Thoracic Ultrasound in the diagnosis of Malignant Pleural Effusion

Authors: Nagmi R Qureshi FRCR
Najib M Rahman MRCP*
Fergus V Gleeson FRCR

Affiliations:
1 Department of Radiology, Papworth Hospital NHS Foundation Trust
   Papworth Everard, Cambridge CB23 3RE.
2 Oxford Centre for Respiratory Medicine and University of Oxford, Oxford
   Radcliffe Hospital, Headington, Oxford. OX3 7LJ, U.K.
3 Department of Radiology, Oxford Radcliffe Hospital, Headington, Oxford. OX3
   7LJ, UK.

*Joint 1st authors with equal roles in design, delivery and publication

Correspondence:
Dr F V Gleeson, Consultant Radiologist, Department of Radiology, Oxford Radcliffe
Hospital, Headington, Oxford. OX3 7LJ, UK.
Tel. No. +44 1865 225795
E-mail: Fergus.Gleeson@nds.ox.ac.uk

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ABSTRACT

Rationale: Malignant pleural effusion (MPE) is a common clinical problem with described investigation pathways. While thoracic ultrasound (TUS) has been shown to be accurate in pleural fluid detection, its use in the diagnosis of malignant pleural disease has not been assessed.

Objectives: To assess the diagnostic accuracy of TUS in differentiating malignant and benign pleural disease.

Methods: 52 consecutive patients with suspected MPE underwent TUS and contrast enhanced CT (CECT). TUS was used to assess pleural surfaces using previously published CT imaging criteria for malignancy, diaphragmatic thickness/nodularity, effusion size/nature and presence of hepatic metastasis (in right sided effusions). A TUS diagnosis of malignant or benign disease was made blind to clinical data / other investigations, by a second blinded operator using anonymised TUS video clips. TUS diagnosis was compared to definitive clinical diagnosis, and in addition to the diagnosis found at CECT.

Results: Definitive malignant diagnosis was based on histocytology (30/33 (91%)) and clinical / CT follow up (3/33 (9%)). Benign diagnoses were based on negative histocytology and follow up over 12 months in 19/19 patients. TUS correctly diagnosed malignancy in 26/33 patients (sensitivity 73%, specificity 100%, Positive Predictive Value 100%, Negative Predictive Value 79 %) and benign disease in 19/19. Pleural thickening >1cm, pleural nodularity and diaphragmatic thickening >7mm were highly suggestive of malignant disease.

Conclusion: TUS is useful in differentiating malignant from benign pleural disease in patients presenting with suspected malignant pleural effusion and may become an important adjunct in the diagnostic pathway.
INTRODUCTION
Investigation of pleural effusion of unknown aetiology is well described in British, American and European guidelines(1-3). These guidelines and other papers(4) recommend clinical evaluation, basic radiological investigation, and diagnostic pleural fluid sampling in the majority of unilateral pleural effusions. Malignancy remains the most common cause of unilateral pleural effusion in the UK and USA, with an estimated 250,000 new cases of malignant pleural effusion per year(2;5). Cytology positive pleural fluid is found in 60% of cases of malignant pleural effusion(1;6-8), with a substantially lower positive rate in mesothelioma(9), and further investigations to establish diagnosis are recommended in the context of cytology negative unilateral pleural exudate(1-4;10). Thoracic CT scanning with contrast enhancement (Contrast enhanced CT, CECT) is a sensitive and specific test for malignant pleural disease(11), with morphological criteria established in previous studies(12;13). CECT is recommended as the next investigation, with a view to subsequent histological diagnosis (blind, image guided or thoracoscopic pleural biopsy)(4;14).

Thoracic Ultrasound (TUS) is a valuable clinical tool which is increasingly being performed by chest physicians. In the UK, guidelines have recently been published with suggested training for physicians with an interest in practising TUS(15). Hitherto, the role of TUS has been limited to pleural fluid detection (with high sensitivity), and image guided techniques (thoracoctentesis, drain placement, lung biopsy)(14).

The sonographic appearance of malignant pleural effusion, and the value of ultrasound in determining the nature of pleural effusion have been described in previous studies(16;17). However, there are no published studies to our knowledge which have assessed the diagnostic accuracy of ultrasound for malignancy in patients with suspected but undiagnosed malignant pleural effusion.

The primary aims of this study were therefore to:
1. Assess the sensitivity and specificity of ultrasound in the detection of malignant disease in patients with suspected malignant pleural effusion, using established morphological criteria from CECT.
2. To investigate the use of other morphological characteristics on TUS associated with malignant pleural disease

In addition, overall TUS diagnostic rate and CECT diagnostic rate were compared, in comparison to definitive clinical diagnosis for malignant effusion.
METHODS

Subjects
The study was undertaken in a tertiary referral centre for respiratory / pleural disease, and involved consecutive patients presenting with unilateral pleural effusion of unknown aetiology from both in- and out-patient settings.

Inclusion Criteria
1. Chest radiograph evidence of pleural effusion(s)
2. No established diagnosis (malignant or otherwise) of the cause of pleural effusion
3. The patient would in normal clinical practise undergo further investigations to establish the cause of pleural effusion

Exclusion Criteria
1. A clinical and / or histological diagnosis had been established
2. Clinical and radiographic features of empyema
3. The patient was too ill to warrant further investigation in normal clinical practise (e.g. moribund patients)

Patients were identified by a respiratory trainee (NMR) and referred for TUS with no clinical information on past history, presenting features or relevant investigations.

We routinely perform a TUS in all patients presenting as above prior to biopsy, drain insertion or thoracoscopy, and as such this study was considered an audit of our current practise and local Ethics Committee approval is not required for these studies in our Institution.

Ultrasound
Precise details of ultrasound technique and operators are presented in the on-line supplement. All patients underwent TUS, prior to which the most recent chest radiograph was reviewed. TUS was performed without clinical history and previous three dimensional (CT / MRI) imaging data. Anonymised video clips and still images of the examination were generated. From these TUS findings an overall diagnosis of malignant or benign pleural disease was recorded on a reporting proforma (see on-line supplementary data). Anonymised TUS data was then reviewed separately by a consultant radiologist experienced in thoracic ultrasound (FVG), blind to clinical history, previous investigations (including radiology), physical status and appearance of the patient. The final results of blind analysis were recorded by one of the authors (NQ).

TUS Diagnosis
Morphological criteria established as sensitive and specific to malignant pleural disease on CECT were used as the basis of TUS diagnosis. If a patient had any one of the following criteria on TUS, a diagnosis of malignant disease was recorded:
1. Diaphragmatic and parietal pleural nodule or nodules
2. Pleural thickening greater than 1 cm
3. Hepatic metastasis

A provisional diagnosis of malignant or benign pleural disease was recorded on the proforma prior to other investigations and separately by each operator.
Contrast enhanced CT

Precise details of CECT examinations are presented in the on-line supplement. CECT examinations were reviewed in all cases and were reported blind to the previous TUS result (as the TUS results were anonymised). In 40/52 patients CECT was conducted in our institution; in 12/52 patients CECT studies had already been performed at the referring hospital. It was not considered ethical to subject these patients to further radiological examination for the purpose of this study. The hard copy CT images from these institutions were reviewed blind to TUS result. An overall CT diagnosis of malignant or benign disease was recorded based on the criteria of Leung et al(12), in addition to the presence of metastatic disease or clear intraparenchymal evidence of malignancy (see on-line supplement).

Definitive diagnosis

Histocytopathological diagnosis of malignancy was taken as definitive confirmation of malignant aetiology. Microbiological confirmation (most commonly TB) was taken as definitive confirmation of benign aetiology. In the absence of the above, the combination of clinical features and/or prolonged radiological follow up as appropriate was used to define the final diagnosis. Given that around 8% of patients with apparently benign histology on pleural biopsy develop malignancy over time(18), all patients with benign disease were followed up (as part of routine clinical practise in our or the host institution) for a minimum of 12 months, to confirm that malignant disease did not develop. For the purposes of this study, “definitive diagnosis” was considered to be the diagnosis imparted to the patient and on which basis the patient was treated (see results).

Statistical analysis

Please see on-line supplement.
RESULTS

Patients
From January to September 2005, 52 consecutive patients were recruited.
Baseline characteristics are summarised in Table 1

Definitive Diagnosis

Malignancy
Thirty three patients were diagnosed with malignant disease (median age 68 years, range 41-89 years) and 19 with benign disease (median age 68 years, range 22-88 years) (Table 1). The mode of final diagnosis is detailed in Table 2. In 30/33 (91%) of cases, definitive diagnosis of malignancy was based on histocytological confirmation. In 3/33 (9%), the diagnosis of pleural malignancy was based on follow-up CT appearances over a period of six months, in association with a clinical course (including death in all cases) consistent with malignant disease.

Benign Disease
After initial negative histocytological investigations, all cases of benign disease (19/19) were followed up for a minimum period of 12 months. This includes patients with positive microbiology or "inflammation" on pleural biopsies. There were no clinical or radiological features of malignancy during the follow-up period.

TUS overall characteristics
Pleural effusion was right sided in 32 patients, left sided in 13 and bilateral in 7 (in which cases the larger effusion was assessed as this was considered to be the clinically relevant side). The effusions were considered large in 13 patients, moderate in 24 and small in 15 cases (Table 3). Effusions were anechoic in 47/52 (= 90%), 22 were septated and 5 were diffusely echogenic. Liver ultrasound demonstrated metastases in 2 patients and was the sole abnormality suggestive of malignancy in 1 (Table 3).

TUS diagnoses compared to definitive diagnosis
There was good inter-observer agreement between the two TUS operators in the overall diagnosis of benign or malignant pleural effusion (kappa 0.96, p<0.001), and the results of the more experienced operator (FVG) have been used for analysis in all subsequent results.

The diagnosis based on the TUS overall correctly diagnosed 26/33 patients with malignant disease, and all (19/19) patients with benign disease (sensitivity 79% (95% CI = 61 to 91%), specificity 100% (95% CI 82 to 100%), Positive Predictive Value (PPV) 100% and Negative Predictive Value (NPV) 73% for differentiating malignant from benign pleural disease, with a likelihood ratio (LR+ve) = infinite).

Parietal pleural thickening was detected in 21 patients, measuring >1cm in 14/33 (42%) malignant and 1/19 (5%) benign patients (χ² 1df 8.11, p=0.004), and <1cm in 2/33 (6%) malignant and 4/19 (21%) benign patients (χ² 1df 2.66, p=0.10). Using a TUS threshold value of pleural thickening > 1cm as suggestive of malignancy, TUS has a sensitivity of 42% (95% CI 26 to 61%), specificity 95% (95% CI 74 to 99%), PPV 93% and NPV 49% for differentiating malignant from benign disease (LR+ve = 8.4). (Figure 1a and Figure 1b on-line supplement).

The presence of nodular pleural thickening was observed in 14/33 (42%) malignant and 0/19 benign cases (χ² 1df 11.03, p=0.009), giving a sensitivity of 42% (95% CI 26 to 61%), specificity 100% (95% CI 82 to 100%), PPV 100% and NPV 50%, LR+ve = infinite).
Thickening / nodularity of the visceral pleura was detected on TUS in 5/33 (15\%) malignant and 0/19 benign cases (sensitivity 15\%), and was not seen on CECT in any case.

Other TUS morphological characteristics
Visceral pleural thickening was observed in 5 patients (all with malignancy), and seen in the absence of associated parietal pleural thickening in 4 cases (Figure 2 on-line supplement).

Pleural thickening was hypoechoic relative to the intercostal muscles in all patients with benign pleural thickening (n=5) (Figure 3a, Figure 3b on-line supplement). In malignant pleural thickening echotexture was non-specific and appeared hypoechoic, hyperechoic or isoechoic.

The morphological characteristics of the diaphragm were compared between malignant and benign groups. Resolution of all 5 layers of the diaphragm was not possible in 10/33 (30\%) malignant and 1/19 (5\%) benign cases ($\chi^2$ 1df 4.53, p=0.033) (Figure 4a on-line supplement). Diaphragmatic nodules measuring 2-22mm in size were identified in 10/33 malignant patients and no patients with benign disease (Table 3) (Figure 4b on-line supplement). The diaphragm was thickened in 23 patients; this was nodular/irregular in 15 cases (Figure 4c on-line supplement) and smooth in 8. Using a TUS threshold value of diaphragmatic thickness >7mm as suggestive of malignancy, TUS has a sensitivity of 42\% (95\% CI 26 to 61\%), specificity 95\% (95\% CI 74 to 99\%), PPV 93\% and NPV 49\% (LR+ve = 8.4) for differentiating malignant from benign disease.

CT diagnosis
The median time interval between the CT examinations and the ultrasound examination was 1 day (range 0-41 days). CT correctly differentiated malignant from benign pleural effusion in 49/52 patients (sensitivity of 97\% (95\% CI 84 to 99\%), specificity 89\% (95\% CI 67 to 99\%), PPV 94\% and NPV 94\%, LR+ve = 8.8). CT identified two patients as false positive (i.e. scored malignant on CT, final diagnosis benign). Both of these patients had extensive supraclavicular and mediastinal lymphadenopathy with distortion of the airways and bilateral effusions suggestive of lymphoma. Subsequent ultrasound guided core biopsy of the supraclavicular lymphadenopathy diagnosed TB in both cases.

TUS versus CT diagnosis
Comparison of TUS and CECT diagnosis is made as CECT is considered to be the gold standard investigation for patients with suspected malignant effusion. The CECT true positive rate was 97\% (32/33) compared to 79\% (26/33) for TUS. Of the 7 false negative TUS patients, in 6/7 the pleural surfaces appeared normal on both US and CT, and the CT diagnosis of malignancy was based on the presence of intraparenchymal masses, nodal enlargement or pulmonary metastasis. In the remaining patient (false negative on both CECT and TUS), there was a prior history of asbestos exposure, smooth pleural thickening on CT which was not visualised on TUS and subsequent thoracoscopic guided biopsy showing benign fibrinous thickening. Repeat CT performed 3 months later due to increasing chest pain and clinical deterioration showed increased pleural thickening, and a clinico-radiological diagnosis of mesothelioma was made. The patient’s clinical course was consistent with this diagnosis (death occurred 2 weeks later). Benign disease (n=19) was correctly diagnosed in all cases using TUS and in 89\% (17/19) using CECT (TB misdiagnosed as malignancy in 2 cases as above).
DISCUSSION

This is the first analysis to specifically assess the utility of TUS in the diagnosis of suspected malignant pleural effusion. The “definitive” diagnosis used in this patient population was well defined and included clinical follow up data of 12 months for all patients with presumed benign disease. Hitherto, TUS has been used as a technique to confirm the presence of fluid, assess fluid characteristics (e.g. septated / echogenic) or guide intervention. Using similar morphological criteria as used in CECT(12), our results show that TUS is able to distinguish malignant from benign effusion with an overall sensitivity of 79% and specificity of 100% (Table 3). These figures are comparable to the previously published data on malignant effusion diagnosis with CECT alone (Table 4), although this was not the primary aim of the study. TUS is a quick, relatively inexpensive and harmless procedure which is increasingly being performed by chest physicians; if these results are confirmed in larger studies, TUS may become a valuable adjunct in the diagnosis of malignant pleural effusion.

Beyond the criteria defined in previous CT studies, we have found several TUS morphological features apparently associated with malignant pleural effusion. In the absence of parietal pleural thickening, visceral thickening and visceral nodularity were associated with malignancy, and not apparently visible on CECT. Autopsy reports have shown that the parietal pleura may be less frequently involved with metastatic disease than the visceral pleura(19). This suggested pathogenesis would be in keeping with our findings in which 4/5 patients demonstrated visceral pleural thickening or nodularity suggestive of visceral deposits in the absence of associated parietal pleural thickening.

Diaphragmatic abnormalities have been shown in this study to predict malignant disease. The normal diaphragm is usually well defined on TUS (due to the presence of fluid in the costophrenic recess), <5mm thick and divided in to 5 distinct layers sonographically. Inability to resolve diaphragmatic layers, the presence of diaphragmatic nodules, and diaphragm thickness of >7mm were associated with malignant pleura disease in this study. TUS appears to be more sensitive than CECT at demonstrating visceral pleural disease and diaphragmatic nodularity.

Although previous studies suggest that differentiating malignant parietal pleural thickening and chronic pleural fibrosis can be difficult on TUS(20), our results suggests that TUS is relatively accurate. In our series, 6 patients were diagnosed with chronic pleural fibrosis following percutaneous or thorascoscopic biopsy, and TUS diagnosed all 6 cases as benign. In contrast to this, the CT appearances were highly suspicious of malignancy in 1 patient, indeterminate in 1 and benign in 4 cases.

Of the 7 false negative TUS cases, 6 (86%) had normal pleural surfaces when assessed by CECT. The absence of detectable pleural disease on thoracic CT in the presence of a malignant pleural effusion has been previously reported (21). In this case, CECT has the clear advantage over TUS of being able to assess for the presence of disease elsewhere (e.g. lung parenchyma, mediastinal nodes, distant metastases), although TUS may be used to assess for the presence of liver metastasis, which was the only abnormality found in one patient.

There are several limitations to this study. Initial TUS examinations were performed by a single observer with 5 years experience in ultrasound but only 6 months experience in pleural US. Although the results may have been improved if a more experienced operator had performed the scans, the close agreement achieved between observers is reassuring. Secondly, the mediastinal surfaces
were not scanned in this study. Although technically challenging, this is possible in patients with large pleural effusion and may have improved our diagnostic accuracy. Thirdly, this is a relatively small study (n=52) in patients recruited from a tertiary referral centre for pleural disease. The incidence of malignancy in this population is likely to be higher than that seen in a less specialist centre, and many of these patients had already undergone prior investigations with negative results (most commonly cytology negative pleural aspirate). However, there is no reason to believe that the morphological characteristics on TUS here shown to be associated with malignant pleural disease should be any different. The relatively high incidence of mesothelioma in this series is likely to be attributable to the institution being the local tertiary referral centre for pleural disease. This may have resulted in a biased estimate of TUS diagnostic performance, if mesothelioma is more easily detected at ultrasound. Finally, although we have compared the specificity and sensitivity of TUS to CECT, this study is underpowered to conduct a non-inferiority analysis of the two techniques.

What implications does this study have to clinical practice? Contrast enhanced CT has a high sensitivity and specificity for malignant pleural effusion, and is the usual next radiological investigation after the chest radiograph. The sensitivity of CECT in published studies is high, although the specificity for TUS in this study is higher than that reported for CECT (table 4). However, there are often delays in obtaining CT and TUS is easier to access, and increasingly being performed by chest physicians. The reasonable specificity and high positive predictive value demonstrated using TUS in this study suggest that TUS may be useful as an initial test (for example in the out patient setting) in the investigation of patients with pleural effusion of unknown aetiology, which may streamline the diagnostic process. Larger studies in populations with a lower pre-test probability of malignant pleural disease are required to assess this fully, including studies to assess if TUS conducted by non-radiologists has a similar predictive value.

CONCLUSION
Blinded assessment of TUS has demonstrated the technique to have a reasonable sensitivity and high specificity and PPV for malignant pleural effusion in the absence of empyema. The presence of pleural thickening >1cm, diaphragmatic nodularity or thickening >7mm, visceral pleural thickening and pleural nodularity/irregularity are associated with malignancy. TUS may therefore be useful not only in guiding thoracocentesis and biopsy, but also as an adjunct to aid diagnosis. Further studies are required to confirm this finding.
### TABLES AND FIGURES

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
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<td><strong>Demographics</strong></td>
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<tr>
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</tr>
<tr>
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<td>17</td>
</tr>
<tr>
<td>Median age (range) years</td>
<td>68 (22-89)</td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
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<tr>
<td>Median age (range) years</td>
<td>61 (41-86)</td>
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<th><strong>Group + diagnosis</strong></th>
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<tr>
<td>Squamous cell lung carcinoma</td>
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<td>Bronchogenic carcinoma (radiological diagnosis only)</td>
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<td>Benign asbestos related effusion</td>
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<tr>
<td>Constrictive pericarditis</td>
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Table 1: Summary of baseline patient characteristics and final diagnoses
*12 mesothelioma cases were diagnosed histocytoplogically, with the remaining 2 diagnosed on clinical and radiological follow up with a history of asbestos exposure.
<table>
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<th>Number of patients</th>
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<tr>
<td><strong>Malignant disease (n=33)</strong></td>
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<td>Pleural histology:</td>
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<td>Percutaneous biopsy</td>
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<td>Thoracoscopic biopsy</td>
<td>4</td>
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<tr>
<td>Other histology:</td>
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<tr>
<td>Supravacular lymph node biopsy</td>
<td>2</td>
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<tr>
<td>Axillary lymph node biopsy</td>
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<tr>
<td>Pleural fluid cytology:</td>
<td>11</td>
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<td>Clinical follow up and repeat radiology</td>
<td>3</td>
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**Benign disease* (n=19)**

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<td>Thoracoscopic biopsy</td>
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<td>Supravacular lymph node biopsy</td>
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<tr>
<td>Pericardectomy</td>
<td>1</td>
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<tr>
<td>Pleural fluid cytology negative:</td>
<td>10</td>
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<td>19</td>
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*Table 2. Method of final diagnosis. Pleural fluid cytology was taken as confirmation of malignancy only in the presence of a confident histopathology opinion reporting confirmed malignant cells on cytology +/- immunostaining as required. In these cases, no further investigation to establish diagnosis was required. Negative pleural fluid cytology was not taken as definitive proof of benign aetiology (hence clinical follow up as below was pursued).

*All patients with a diagnosis of benign disease were followed up for a period of 12 months (at our institution or the referring institution), in which time there was no evidence of malignancy developing within the pleura or elsewhere as the cause of the presenting pleural effusion.

†Two patients underwent non-diagnostic percutaneous pleural biopsy, and subsequent diagnostic thoracoscopy. These patients are only listed once as thoracoscopic biopsies.
<table>
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<tr>
<th>Sonographic finding</th>
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<th>Benign disease n=19</th>
<th>Statistical significance p value (Fisher’s Exact $\chi^2$)</th>
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<tr>
<td>&gt; 1 cm</td>
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<td>1</td>
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<tr>
<td>&lt; 1 cm</td>
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<td>4</td>
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</tr>
<tr>
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<tr>
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<td>0</td>
<td>0.145</td>
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<tr>
<td>Size of effusion</td>
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<tr>
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<tr>
<td>Liver Metastases*</td>
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<tr>
<td>Overall TUS Diagnostic Rate†</td>
<td>26/33</td>
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<tr>
<td>Sensitivity 79%</td>
<td>Specificity 100%</td>
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<tr>
<td>NPV = 73%</td>
<td>PPV = 100%</td>
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**Table 3**: Sonographic findings in patients with malignant and benign pleural effusions. *Liver metastases were the sole abnormality detected in one patient on TUS. †Diagnostic rate of TUS based on the criteria mentioned in the methods section (i.e. diaphragmatic and parietal pleural nodule or nodules, pleural thickening greater than 1 cm or hepatic metastasis)
The study by Leung et al. (12) compared ultrasound (US) and computed tomography (CT) in the diagnosis of malignant pleural disease. The table below summarizes the results of sensitivity and specificity for different pleural changes:

<table>
<thead>
<tr>
<th>Study type</th>
<th>This study (Sensitivity, Specificity)</th>
<th>Leung et al. (12) (Sensitivity, Specificity)</th>
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<td>Parietal pleural thickening &gt;1cm</td>
<td>42% 95%</td>
<td>56% 88%</td>
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<tr>
<td>Nodular pleural thickening</td>
<td>42% 100%</td>
<td>36% 85%</td>
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<tr>
<td>Visceral pleural thickening</td>
<td>15% 100%</td>
<td>NA NA</td>
</tr>
<tr>
<td>Diaphragmatic thickening &gt;7mm</td>
<td>42% 95%</td>
<td>NA NA</td>
</tr>
<tr>
<td>Diaphragmatic layers resolved</td>
<td>30% 95%</td>
<td>NA NA</td>
</tr>
<tr>
<td>Diaphragmatic nodules</td>
<td>30% 100%</td>
<td>NA NA</td>
</tr>
<tr>
<td>Overall</td>
<td>79% 100%</td>
<td>72% 83%</td>
</tr>
</tbody>
</table>

NA: Not assessed

**Table 4:** Sensitivities and specificities for ultrasound and CT determined criteria that are suggestive of malignant pleural disease.
ACKNOWLEDGMENTS
Nil

COMPETING INTERESTS
None

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Thoracic Ultrasound in the diagnosis of malignant pleural effusion

Online Supplement Information

Methods

Ultrasound details

Operators

Prior to TUS, the most recent chest radiograph was reviewed. All ultrasound examinations were performed on a single Esaote Technos MPX 25 ultrasound machine by a single observer (NQ, fellow in thoracic imaging), blind to clinical history and previous imaging at the time of scanning and interpretation. Anonymised video clips and still images of the entire examination were generated. From these TUS findings as detailed below an overall diagnosis of malignant or benign pleural disease was recorded on a reporting proforma The anonymised TUS data was then reviewed separately as a batch by FVG (consultant radiologist), blind to clinical history, previous investigations (including radiology) and physical status and appearance of the patient. The final results of blind analysis were recorded for each observer by NQ.

Technique

Patients were scanned using a 3-5 MHz frequency curvilinear probe that allowed simultaneous visualization of a wider field of view and assessment of the pleural surfaces and effusion. More detailed imaging of the pleura and chest wall was performed using a high frequency high resolution 8-15 MHz linear probe. The chest was scanned along the intercostal spaces from the level of the lateral and posterior costophrenic angles to the apex.
All patients were initially imaged in the upright position during gentle respiration. If visualisation proved difficult at TUS, patients were placed in the lateral decubitus position with their ipsilateral arm raised above or across their chest in order to widen the intercostal space. In addition subtle angulation of the probe allowed the subcostal regions to be more clearly delineated.

During the course of the study, in most cases the pleural surfaces were most readily visualised at the level of the lateral costophrenic angle. This allowed simultaneous assessment of the diaphragm and basal pleura that are generally the most frequently involved in malignant disease. The curvilinear probe proved sufficient in all cases and the higher frequency linear probe added no additional useful information.

For each ultrasound examination the following was recorded:

1) Size of the pleural effusion; recorded as;
   - Large if it occupied greater than two thirds of the hemithorax
   - Moderate if it occupied less than two thirds but greater than one third
   - Small if it involved less than one third of the hemithorax.

2) Nature of the effusion; defined as
   - Anechoic and simple
   - Anechoic with septations
   - Echogenic.

3) Pleural thickening; defined as
   - Thickening measuring > 3mm
   - This was further delineated as smooth, irregular or lobulated
   - The site and maximum pleural thickness documented.
4) The echogenicity of pleural thickening relative to the intercostal muscles.

5) The presence of pleural nodularity (scored as present or absent).

6) Diaphragm (assessed with the 3-5Mhz probe. The available visualisable surface of the diaphragm was assessed in all cases):
   - Thickening (increased thickness along surface of diaphragm)
   - Presence of nodules (defined as a discrete expanded area on top of the diaphragm surface)
   - Number of diaphragmatic layers that could be visualised (binary score - all present or not).

7) For right sided effusions, the liver echotexture for the presence or absence of hepatic metastases.

Where the differentiation of tenacious echogenic fluid from pleural thickening was difficult, colour doppler was used. Absence of colour flow Doppler signal and failure to change position with movement were reported as indicative of a solid mass or pleural thickening (in the absence of heavily septated fluid).

**TUS Diagnosis**

The morphological criteria established as sensitive and specific to malignant pleural disease on CECT was used as the basis of the TUS diagnosis. If a patient had any one of the following criteria on TUS, a diagnosis of malignant disease was recorded:

1. Diaphragmatic nodule or nodules
2. Pleural thickening greater than 1 cm
3. Hepatic metastasis

A provisional diagnosis of malignant or benign pleural disease was recorded on the proforma prior to other investigations and separately by each radiologist.
**Contrast enhanced CT details**

CT examinations were reviewed in all cases. In 40 patients these were obtained on a GE LightSpeed scanner (General Electric, Milwaukee, WI, and U.S.A) with overlapping 5mm sections from the level of the lung apices to the adrenals following intravenous injection of 100mls of Niopam 300 with a 60 second delay, performed at end inspiration. Axial CT and 3D multiplanar reformats were viewed as a batch on a GE Advantage windows workstation on both mediastinal (window level 50 HU, window width 350 HU) and lung (window level -500HU, window width 1500HU) settings by a single observer (FVG, 19 years experience in reporting thoracic CT). The CECT scans were reported blind to the previous TUS result (as the TUS results were anonymised).

In the remaining 12 patients CT studies had already been performed at other regional institutions prior to transfer for further diagnostic workup, and it was not considered ethical to subject these patients to further radiological examination solely for the purpose of this study. The hard copy CT images from these institutions were reviewed blind to the previous TUS result.

The pleura was evaluated on CECT using the previously described criteria by Leung et al. and Lynch et al. for malignant and benign disease(1;2). In addition the presence of parenchymal nodules/masses, lymphadenopathy with a short axis > 1cm, cardiomegaly and bone, hepatic or adrenal metastasis was documented. An overall CT diagnosis of malignant or benign disease was recorded based on the criteria of Leung et al in addition to the presence of metastatic disease or clear intraparenchymal evidence of malignancy.
**Definitive diagnosis**

Definitive diagnosis was obtained by histological, cytological or microbiological confirmation. In the absence of the above, the combination of clinical features and/or prolonged radiological follow up as appropriate was used to define the final diagnosis. All patients with benign disease were followed up (as part of routine clinical practise in our institution or at the host institution) for a minimum of 12 months, to confirm that malignant disease in evolution did not develop. For the purposes of this study, “definitive diagnosis” was considered to be the diagnosis which was imparted to the patient and the diagnosis on which basis the patient received appropriate treatment (see results).

**Statistical analysis**

The data was analysed using the Graph Pad In Stat version 3.08 for windows 98, Graph Pad software, San Diego California, USA software program. 2X2 tables were created to evaluate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of:

1. TUS in detecting malignancy and differentiating between malignant and benign disease
2. The comparative diagnostic accuracy of US and CT
3. Assessment of the appearances of the parietal, visceral and diaphragmatic pleural surfaces between benign and malignant disease.

A p value of <0.05 was considered statistically significant.
FIGURES + LEGENDS

Figure 1a. Thoracic ultrasound performed with a right lateral intercostal approach demonstrates gross lobulated parietal pleural thickening and nodularity (arrow) in a 50 year old man with sarcomatous mesothelioma. The pleural effusion is contains echogenic debris suggestive of an exudative effusion.

Figure 1b: Axial contrast enhanced CT confirmed the sonographic findings.
**Figure 2.** There is wedge shaped collapse of the right lower lobe due to mass effect from the large anechoic pleural effusion. The visceral pleura is thickened and irregular in keeping with visceral deposits (arrow). Note the adjacent parietal pleural surface is normal.
Figure 3a. A 23 year old patient who presented with recurrent bilateral exudative pleural effusions. CT showed bilateral smooth pleural thickening < 1cm in thickness of indeterminate aetiology (arrows).

Figure 3b. The ultrasound demonstrated multi-septated and complex pleural effusions with smooth pleural thickening (arrow) hypoechoic compared to intercostal muscle. Percutaneous CT guided biopsy was performed and a diagnosis of chronic inflammation established.
**Figure 4a.** Ultrasound showing the typical appearance of the normal diaphragm where the 5 layers can be delineated in real-time as alternate hypo (arrow) and hyperechoic bands (green cursor).

**Figure 4b.** Multiple hyperechoic diaphragmatic nodules in a 73 year old female with metastatic adenocarcinoma (arrow).
Figure 4c. Irregular thickening of the diaphragm and nodularity measuring < 5mm in diameter (arrow).

REFERENCE LIST

