**

Advanced lung cancer is one of the most common causes of an undiagnosed large exudative pleural effusion. Thoracoscopy is usually considered when pleural fluid analysis and pleural biopsy has failed to provide a diagnosis. This procedure can now be carried out with patients under conscious sedation, and permit direct visualisation of the pleura with subsequent biopsy plus removal of fluid and talc pleurodesis. This technique is gaining popularity and may play an increasingly important role in departments with no on-site thoracic surgeons and those unfit for general anaesthesia.

![Figure 4. Simplified algorithm showing staging procedure in patients with NSCLC and where ultrasonically guided sampling may obviate the need for mediastinoscopy.](image-url)

**Conclusions**

It is well established that early diagnosis and accurate staging of lung cancer—thereby permitting early and appropriate treatment—is one of the main strategies by which to potentially improve the dismal 5-year survival rates. Once the diagnosis of lung cancer has been confirmed, patients need to be quickly, conveniently and accurately staged to help decide appropriate treatment and whether a potentially curative procedure can be considered (Figure 4).

One of the most recent introductions into the staging armamentarium has been PET/CT. This technique has been a major step forward in detecting local and distant metastasis and is more accurate than CT. Moreover, it has now become an established investigative tool in the staging algorithm of NSCLC and an increasing number of regional cancer centres have the necessary equipment on-site. However, FDG-avid mediastinal nodes on PET/CT still mean that tissue confirmation of lymph node involvement is necessary (usually with mediastinoscopy), while a negative result in clinical stage I obviates this need. The introduction of ultrasound guided transbronchial and transoesophageal biopsy facilitates a less invasive method of staging the mediastinum, both of which display encouraging results in recent clinical trials. Current data suggest that in the future, these less-invasive methods of sampling mediastinal lymph nodes, may become the gold standard diagnostic and staging tools in
centres possessing the necessary equipment and expertise (thereby perhaps replacing mediastinoscopy in some cases), in patients with NSCLC.

References