Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial

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Summary

Background Over 200 000 pleural effusions are attributable to cancer in the UK and USA every year. Cytological examination of pleural fluid classifies about 60% of malignant effusions. Pleural biopsy needs to be done in the remaining cases. We aimed to assess whether CT-guided biopsy is an improvement over standard pleural biopsy in this setting.

Methods 50 consecutive patients with cytologically negative suspected malignant pleural effusions were recruited. All had a contrast-enhanced thoracic CT scan to assess pleural thickening. Patients were randomly allocated, stratified by baseline pleural thickening, to either Abrams' pleural biopsy (standard care; n=25) or CT-guided cutting needle biopsy (n=25). Sensitivity for pleural malignancy from the biopsy specimen was the primary endpoint, with the patient's clinical outcome after 1 year being the diagnostic gold standard. Analysis was per protocol.

Findings Three patients did not undergo biopsy. Abrams' biopsy correctly diagnosed malignancy in eight of 17 patients (sensitivity 47%, specificity 100%, negative predictive value 44%, positive predictive value 100%). CT-guided biopsy correctly diagnosed malignancy in 13 of 15 (sensitivity 87%, specificity 100%, negative predictive value 80%, positive predictive value 100%; difference in sensitivity between Abrams' and CT-guided 40%, 95% CI 10–69, p=0·02). Diagnostic advantage was similar in patients proving to have mesothelioma.

Interpretation Primary use of CT-guided biopsy would avoid doing at least one Abrams' biopsy for every 2·5 CT-guided biopsies undertaken. In cytology-negative suspected malignant pleural effusions, CT-guided pleural biopsy is a better diagnostic test than Abrams' pleural biopsy.

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Introduction

About 40 000 cases of pleural effusion are attributable to cancer every year in the UK, and 175 000 in the USA.[1] Incidence of primary pleural malignant disease—mesothelioma—is rapidly rising in the UK, and is predicted to account for about 1% of all deaths in UK men born in the 1940s.[2,3] Cytological examination of pleural fluid for malignant cells establishes a positive diagnosis of malignancy in only 60% of carcinomatous effusions[4–11] and 30% of effusions secondary to mesothelioma.[12,13] Pleural biopsy to enable histological examination is needed for accurate diagnosis in the remainder. Pleural biopsy is therefore an important diagnostic method, which will be of growing relevance during the predicted mesothelioma epidemic of the next 20 years.[2,3]

Despite the substantial burden of disease for which pleural biopsy is indicated, to our knowledge, no randomised trials have been done to assess the optimum diagnostic method, and no improvement has been made in the technique, which has been used for over 40 years. The standard technique uses a reverse bevel needle, such as the Abrams' needle,[8,14,15] with local anaesthetic and without image guidance. This technique is associated with a substantial incidence of complications, including pneumothorax, haemothorax, and empyema, and in rare cases can be fatal.[4,6–8,16] Furthermore, yield over pleural fluid cytology alone is increased by only 7–26%,[5,7,16] and the procedure is painful, especially when done by inexperienced operators.

CT-guided cutting-needle biopsy of pleural tissue associated with a pleural effusion is a relatively new technique compared with Abrams' biopsy.[17,18] Results of observational series suggest this technique might improve diagnostic sensitivity to about 80% for pleural malignancy.[17–20] However, these studies are non-randomised, tend to include CT-guided and ultrasound-guided procedures, and are mainly done in patients without pleural effusions.[19,20] If CT-guided biopsy is strikingly superior to traditional Abrams' biopsy, this technique would produce better diagnostic information from fewer passes—and by inference fewer complications and greater acceptability to patients. Reduction of the number of pleural procedures in patients with mesothelioma is especially important, because one in three biopsy sites are invaded by this tumour unless the sites are irradiated.[21]

We therefore did a prospective trial to measure sensitivity for malignant disease with standard Abrams' biopsy and with CT-guided needle biopsy, to assess whether CT-guided biopsy was an improvement over the standard technique.

Methods

Study design and setting

This study was a prospective, parallel, randomised trial done in one centre (Oxford Centre for Respiratory

Medicine, Oxford, UK). Patients with undiagnosed pleural effusions are referred to the Oxford unit directly from general practitioners (60%), from other local hospital consultants (30%), and occasionally from respiratory consultants in other neighbouring health authorities (10%). The population served by this unit has a low prevalence of asbestos exposure and hence a low frequency of mesothelioma when compared with centres in more industrialised areas.

Patients

All patients eligible for the trial who presented over the 18-month recruitment period (April, 2000, to September, 2001) were offered entry into the study. Two of us (NAM and RJOD) enrolled patients. Inclusion criteria for the trial were: (1) unilateral pleural effusion with clinical suspicion of malignant pleural disease; and (2) at least one negative pleural fluid cytological examination for malignant cells. Exclusion criteria were: (1) bilateral pleural effusions; (2) transudative pleural effusions (pleural fluid protein <35 g/dL) associated with heart failure or hypoalbuminaemia such that the clinical prior probability of a hydrostatic effusion was high; (3) any pleural fluid cytological examination showing definite malignant cells; (4) any bleeding diathesis sufficient to make pleural biopsy unusually hazardous; (5) inability to give informed consent; and (6) age younger than 18 years. The study was approved by the central Oxford research ethics committee (number 00.155), and all participants gave informed consent.

Procedures

All patients underwent initial contrast-enhanced CT of the thorax without previous removal of pleural fluid. We did scans on a GE light-speed multi-slice CT scanner (General Electric, Milwaukee, USA) with overlapping 5-mm sections from the apex of the lungs to the costophrenic recess. We infused 100 mL iohexol (omnipaque; Nycomed Amersham, UK) via an arm vein, and scanning started 60 s after infusion. We measured the amount of parietal pleural thickening, and participants were divided into those with maximum thickening of less than 5 mm or 5 mm or more (figure 1).

We randomly assigned patients to either CT-guided pleural biopsy or Abrams' pleural biopsy by a series of presealed and numbered opaque envelopes containing the randomisation status written on card, with a block size of four. An administrator for the Oxford unit, who was not
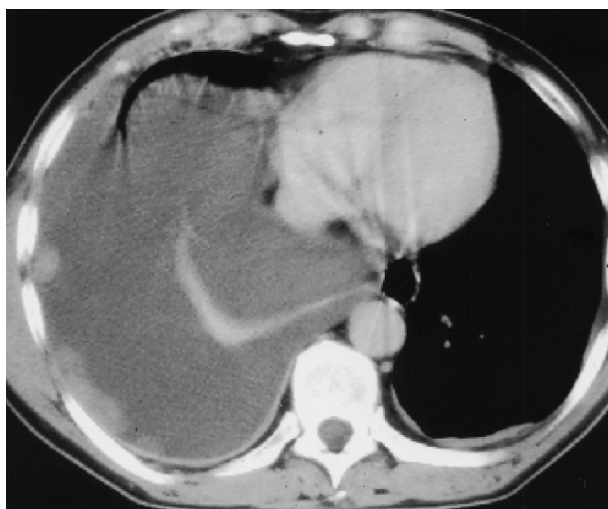

Figure 1: **Contrast-enhanced thoracic CT image of an exudative pleural effusion showing enhancement of the pleural tumour**

involved in the trial, prepared the allocation sequence. One of us (NAM) assigned the type of biopsy by selecting the next numbered envelope. Randomisation was stratified by the depth of maximum baseline pleural thickening (<5 mm or ⩾5 mm), quantified from the thoracic CT scans, since this depth is likely to be a powerful predictor of the accuracy of the cutting needle biopsy. The assigned type of biopsy was done within 2 weeks of randomisation. Prothrombin time, activated partial thromboplastin time (APTT), and platelet count were confirmed to be normal before biopsy, and both biopsy types were done as day-case procedures.

Abrams' biopsy procedures were done by an experienced operator (NAM). This operator was only aware of whether the patient had maximum pleural thickening less than 5 mm or 5 mm or more on the CT scan; he was masked to all other information from the scan, including distribution of pleural thickening. Standard aseptic technique was used, and local anaesthetic was given, with about 10 mL 2% lidocaine infiltrated into the skin, intercostal space, and parietal pleura. Four to six biopsy specimens were taken from the upper surface of the rib below the entry site and were immediately fixed in formalin for later histological analysis. One further biopsy specimen was taken and sent in saline for bacterial culture, including mycobacterial studies. Haemostasis was achieved, and we closed the skin incision with one suture if needed. A chest radiograph was done 2–4 h after the procedure to identify any pneumothorax.

CT-guided biopsy procedures were done by an experienced operator (FVG) with an 18-gauge needle (Biopsy TM AB, Radiplast, Sweden) and with image guidance. After identification of the maximum area of pleural thickening, standard aseptic technique was used, and local anaesthesia induced. The cutting needle was then inserted into the patient such that it was aligned to pass along the plane of the pleura, enabling successful biopsy of even minimum thickening (figure 2).[19] Biopsy specimens were taken from the parietal pleural in all patients, from the area of maximum thickening. None of the biopsy samples was obtained from the diaphragm. Generally, only one biopsy pass was needed, but a second pass was done if the initial sample was deemed macroscopically unsatisfactory. No more than two biopsy passes were made in any patient. A chest radiograph was done 2–4 h after the procedure to detect any pneumothorax.

Biopsy samples were processed by the Oxford Radcliffe Hospital histology service as part of normal practice. Histology request cards did not include information about any CT features. Identification of malignant from benign tissue, and cellular classification of any identified tumour, was based on morphological characteristics. A range of immunohistochemical stains was used to differentiate tumours of epithelial origin from those of mesothelial origin and so lend support to the morphological assessment. These stains included the epithelial markers carcinoembryonic antigen and BerEp4, and the mesothelioma markers calretinin, thrombomodulin, and cytokeratin 5. If we suspected sarcomatous mesothelioma, we used broad-spectrum cytokeratin (MNF 116) and occasionally TP53.

The pathologist attempted to conclude categorically malignant or benign disease. When he found it impossible to do this—and therefore issued an indeterminate or suspicious but not diagnostic report—the biopsy result was treated as a negative result for diagnosis of malignancy and the patient underwent a further biopsy procedure. If malignancy was later diagnosed, we treated the original non-diagnostic report as a false negative.
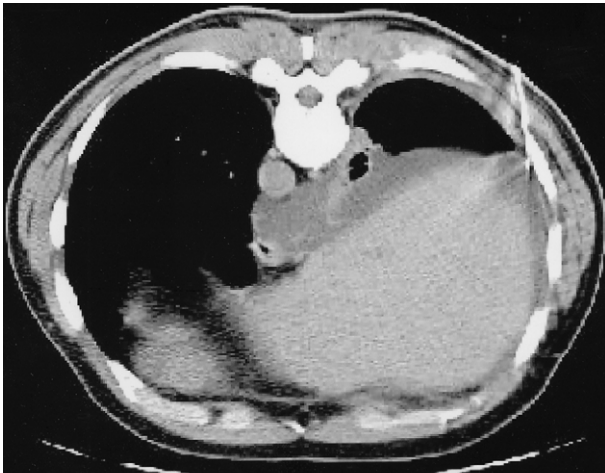
Figure 2: **Thoracic CT showing a CT-guided cutting needle pleural biopsy**
The needle is inserted tangentially to gain an adequate core of pleural tissue despite the limited degree of pleural thickening.

Patients whose biopsy findings established a diagnosis of malignancy were managed appropriately, with clinical follow-up being maintained to confirm a clinical course consistent with malignant disease. Patients whose initial biopsy sample was judged either benign or indeterminate underwent clinical review. Participants in whom we still regarded malignancy as the likely diagnosis proceeded to further needle biopsy, thoracoscopy, or both for definitive diagnosis. In patients in whom the probable clinical diagnosis was benign disease, we did thoracic MRI as a further non-invasive test to seek malignancy, and we pursued a period of expectant clinical follow-up to ensure that undiagnosed malignant disease did not later become evident. Benign diagnoses needing specific therapy (such as tuberculosis) were treated appropriately. The period of expectant clinical follow-up was at least 1 year in all patients. All those with malignant mesothelioma received radiotherapy at a dose of 21 Gy in three fractions to their biopsy site.

Statistical analysis

The primary endpoint was sensitivity of each biopsy method for detection of pleural malignancy. Secondary endpoints were other elements of the decision matrix (specificity, positive predictive value, and negative predictive value) and complication rates. We did all analyses with SPSS version 10 (SPSS, Chicago, USA) and sensitivities were compared with the χ^2 test. Subgroup analysis of sensitivity in patients with an eventual diagnosis of malignant mesothelioma was also done.

We estimated the sample size for this trial from results of observational reports of the efficacy of Abrams' needle biopsy and CT-guided cutting needle pleural biopsy.[5,7,16–20] In these studies, Abrams' biopsy has a true positive rate of about 20% and CT-guided cutting needle biopsy of about 85%. From these figures we estimated that 50 patients would be needed for the trial (90% power, 5% significance). We did one planned interim data review after 25 patients were randomised, to check this power calculation.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the report for publication.
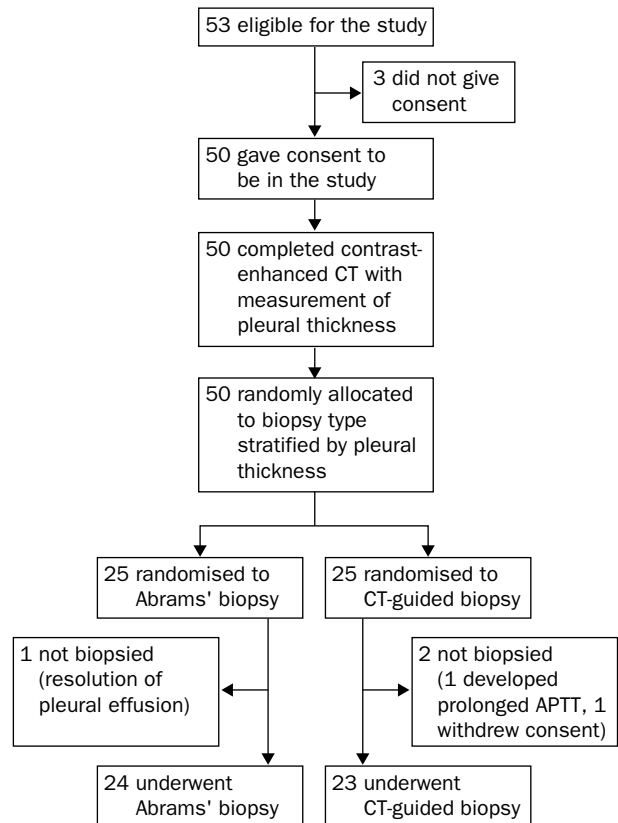
Figure 3: **Trial profile**

Results

During the recruitment period, 53 patients who were eligible for the study were identified; 50 consented to enter the study (figure 3). 45 of these presented directly to the Oxford Centre for Respiratory Medicine, the other five were referred from other hospitals in the region. 46 of the patients had one non-diagnostic pleural aspiration before randomisation; the remaining four had two negative aspirations. None had undergone a pleural biopsy procedure before trial entry. Characteristics of patients agreeing to take part in the study are shown in table 1. Of the 50 randomly allocated patients, three did not undergo pleural biopsy (figure 3). 33 (66%) of the 50 had a diagnosis of pleural malignancy, confirmed by more than 1 year of clinical follow-up (table 2).

Pleural tissue for histological assessment was obtained in all 23 patients who underwent CT-guided biopsy and in 23 of 24 receiving Abrams' biopsy. In the patient who did not have pleural tissue on histology, the cause of pleural effusion was tuberculosis, with *Mycobacterium tuberculosis* cultured from a sputum sample; the effusion resolved after 6 months of antituberculosis treatment. The sample was therefore classified as benign for statistical tests.

Characteristic	Abrams' pleural biopsy (n=25)	CT-guided cutting-needle biopsy (n=25)
Age (years, mean [SD])	70·2 (13·8)	66·8 (13·8)
Sex (M/F)	16/9	17/8
Side of effusion (left/right)	14/11	10/15
Maximum degree of pleural thickening on CT (<5 mm)	17	17

Data are number of patients unless otherwise stated.

Table 1: **Patients' characteristics**

	Abrams' needle biopsy group (n=25)	Cutting needle biopsy group (n=25)
Malignant neoplasms	17	16
Adenocarcinoma	3	4
Squamous cell carcinoma	0	1
Undifferentiated cell carcinoma	1	1
Lymphoma	0	1
Mesothelioma	11	9
Chrondrosarcoma	1	0
Atypical carcinoid tumour	1	0
Non-malignant disease	8	9
Inflammatory pleuritis	3	2
Pleural fibrosis and pleural plaques	3	4
Benign pleural thickening	0	2
Chronic empyema	0	1
Tuberculosis pleuritis	1	0
Chronic heart failure (unilateral)	1	0

Data are number of patients. Diagnosis based on biopsy findings and more than 1 year of clinical follow-up.

Table 2: **Final diagnoses of the causes of the pleural effusions in all 50 patients who entered the trial**

No complications were reported in the group receiving CT-guided biopsy, and one moderate sized subcutaneous haematoma was seen in the Abrams' biopsy group (needing conservative treatment only).

Sensitivity for pleural malignancy was significantly higher with CT-guided biopsy than with Abrams' biopsy (CT biopsy 87% [13/15], Abrams' biopsy 47% [8/17]; difference 40%, 95% CI 10–69, p=0·02). The specificity, positive predictive value, and negative predictive value of CT-guided biopsy was 100%, 100%, and 80%, respectively, and the corresponding values for Abrams' biopsy were 100%, 100%, and 44% (table 3). Both biopsy procedures were specific, with no firmly established histological diagnosis of malignancy being changed on clinical follow-up.

19 patients had a final diagnosis of malignant mesothelioma, eight in the CT-guided biopsy group (seven by biopsy alone) and 11 in the Abrams' biopsy group (six by biopsy alone). The results in this subgroup accord with the overall study result but, because of the small sample size, were not significant (p=0·13). For diagnosis of mesothelioma, CT-guided biopsy had a sensitivity of 88%, specificity 100%, negative predictive value 94%, and positive predictive value 100%. Abrams' biopsy had respective values of 55%, 100%, 72%, and 100%.

Discussion

We have shown that CT-guided pleural biopsy is more effective than standard Abrams' biopsy in diagnosis of malignant pleural disease. The size of this advantage is considerable. Standard Abrams' biopsy correctly diagnosed malignancy in 47% of patients eventually proved to have pleural malignancy, whereas CT-guided biopsy accurately identified 87%. Thus, undertaking CT-guided biopsy as the initial procedure would avoid doing repeated biopsy in 40%

	Final diagnosis of malignancy	Final diagnosis of benign disease
Abrams' needle biopsy		
Positive for malignancy	8	0
Negative for malignancy	9	7
CT-guided cutting needle biopsy		
Positive for malignancy	13	0
Negative for malignancy	2	8

Data are number of patients.

Table 3: **Comparison of final diagnosis with the two biopsy methods in the 47 patients who actually underwent pleural biopsy**

of patients compared with current practice, equating to one avoided biopsy procedure for every 2·5 CT-guided procedures done. This advantage is achieved with a technique that usually needs only one biopsy pass and at most two, compared with four to six biopsy passes needed with the standard Abrams' technique.

Since incidence of malignant mesothelioma is rapidly rising,[2,3] it is important to address whether the benefits seen in this study group as a whole are reproducible in the subgroup eventually diagnosed with malignant mesothelioma. We therefore did a subgroup analysis in these patients. We reported a similar benefit with CT-guided biopsy, with a sensitivity of 88% for mesothelioma, which is substantially higher than 55% sensitivity with Abrams' biopsy. The diagnostic advantage of CT-guided cutting-needle biopsy over Abrams' biopsy was also similar in the subgroup with malignancies that were not attributable to mesothelioma (sensitivity 33% with Abrams' vs 86% with CT-guided cutting-needle; data available from authors).

During the 18 months of recruitment to this study, our unit saw 53 patients with cytology-negative pleural effusions needing biopsy for possible pleural malignancy. These cases arose from our local population of 500 000. Since CT-guided biopsy accurately classifies 40% more participants than standard Abrams' biopsy, and assuming the populations of the UK and USA are 60 million and 280 million, respectively, our data imply that first use of CT-guided biopsy would avoid about 1700 further biopsy procedures per year in the UK and 8000 in the USA. This estimate is likely to be conservative.

Oxford (UK) has a low community prevalence of asbestos exposure and hence a low incidence of pleural mesothelioma. The UK Institute of Cancer Research estimates the present incidence of this disease in the UK at about 57 per million men per year (http://www.hse. gov.uk). This estimate predicts that about 60 new cases of pleural mesothelioma should arise in the population our hospital serves over the 18-month recruitment period to our trial—three times as many as we reported in our study.

Some patients failing standard Abrams' biopsy will need more than one subsequent biopsy procedure. Also, we had an unusually high sensitivity (47%) with our Abrams' biopsy procedures, emphasising that this procedure was done competently in this study. This finding might suggest that the clinical advantage of CT-guided biopsy would be even greater in centres in which the Abrams' success rate is more typical (7–27%).[5,7,16]

In western Europe, the incidence of malignant mesothelioma is forecast to double over the next two decades,[13] and 1% of UK men born in the 1940's cohort could die from this disease.[2] About 90% of these patients will present with an undiagnosed pleural effusion.[22,23] For these patients, an improved pleural biopsy procedure will be especially valuable. Rapid diagnosis with a minimum of invasive procedures is needed, since tumour invades 30% of biopsy tracks in mesothelioma, requiring early radiotherapy to the biopsy site.[24]

Several possible factors could contribute to the diagnostic advantage of CT-guided pleural biopsy seen in this trial. The most obvious of these is the ability of imaging to ensure that the biopsy specimen is taken from an area of abnormal pleural tissue. Pleural malignancy is characteristically patchy and typically preferentially basal or on the diaphragm.[25] Tumour in this distribution might either be missed by standard Abrams' biopsy or actually be out of reach by this technique. Results of observational series have suggested a substantial improvement in quality of samples in these situations when CT-guided biopsy is used.[26] The cores of tissue generated by this technique might also have less crush

artifact than typically seen with Abrams' biopsy samples.[27]

Only two patients with pleural malignancy were not diagnosed with the first biopsy in the CT-guided cutting-needle biopsy group. Maximum pleural thickening on baseline CT was less than 5 mm in both patients. This outcome results in 75% sensitivity for malignancy in patients in whom pleural thickening was less than 5 mm and a sensitivity of 100% for those in whom it was more than this.

The diagnostic advantages of CT-guided biopsy might also be associated with fewer adverse events. In this study, only one significant complication was noted (a moderate haematoma in the Abrams' group). However, in other series, Abrams' biopsy has been shown to be associated with pneumothorax in 3–20% of cases, and haematoma, pleural infection, haemothorax, and vagal syncope.[4,6–8,16] By contrast, CT-guided cutting needle biopsy seems to be safe.[19,20,26]

The CT-guided biopsy technique used in this trial has several novel features. In previous reports, use of CT-guided biopsy has been described in pleural thickening without pleural fluid.[22,23,26] We showed it is also effective when fluid is present, and we have also used it in cases of very thin pleural thickening. To achieve adequate diagnostic samples in patients with thin pleural thickening, we used a tangential approach,[19] which proved effective in gathering of biopsy tumour, even when parietal pleural thickening was less than 5 mm at its maximum thickness. In the subgroup of patients with less than 5 mm pleural thickening, sensitivity was still 75%.

Sensitivity for diagnosis of malignancy with CT-guided cutting-needle biopsy in this study (87%) is only slightly lower than published sensitivities from two large thoracoscopy series (95%).[28,29] Thoracoscopy has the added advantage of being able to undertake other therapeutic options at the same time, in particular talc poudrage, but has the disadvantages of being more invasive, costly, and hazardous in very frail patients.

Universal uptake of obtaining pleural tissue via CT-guided cutting needle biopsy instead of Abrams' needle biopsy would imply greater CT usage and hence cost. This extra cost might be offset by savings made through the fewer pleural biopsy procedures needed to obtain a definitive diagnosis, reduced post-biopsy radiotherapy needs, and lower palliative care costs (secondary to decreased rates of chest wall invasion and pain). We have not done a health-care economic analysis in our study, and so cannot directly address whether this approach is cheaper or more expensive overall.

In conclusion, we recorded a clinically and statistically significant improved sensitivity for diagnosis of pleural malignant disease with CT-guided pleural biopsy compared with traditional Abrams' biopsy. This advantage was gained with the need for fewer passes. CT-guided pleural biopsy should be the preferred biopsy method in patients needing biopsy for possible malignant disease.

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