The importance of ultrasound in staging and gaining a pathological diagnosis in patients with lung cancer—a two year single centre experience

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ABSTRACT

Background Initial studies on the use of ultrasound in the detection and sampling of supraclavicular lymph nodes in patients with suspected lung cancer show this to be a promising technique, giving both a cytological diagnosis and pathological N3 (pN3) stage. Leicester published its initial experience in 2005 and the aim of this study was to establish if this had been embedded into the diagnostic pathway, and further to examine the use of ultrasound in diagnosing and staging lung cancer by imaging other areas including pleural effusions, chest wall, bone and liver lesions.

Methods All patients diagnosed with lung cancer, registered on the Leicester lung cancer database over a two year period between January 2007 and December 2008, had their imaging and pathology retrospectively reviewed; 996 primary lung cancer patients were identified (n=996). Of these, 318 patients underwent an ultrasound examination (n=318), consisting of ultrasound of the neck, pleural cavity, and metastatic lesions potentially amenable to ultrasound guided aspiration/biopsy.

Results The overall malignant yield was 45% of patients scanned (95% CI 39.5% to 50.4%) and 81.3% of patients sampled (95% CI 75.5% to 87%). Of the 996 patients, 14.4% (n=143) had a positive ultrasound guided cytological diagnosis (95% CI 12.2% to 16.5%). Of all the pathological diagnoses (n=765), 18.7% were ultrasound guided (95% CI 15.9% to 21.5%). In particular, 32.2% of patients with CT detected neck or mediastinal nodes had a diagnosis and stage achieved by neck ultrasound.

Conclusion The use of ultrasound gives a rapid and less invasive method of diagnosing and staging lung cancer and has become embedded into the diagnostic pathway. We advocate its increased use and availability in patients with lung cancer.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths in men and women worldwide. In the UK alone, there are approximately 39 000 cases of lung cancer reported annually, with over 34 000 deaths.[1]

Ultrasound guided cytological aspiration of supraclavicular lymph nodes has been well described.[2] Initial reports of the use of ultrasound in the detection and sampling of patients with supraclavicular lymph nodes in patients with suspected lung cancer showed this to be a promising technique,[3–8] and gives both a cytological diagnosis and pathological N3 (pN3) stage.

The authors first published an initial experience of ultrasound guided supraclavicular lymph node sampling in 2005.[9] The purpose of the current study was first to evaluate whether this had been embedded into the local diagnostic pathway of patients with suspected lung cancer and, in addition, to present the largest series of neck-node ultrasounds for staging published to date. Furthermore, the authors examined the use of ultrasound in the pathological diagnosis of lung cancer by imaging other areas, including ultrasound guided pleural effusion taps and other sites including the chest wall, bone and liver lesions. Again, this could provide both a cytological diagnosis and pM1a or pM1b stage respectively.

All staging in this study has been updated to the seventh edition, as presented by the International Association for the Study of Lung Cancer (IASLC).[10]

METHODS

All patients diagnosed with lung cancer registered on the local Leicester lung cancer database for the National Lung Cancer Audit (LUCADA)[11] over a two year period between January 2007 and December 2008, had their imaging retrospectively reviewed on the radiology information system (RIS) application. Patients who had ultrasound procedures in the diagnosis of lung cancer were identified. Where samples were taken, the results were correlated with the pathology information system database (APEX). Exclusion criteria were set out as follows: mesotheliomas; benign tumours; and mediastinal tumours.

Nine hundred and ninety six primary lung cancer patients were identified (n=996). These included those with a pathological diagnosis (n=765) and a clinical diagnosis (n=231) made by the Thoracic multi-disciplinary team (MDT). Of these, 591 (59.3%) were male. Mean age at diagnosis was 71 years (range 24–98). A subgroup of these patients were then selected to be included in the study as divided into the following groups: (i) ultrasound neck; (ii) ultrasound pleural effusion; (iii) ultrasound other. Ultrasound neck was performed in patients with CT demonstrated supraclavicular nodes or enlarged mediastinal nodal (short axis greater than 1cm) on staging CT (n=245). Pleural cavity ultrasound was performed on patients with significant sized effusions on chest x-ray (CXR) or CT (n=69), aspiration was performed if this was thought to be suitable by the

scanning radiologist. A third heterogeneous group of patients with lesions potentially amenable to ultrasound guided fine needle aspiration cytology (FNAC)/biopsy of areas such as the liver, chest wall, lung and bone were identified (n=32). Some patients had more than one procedure. Allowing for overlap between the subgroups, 318 patients underwent at least one ultrasound examination.

Ultrasound of the neck was performed using a high frequency (6–15 Mhz) linear array probe on a General Electric Logiq E9 system (Japan) as previously described.[9] No patient refused sampling, and there were no recorded complications. The procedure typically took 10–15 min.

Ultrasound of the pleural cavity was carried out in those patients who had a pleural effusion identified on CXR or CT. A low frequency (1–5 MHz) curvilinear probe was used for this examination. Those patients with large easily drainable effusions were marked for ward drainage. Those patients with smaller effusions either had an aspiration performed or an ultrasound guided 12-French drain inserted as clinically appropriate. In either case, pleural fluid was sent for cytological analysis. Finally, ultrasound and guided biopsies of other areas including chest wall mass, liver and bone lesions were carried out. Written consent was obtained for these procedures, which were performed by an appropriate Consultant Radiologist or Registrar/Resident. Samples obtained were sent for pathological analysis.

Cytology fine needle aspirates (FNAs) were prepared using the cytospin technique as described previously.[9]

Serous fluids were assessed macroscopically, and any clots removed and processed as histological samples. Fluid samples were spun down, the supernatant removed, and an aliquot from the residual cell pellet was spread as a direct smear and stained with PAP unless there was a risk of infection. The cell pellet was then resuspended in Cytorich red and 2× cytospin preparations were made and stained as above.

For cases requiring immunocytochemistry or special stains, cell pellets were made from spun-down fixed material (either FNA or serous fluids) and processed as a histological sample to produce a cytoblock.

Tissue samples were fixed in 10% formal saline, processed and cut at 4 μ.

RESULTS

Of the 996 patients with primary lung cancer, 765 patients (76.8%) had their diagnosis confirmed pathologically. Three hundred and thirty eight patients had one or more ultrasound examinations.

Two hundred and forty five patients (24.6% of the total number of lung cancer patients) had neck ultrasounds performed. Of these, 111 patients underwent FNAC of an enlarged node with a positive cytological diagnosis (and therefore pN3 staging) obtained in 79 of these patients. This accounted for 10.3% of all pathologically diagnosed lung cancers. In particular, 32.2% of patients with CT detected neck or mediastinal nodes had a diagnosis and stage achieved by neck ultrasound. There were no recorded immediate complications.

Sixty nine patients (6.9%) had ultrasound of their pleural cavity performed. Of these, 41 patients were sampled in the ultrasound department (either by aspiration or intercostal chest drain insertion) and 20 patients had a suitable drainage site marked for ward intercostal drain insertion. A positive cytological diagnosis (and therefore M1a staging) was obtained in 40 of these patients. This accounted for 5.2% of all pathologically diagnosed lung cancers. Again, there were no clinically recorded pneumothoraces or other complications.

Thirty two patients (3.2%) underwent ultrasound guided sampling of other areas. A positive cytological diagnosis was obtained in 31 of these patients, which gave either a pathological diagnosis of the primary tumour (if the chest wall was biopsied), or confirmed metastatic disease (M1b) in other cases. This accounted for 4.1% of all pathologically diagnosed lung cancers.

Of the 318 patients who underwent ultrasound examinations, 28 patients had an ultrasound of two regions at the same sitting. Of these 28 patients, seven had a positive cytological diagnosis from both of these regions and in these seven patients, positive cytology was only accounted for once on calculation of the final malignant yield.

A further breakdown of the staging and cell type of the positive ultrasound guided cytological diagnoses are provided (table 1 and 2).

Forty seven of the patients with a positive cytological diagnosis were classified as non-small cell lung cancer (NSCLC) without further differentiation of cell type. Of the patients who had image guided sampling performed, 19 patients had an inadequate sample. A further 10 patients were reported as being suspicious for malignancy. These were not regarded as diagnostic in this series and none of these patients had repeat sampling. If the patient was fit for an alternative diagnostic means, such as CT guided lung biopsy, then this was performed, otherwise a clinical diagnosis was made.

The overall malignant yield was 45% of patients scanned (95% CI 39.5% to 50.4%) and 81.3% of patients sampled (95% CI 75.5% to 87%). Of the lung cancer population of 996 patients, 14.4% (n=143) had a positive ultrasound guided cytological diagnosis (95% CI 12.2% to 16.5%). Of all the pathological diagnoses (n= 765), 18.7% were ultrasound guided (95% CI 15.9% to 21.5%).

DISCUSSION

Prognosis of patients with lung cancer depends on both the pathological subtype and staging at the time of presentation. Recently implemented data from the IASLC lung cancer staging project reveals a five year survival rate of 8% for Stage IIIB and 2% for Stage IV for clinically diagnosed disease.[10] For these inoperable cases, a swift, relatively non-invasive and reliable pathological diagnosis and staging would allow prompt commencement of appropriate palliative treatment.

At this centre, ultrasound plays a key role in the management of lung cancer. Patients referred with suspected lung cancer are reviewed at a single MDT meeting, which covers a population of approximately one million. Data from the National Lung Cancer Audit shows that the lung cancer population as seen by the Leicester clinical team is in no way atypical of that seen in the rest of the UK, in terms of age, sex, stage, performance status, deprivation index or cell type. The majority of patients referred urgently by primary care physicians will be scanned with CT and have a multi-disciplinary review prior to being seen in clinic (figure 1). There is a single main lung cancer clinic with up to four Consultant Respiratory Physicians with a special interest in lung cancer. This is supported by a body of three Consultant

Table 1 Breakdown of stage of patients with a positive ultrasound guided pathological diagnosis

Lung cancer staging	Patient number (n)
IIIa	2
IIIb*	72
IV	69

*minimum staging for this subgroup.

Table 2 Breakdown of histological cell type of patients with a positive ultrasound guided pathological diagnosis

Cell type	Patient number (n)
Small cell	46
Non small cell: adenocarcinoma	44
Non small cell: squamous	6
Non small cell: not specified	47

Radiologists with a special interest in thoracic imaging. Same day ultrasound service, which runs in parallel, is offered to those patients seen in clinic and those who meet the radiological criteria.

There is an argument that a combination of pre clinic CT, and ultrasound in clinic or at the time of clinic, would reduce the need for physicians to wield their stethoscopes unless there were specific concerning symptoms and signs with no cause identified by imaging. CT imaging would still of course be required however, as this provides a more holistic staging, aiding further appropriate management.

Ultrasound examination is a fast, non-invasive, cost effective and readily available imaging modality which offers patients who are referred with suspected lung cancer the possibility of a rapid pathological diagnosis and a minimum, if not final, disease stage. We have demonstrated that ultrasound can give a malignant yield of 45% in those patients who are deemed suitable for scanning, and in 81% of those patients sampled. Ultrasound normally confirms advanced disease and patients can be triaged to the appropriate palliative treatment.

Ultrasound detection of supraclavicular nodes has been shown to be superior to both clinical examination and detection by CT.

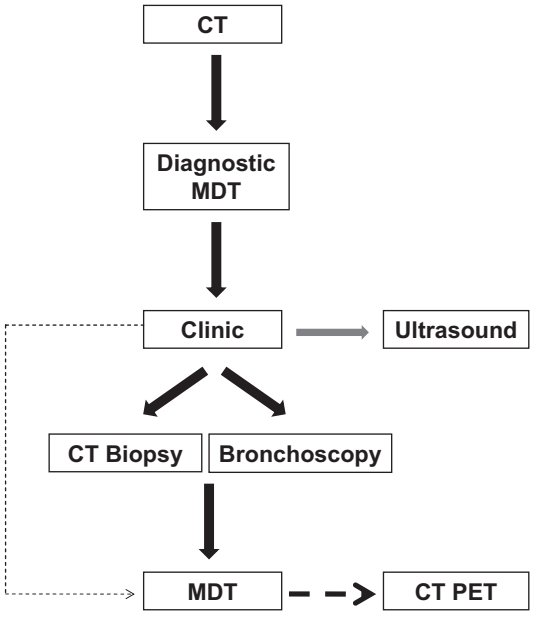

Figure 1 Flow diagram demonstrating patients journey. Patients at the centre who are referred from primary care physicians as 'two week wait' suspected lung cancer cases, or those with a suspicious CXR, undergo CT before being consulted in the respiratory clinic. The CT imaging is reviewed at a pre-clinic diagnostic MDT, and those patients who are deemed suitable undergo neck node ultrasound or pleural effusion aspiration/drainage in a radiology clinic which runs parallel to the respiratory clinic. If required, further CT guided or bronchoscopic intervention may be performed, or further analysis by positive emission tomography CT (PET-CT) in appropriate cases. Final MDT patient review then determines the management plan.

Ultrasound guided FNAC using the capillary technique is well described, easily reproducible and can be performed by a single operator. A positive cytology sample gives a pN3 stage. In this series, we had no recorded complications. However, potential complications could include haemorrhage, bleeding, pneumothorax and air embolism.[12–14] Pain is likely to have been underreported. Some patients who may have had clinically palpable supraclavicular lymph nodes when seen in clinic, also underwent ultrasound guided aspiration on the same day within the department due to the centre's experience and service setup. FNAC is minimally invasive, well tolerated, and if positive will avoid more invasive sampling techniques. Normal criteria for enlargement is a node equal to or greater than 5 mm in short axis diameter.

Those patients with CXR or CT evidence of a pleural effusion potentially deemed suitable for aspiration or drain insertion underwent ultrasound of the pleural cavity. A positive cytology sample gave a pM1a stage. Again, there were no immediate complications or clinically significant pneumothoraces detected in this group, and potential complications would be similar to those described above.

For those patients with masses/lesions in other areas, ultrasound guided FNAC or biopsy allowed pM1b staging, avoiding further, and perhaps more invasive diagnostic procedures. Within this group, there were two patients who underwent ultrasound guided lung biopsy, with both patients generating positive histology. Although these patients form a minute number in the entire cohort, ultrasound guided lung biopsy is a well described technique for peripheral lung lesions or those abutting the mediastinum or pleura —[15 16] although it is not practised frequently at our centre due to good access to CT. A subgroup of patients had ultrasound guided pericardial fluid aspiration, with a positive cytology result staging the patient as pM1b. As these were performed by echocardiography and led by the Cardiologists, these procedures were not captured and entered onto the RIS and hence were excluded from this study. Further, any patients whose ultrasound examination may not have been entered on the RIS, or those patients scanned and biopsied in the independent sector would also not have been included in this study. This, in turn, may have led to the under reporting of the usefulness of this technique. Finally, the exclusion of carcinoid tumours from the analysed lung cancer population would also have slightly increased the diagnostic yield.

Lung cancer treatment is rapidly evolving. There are a number of promising new agents in non small cell lung cancer including the tyrosine kinase inhibitors.[17] If approved these may broaden the range of patients that we will need to gain a pathological diagnosis in advanced disease and may include patients with poorer performance status. Less invasive ultrasound sampling techniques may be suitable to gain a pathological sample in many of these patients. Recent publications have demonstrated promise in testing for epidermal growth factor receptor (EGFR) mutation on cytological samples.[18 19]

The differentiation of small cell carcinoma from NSCLC can usually be confirmed on cytological samples, often on morphology alone but with additional use of immunocytochemistry in difficult cases. With the recent National Institute for Health and Clinical Excellence (NICE, UK) approval of Pemetrexed in combination with Cisplatin for the first-line treatment of patients with locally advanced non squamous NSCLC, the histological differentiation of tumour types has become more important.[20 21] Differentiating histological subtypes of NSCLC may be more challenging with smaller

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samples but is still possible.[22 23] In a group of patients where this is not possible and it is still clinically important, a second sample may be required. A core biopsy of larger neck nodes is possible or a biopsy of the most accessible site with a second technique may be needed.

In this centre we are able to provide a prompt service at the same time as the main lung cancer clinic. This may not be possible in all centres. A General Radiologist or appropriately trained respiratory physicians could offer this service. The Royal College of Radiologists in the UK has recommended thoracic ultrasound training for respiratory physicians with designated procedure numbers to gain competency.[24] There are no recommendations for neck ultrasound. In the authors' experience, neck ultrasound and biopsy is significantly more difficult than imaging the pleura and may be more challenging for non radiologists to learn.

CONCLUSION

The use of ultrasound gives a rapid and non invasive method of diagnosing and staging lung cancer and has become embedded in the diagnostic pathway. The authors advocate its increased use and availability in patients with lung cancer.

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