Original Article

Diagnostic value and safety of medical thoracoscopy in undiagnosed pleural effusions—a prospective observational cohort study

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Background: With the need for "actionable histology" in the current era of targeted cancer treatment, and the increasing practice of upfront thoracoscopy (without a prior diagnostic thoracentesis) or a "biopsy first" approach in suspected malignant pleural effusions (MPEs), we sought to prospectively evaluate the diagnostic accuracy, including full molecular profiling of cancer, and safety of medical thoracoscopy (MT) at a tertiary referral hospital.

Methods: Patients with MT performed for an undiagnosed pleural effusion between January 2020 and December 2022 were included in this observational cohort study. All procedures were performed with a semirigid thoracoscope under conscious sedation. Clinical outcomes and adverse events were recorded prospectively.

Results: We evaluated 141 patients, with a mean age of 67±12 years. Talc poudrage was performed in 67 (47.5%) patients with a median of 2 [interquartile range (IQR), 1–4] hospitalisation days after MT. Upfront thoracoscopy was performed in approximately half (55.3%) of patients. The overall diagnostic accuracy of MT was 95.7% in our cohort. A final diagnosis of cancer was made in 116 (82.3%) patients, with lung (67.2%) and breast cancer (8.6%) the most common. The diagnostic sensitivity of MT for malignancy was 94.8%, and molecular profiling of relevant cancer types for oncogenic mutations was achieved in all patients with malignancy seen on histopathology. The most common non-malignant diagnosis was tuberculous pleuritis in 14 patients (9.9%). Major complications occurred in 3 (2.1%) patients. Two patients had re-expansion pulmonary edema that resolved with low flow oxygen supplementation in the general ward, and one patient required intensive care unit admission for cardiac tamponade from a malignant pericardial effusion. There were no cases of mortality, bleeding complications or persistent air leaks.

Conclusions: MT is a well-tolerated and effective option for the evaluation of undiagnosed pleural effusions. With expanding utility and expertise with MT and other pleural interventions, the challenge for respiratory physicians is integrating these into expeditious diagnostic and effective therapeutic pathways, individualised to patients' needs.

Keywords: Thoracoscopy; pleural effusion; malignant pleural effusion (MPE); tuberculous pleuritis; cancer

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Introduction

Medical thoracoscopy (MT) is widely used for diagnostic and therapeutic interventions in patients with undiagnosed pleural effusions and is an essential part of any specialist pleural disease service (1,2). Unlike video-assisted thoracoscopic surgery (VATS) which requires general anaesthesia and single-lung ventilation, MT is performed under local anaesthesia and conscious sedation, and in some centres as a day procedure. Pleural biopsies performed under direct visualisation and inspection of the pleural space explains the high diagnostic yield (up to 95% sensitivity) for the undiagnosed pleural effusion, compared to image guided biopsies, closed pleural biopsies, and in particular pleural fluid cytology with only a sensitivity of 50–60% for malignant pleural effusions (MPEs) (3,4). With MT, in addition to diagnostic parietal pleural biopsies, large volume therapeutic drainage of the pleural effusion and definitive intervention for fluid control such as administration of talc poudrage for pleurodesis or insertion of an indwelling pleural catheter (IPC) may also be performed concurrently. This allows for a 'one stop' approach to evaluation and management of symptomatic pleural effusions (5,6).

Rigid thoracoscopy has traditionally been the procedure of choice for MT (2). The alternative is the semirigid thoracoscope, which has the advantage of increased manoeuvrability and visualisation of the pleural space, allowing for biopsies from areas of the parietal pleura that are challenging to reach with rigid instruments. Its similarity with a flexible bronchoscope also enables easy adaptation for respiratory physicians. With rigid thoracoscopy, larger pleural biopsy specimens can be obtained, but whether this results in increased diagnostic yield is unclear, with conflicting reports from randomised trials comparing both techniques (7,8).

The poor sensitivity of pleural fluid cytology for the diagnosis of MPE has encouraged the practice of an "upfront" biopsy approach, where a pleural biopsy is performed (without a prior diagnostic thoracentesis) for patients with suspected MPE (3,9). Furthermore, in the current era of targeted oncological therapy, simply confirming the diagnosis of malignancy is no longer adequate. There is now a need for "actionable" cytology or histology which is defined as having sufficient yield for molecular profiling and identification of targetable oncogenic mutations. With the increasing utility of MT, including upfront thoracoscopy, for the evaluation of undiagnosed pleural effusions, we sought to prospectively evaluate the diagnostic accuracy (including "actionable histology" for MPE) and safety of semirigid thoracoscopy in a Southeast Asian tertiary hospital. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-219/rc).

Highlight box

Key findings

- In this prospective cohort study, where approximately half of patients underwent upfront medical thoracoscopy (MT), the diagnostic sensitivity for malignant pleural effusions (MPEs), including complete molecular profiling of relevant cancers, was 94.8%.

What is known and what is new?

- MT is increasingly utilised for the evaluation of undiagnosed pleural effusions.
- MT has a good safety profile and an excellent yield of "actionable histology"—where adequate profiling of oncogenic mutations is achieved in addition to histological diagnosis.

What is the implication, and what should change now?

- Upfront MT is an attractive approach to suspected MPE. More studies are required to determine which patients will benefit most from a "biopsy-first approach".

Methods

We performed a prospective observational cohort study including all consecutive patients who underwent MT between January 2020 and December 2022 at the Singapore General Hospital (SGH). SGH is the largest tertiary hospital in Singapore, with a 2,000-bed capacity. Clinical data including patient demographics, clinical characteristics, imaging findings and outcomes were recorded prospectively. Pleural fluid biochemistry was determined based on analysis performed from pleural aspirations prior to MT, or from pleural fluid samples collected during MT, whichever was earlier. After discharge from hospital, patients were reviewed in our pleural clinic, with subsequent follow-up appointments determined by their clinical course and diagnosis.

The decision to perform thoracentesis or pleural drainage before referral to the hospital's pleural service for MT was determined by the primary physician. For patients who were referred to the pleural service with no prior pleural procedure performed, the decision for upfront MT was made based on the clinical suspicion for MPE and

a shared decision making with the patient regarding the options for evaluation. MT procedures were performed by three Respiratory physicians who led the pleural service in the hospital (K.J.G., C.K.L. and Q.L.T.).

All MT procedures were performed in a dedicated endoscopy suite, with a semirigid thoracoscope (Olympus LTF 160). Patients were placed in the lateral decubitus position, and transthoracic ultrasound was performed to identify the site of entry, generally along the mid axillary line between the 4th and 7th intercostal space. All patients had the procedure performed under light to moderate sedation using titrated dosages of intravenous midazolam and fentanyl. Supplementary oxygen was applied via nasal cannula, with vital signs and continuous cardiac rhythm monitored. A single dose of intravenous antibiotics (amoxicillin/clavulanic acid or clindamycin in event of penicillin allergy) was administered prior to the procedure. After skin sterilisation and infiltration of local anaesthesia (10–20 mL of 1% lidocaine), blunt dissection using a Kelly forceps was performed to the pleural space, and the semirigid thoracoscope introduced into the pleural space through a trochar. Using a single port entry, pleural fluid was aspirated using a sterile catheter. Inspection of the thoracic cavity followed, and whenever feasible, pleural biopsies were taken under direct vision from abnormal or suspicious areas of the parietal pleura for histopathology and microbiological examination. Pleural biopsies were performed with forceps biopsy only, and on average, between 8–12 biopsy samples were taken for each patient. If indicated, pleurodesis was performed using talc poudrage (talc insufflated into the pleural cavity using a catheter and bulb syringe). For cases where talc pleurodesis was performed after MT, usually due to suspicion for a non-expandable lung including significantly diseased or thickened visceral pleura, in the presence of expandable lung seen on chest radiograph after MT, talc slurry was instilled via the chest tube during the same admission. For both talc slurry and talc poudrage, four grams of talc powder (Steritalc, Novatech, La Ciotat, France) was used for all patients. A 20-F chest tube was inserted at the end of the procedure via the same entry port and connected to an underwater seal drainage system. It was secured by an anchoring suture with a separate locking suture placed. The chest tube was removed when the drained fluid was less than 200 mL/day. For IPCs that were concurrently inserted during thoracoscopy, the IPC was inserted at a separate rib space, and the IPC insertion into the pleural space was made with direct visualisation with the thoracoscope. Both IPC and 20-F chest tube were left in situ, and the 20-F chest tube removed the next day if there was no evidence of an active air leak. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was submitted to the institutional review board. The informed consent for this analysis was waived and the study was exempted from formal review, as it was an observational study with subsequent de-identification of data.

Statistical analysis

Descriptive statistics of the variables were expressed with mean and standard deviation, median with interquartile range (IQR), or numbers with percentage. Continuous variables were compared using Student's *t*-test and the Mann-Whitney *U* test, and discrete variables compared using chi-square tests. All statistical analyses were performed using SPSS statistics software version 22.0 (IBM Corp., Armonk, USA). P values of <0.05 were considered to be statistically significant.

Results

One hundred and forty-one patients had MT performed during the study period, and their characteristics are summarised in *Table 1*. The pleural cavity was accessible for thoracoscopic examination in all patients during the study period. The mean age of patients was 67±12 years, and most patients (55.3%) had a large pleural effusion (>50% hemithorax on presenting chest radiograph). All patients had CT imaging as part of the diagnostic workup. A prior thoracentesis or pleural drainage was performed in 63 (44.7%) patients. Procedural details are shown in *Table 2*. The mean volume of pleural fluid removal during thoracoscopy was 1,489±616 mL, and 82 (58.2%) patients received either talc poudrage, or talc slurry during the same hospitalisation. The median length of stay following thoracoscopy was 2 (IQR, 1–4) days.

Thoracoscopy-related complications are shown in *Table 3*. There were no procedure-related deaths, procedure-related prolonged air leaks (≥7 days) or bleeding complications. Major complications were seen in 3 (2.1%) patients. Two patients developed hypoxemic respiratory failure secondary to re-expansion pulmonary edema, which improved with supportive treatment in the general ward, and were weaned off oxygen supplementation by 72 hours. One patient required intensive care unit admission for respiratory failure

Table 1 Characteristics of study population

Clinical characteristics	Values (n=141)
Age (years)	67±12
Female sex	68 (48.2)
Ethnicity	
Chinese	122 (86.5)
Malay	9 (6.4)
Indian	2 (1.4)
Others	8 (5.7)
ECOG performance status	
0	88 (62.4)
1	48 (34.0)
2–3	5 (3.5)
Charlson Comorbidity Index	3 [2–5]
Known or active cancer	20 (14.2)
Smoker or ex-smoker	47 (33.3)
Site of thoracoscopy (left)	63 (44.7)
Size of pleural effusion based on chest radiograph	
<25% hemithorax	5 (3.5)
25–50% hemithorax	58 (41.1)
>50% hemithorax	78 (55.3)
Previous thoracentesis or pleural drainage	63 (44.7)
Pleural fluid lactate dehydrogenase (U/L)	603 [402–1,261]
Pleural fluid protein (g/L)	48 [42–53]
Exudative pleural effusion (Light's Criteria)	140 (99.3)
Malignant cells on pleural fluid cytology[†]	69 (48.9)

Data are presented as mean ± standard deviation, median [interquartile range] or n (%). [†], 17 patients did not have pleural fluid cytology analysis performed. ECOG, Eastern Cooperative Oncology Group.

Table 2 Thoracoscopy procedural details

Procedural details	Values (n=141)
Upfront thoracoscopy	78 (55.3)
Procedural time, mins	40±10
Volume of pleural fluid removed during thoracoscopy, mL	1,489±616
Pleural fluid appearance	
Haemoserous	44 (31.2)
Yellow	95 (67.4)
Chylous	2 (1.4)
Endoscopic findings	
Pleural or diaphragmatic nodular abnormalities	103 (73.0)
Few and discrete	16 (11.3)
Multiple or numerous	87 (61.7)
Pleural thickening	60 (42.6)
Pleural plaques	33 (23.4)
Pleural adhesions without loculations	18 (12.8)
Loculations/septations	14 (9.9)
Pleural biopsies (No.)	10 [10–12]
Talc poudrage	67 (47.5)
Talc slurry following thoracoscopy	15 (10.6)
IPC insertion during thoracoscopy	5 (3.5)
Hospitalisation days following thoracoscopy	2 [1–4]

Data are presented as mean ± standard deviation, median [interquartile range] or n (%). IPC, indwelling pleural catheter.

and hypotension related to re-expansion pulmonary edema and cardiac tamponade from malignant pericardial effusion. The patient responded to pericardiocentesis and supportive care and survived to hospital discharge. One patient passed away from progression of cancer which occurred 28 days after thoracoscopy. Seven (5.0%) patients had intraprocedural hypotension that resolved with intravenous fluid administration. One (0.7%) patient developed non-ST elevation myocardial infarction one day following thoracoscopy, which was not complicated by cardiogenic shock, arrhythmias, or the requirement for urgent intervention (percutaneous coronary intervention). Eighteen (12.8%) of patients developed fever post-procedure, of whom 16 patients had talc pleurodesis performed.

The overall diagnostic accuracy of MT in our patient cohort was 95.7%, and the diagnostic sensitivity of MT for MPEs (110/116) was 94.8% (*Table 4*). The most common cancer diagnosis was lung cancer in 77 (54.6%) patients, with lung adenocarcinoma (69 patients) accounting for most lung cancer subtypes (*Table 4*). The majority (51/69 or 73.9%) of patients with lung adenocarcinoma had a tyrosine kinase inhibitor (TKI) sensitizing epidermal growth factor receptor (EGFR) mutation: 28 patients with exon 19 deletion, 21 patients with exon 21 (L858R), 1 patient with

Table 3 Procedural complications

Complications	Values (n=141)
Patients with one or more complications	44 (31.2)
Major complications	3 (2.1)
Mortality	0 (0.0)
Lung laceration	0 (0.0)
Pleural infection	0 (0.0)
Prolonged air leak (≥7 days) or bronchopleural fistula	0 (0.0)
Re-expansion pulmonary edema[†]	2 (1.4)
Significant haemorrhage	0 (0.0)
ICU admission for re-expansion pulmonary edema and hypotension	1 (0.7)
Intra procedural hypotension	7 (5.0)
Post procedural NSTEMI	1 (0.7)
Air leak <7 days	1 (0.7)
Wound infection	0 (0.0)
Pain requiring escalation of analgesia[‡]	19 (13.5)
Fever[§]	18 (12.8)

Data are presented as n (%). [†], one patient required nasal cannula; one patient required venturi face mask; [‡], nine patients had pain after talc pleurodesis; [§], 16 patients had fever after talc pleurodesis. ICU, intensive care unit; NSTEMI, non-ST elevation myocardial infarction.

exon 19 duplication and one patient with exon 21 (L861Q) and exon 18 (G719X) mutations. All biopsies confirming the primary cancer were also adequate for full molecular profiling. A diagnosis of carcinoma that could not be further classified was made for two patients and necessitated repeat diagnostic procedures (cervical lymph node biopsy and pectoral mass biopsy) to confirm the diagnosis of lung adenocarcinoma and small cell carcinoma respectively.

Thirty-one patients had a non-malignant histology on thoracoscopic pleural biopsy (*Table 5*). The histopathological diagnosis from MT, additional biopsy performed, and final clinical diagnosis of each patient is detailed in Table S1. Fourteen (9.9%) patients were diagnosed with tuberculous pleuritis with granulomatous inflammation present on histopathological examination. Twelve and five patients had mycobacterium tuberculosis isolated from pleural tissue culture and pleural fluid culture respectively. The two patients without positive cultures had a good therapeutic

Table 4 Histopathological findings from thoracoscopic pleural biopsy

Histopathological findings	Values (n=141)
Malignancy	110 (78.0)
Lung	77 (54.6)
Lung adenocarcinoma	69 (48.9)
Squamous cell lung cancer	4 (2.8)
NSCLC NOS	2 (1.4)
Small cell lung cancer	2 (1.4)
Breast	10 (7.1)
Gynaecological	5 (3.5)
Ovarian	4 (2.8)
Endometrial	1 (0.7)
Mesothelioma	6 (4.3)
Epithelioid mesothelioma	4 (2.8)
Sarcomatoid mesothelioma	1 (0.7)
Biphasic mesothelioma	1 (0.7)
Others	8 (5.7)
Primary peritoneal	2 (1.4)
Gastric	1 (0.7)
Pancreatic	1 (0.7)
Renal cell	1 (0.7)
Epithelioid angiosarcoma	1 (0.7)
Nasopharyngeal	1 (0.7)
Laryngeal	1 (0.7)
Synchronous lung adenocarcinoma and chronic lymphocytic leukemia	1 (0.7)
Carcinoma unknown primary	1 (0.7)
Carcinoma insufficient for characterisation[†]	2 (1.4)
Non-malignant	31 (22.0)
Granulomatous inflammation	14 (9.9)
Solitary fibrous tumour	1 (0.7)
Atypical mesothelial proliferation	1 (0.7)
Non-specific pleuritis	15 (10.6)

Data are presented as n (%). [†], based on further biopsy procedures: one patient diagnosed with lung adenocarcinoma (cervical lymph node biopsy); one patient diagnosed with small cell lung cancer (pectoral mass biopsy). NSCLS NOS, non-small cell lung cancer not otherwise specified.

Table 5 Final diagnosis of patients with non-malignant histology on thoracoscopic pleural biopsy (n=31)

Final diagnosis	No. of patients
Malignancy	6
Diffuse large B cell lymphoma[†]	3
Marginal zone lymphoma[‡]	1
Epithelioid mesothelioma[§]	1
Small cell lung cancer[¶]	1
Tuberculous pleuritis	14
Solitary fibrous tumour	1
Other non-malignant causes	10
Heart failure	1
Cirrhosis and chronic kidney disease	1
Uremic pleuritis	1
Parapneumonic effusion	1
Dasatinib-induced pleural effusion	2
Chylous pleural effusion from sclerosing mesenteritis	1
Idiopathic	3

[†], diagnosed following mediastinotomy and mediastinal mass biopsy, video-assisted thoracoscopic surgery with pleural biopsy, and image-guided biopsy of mediastinal mass; [‡], diagnosed following transbronchial lung biopsy of lung mass; [§], diagnosed with epithelioid mesothelioma following video-assisted thoracoscopic surgery and pleural biopsy; [¶], diagnosed following image-guided biopsy of lung mass.

response to tuberculosis antimicrobial therapy. One patient was diagnosed with a solitary fibrous tumour. One patient with atypical mesothelial proliferation underwent a second procedure (VATS and pleural biopsies) to confirm a diagnosis of epithelioid mesothelioma. The remaining 15 patients had non-specific pleuritis seen on pleural tissue histology. Five patients had repeat procedures (image guided lung biopsies, mediastinal mass biopsy and VATS with pleural biopsies) performed soon after thoracoscopy as computed tomography (CT) imaging were suggestive of underlying malignancy, following which three patients were diagnosed with diffuse large B cell lymphoma, one patient with marginal zone lymphoma and one patient with small cell lung cancer. On follow up, seven patients were assessed to have a non-malignant cause for pleural effusion. Three patients had no diagnosis established (idiopathic non-specific pleuritis): two patients had no recurrence of effusion after 12 and 15 months of follow up, and one patient passed away from pneumonia four months following thoracoscopy.

Upfront MT was performed in 78 (55.3%) patients. There was no significant difference in age, comorbidity scores, size of pleural effusion and MT-related complications between both groups (*Table 6*). Patients with upfront MT had more fluid removed during thoracoscopy and a higher proportion of patients with upfront MT had malignant cells seen on pleural fluid cytology (*Table 6*). However, there was no significant difference in the proportion of patients with a final diagnosis of MPE between both groups. In 63 (44.7%) patients without upfront MT, prior thoracentesis

Table 6 Comparing patient demographics and clinical outcomes in patients with and without upfront thoracoscopy

Variables	Thoracentesis first (n=63)	Upfront thoracoscopy (n=78)	P value
Age (years)	66±14	68±10	0.44
ECOG performance status ≥1	21 (33.3)	32 (41.0)	0.35
Charlson Comorbidity Index	3 [2–4]	3 [2–5]	0.61
Size of pleural effusion >50% hemithorax	37 (58.7)	41 (52.6)	0.46
Pleural fluid removed during thoracoscopy (mL)	1,336±576	1,613±623	0.007
Hospitalisation days following thoracoscopy	2 [1–4]	2 [2–5]	0.12
One or more complications from MT	19 (30.2)	25 (32.1)	0.81
Positive pleural fluid cytology	23 (37.1)[†]	46 (74.2)[‡]	<0.001
Malignant pleural effusion	49 (77.8)	67 (85.9)	0.14

Data are presented as mean ± standard deviation, median [interquartile range] or n (%). [†], one patient did not have pleural fluid cytology analysis performed; [‡], 16 patients did not have pleural fluid cytology analysis performed. ECOG, Eastern Cooperative Oncology Group; MT, medical thoracoscopy.

or chest drain insertion was performed at a median of 5 (IQR, 1–13) days before MT. Thoracentesis was performed within 1–2 days before MT in 26 patients, and pleural fluid analyses showed an exudative pleural effusion in all 26 patients. In the remaining 37 patients who had pleural fluid cytology analysis performed before MT, 24 patients had a negative (no malignant cells) or inconclusive (atypical cells) pleural fluid cytology analysis, one patient did not have pleural fluid cytology analysis performed, and 12 patients had malignant cells seen on pleural fluid cytology but had insufficient cellularity for full molecular profiling.

Discussion

MT is an essential component of a comprehensive pleural service in many hospitals, with a high diagnostic accuracy, low procedural risk and the ability to perform concurrent talc poudrage or IPC insertion as part of a single procedure. This study reports our experience in a Southeast Asian tertiary hospital, which is comparable with outcomes from other centres, demonstrating a high diagnostic accuracy and safety profile in the evaluation of undiagnosed pleural effusions (10).

MT is a safe procedure. From more than 40 studies reporting outcomes of MT, the overall mortality rate is 0.3% and major complication rate (significant, bleeding, persistent air leak etc) is 1.8% (9). Our safety profile is comparable, with no cases of mortality related to the thoracoscopic procedure, and no cases of significant bleeding, pleural infection, persistent air leak or lung laceration. One patient required ICU admission for shock and respiratory failure—this was related to re-expansion pulmonary edema and an unrecognised cardiac tamponade from a large pericardial effusion, which resolved following pericardiocentesis and the patient survived to hospital discharge. Two patients with re-expansion pulmonary edema were managed in the general ward and did not require high flow oxygen supplementation (high flow nasal-cannula, non-invasive ventilation, or mechanical ventilation). Eighteen (12.8%) patients had post-procedural fever. Of these, 16 patients had received intrapleural talc instillation before the onset of fever. These patients had no other systemic signs of infection. The fever was short-lived and likely attributable to talc instillation.

In our cohort, the overall diagnostic accuracy was 95.7%. These results are similar to the reported diagnostic sensitivity (with semirigid thoracoscopy) of 91% in pooled studies and meta-analyses (11). Interestingly, in four patients with lymphoma, thoracoscopy was not able to establish a histopathological diagnosis, and three patients required a repeat biopsy at a different site (e.g., mediastinal lymph nodes). All four patients had no pleural nodules or masses seen on thoracoscopic examination. Pleural effusions in lymphoma may be the result of direct malignant involvement of the pleura or obstruction to mediastinal lymphatics (12,13). Although no direct conclusions can be drawn from our study, in the absence of gross thoracoscopic findings, lymphatic obstruction may plausibly have been the pathophysiological mechanism behind these pleural effusions, with a negative pleural biopsy expected as such. In addition, it is not unexpected that the rate of diagnosis made on histopathological findings is lower than the overall diagnostic accuracy. This is because no classical pathognomonic histology has been described in association with pleural effusions from non-malignant conditions such heart failure and chronic kidney disease (14). In the 10 patients without a histopathological diagnosis made, and no other features concerning for malignancy on CT imaging, a clinical diagnosis was eventually established in seven patients on subsequent follow-up.

Compared to the rigid thoracoscopy, the semi-rigid thoracoscope has increased manoeuvrability and a gentler learning curve for physicians already familiar with the flexible bronchoscope. However, it is more expensive, may require more frequent maintenance and repairs, and is less adept at sampling densely thickened pleura and therapeutics such as controlling hemorrhage after biopsy (15). Larger biopsy samples can be obtained with rigid thoracoscopy, however it remains unclear if this leads to an increased diagnostic yield. Two randomised studies have conflicting results. Rozman *et al.* reported the first randomised study with 84 patients which reported similar diagnostic accuracy: 100% with rigid thoracoscopy and 97.6% with semi-rigid thoracoscopy (7). Dhooria *et al.* performed the second randomised study with 90 patients and reported a higher diagnostic yield with thoracoscopy (97.8% *vs.* 73.3%) on an intention-to-treat analysis but similar (100% *vs.* 94.3%) in those with successful biopsy (excluding patients in whom thoracoscopy was not feasible due to extensive adhesions) (8). In a recent meta-analysis diagnostic sensitivity for MPE was similar between rigid and semi-rigid thoracoscopy (92.9% *vs.* 93.1%) respectively. These studies, along with the outcomes observed in our cohort, lend weight to the high diagnostic accuracy achievable with semi-rigid thoracoscopy (10).

It is clear that MT is a vital part of diagnostic workup for undiagnosed pleural effusions, particularly in patients

with suspected MPE. Pleural fluid cytology has a poor diagnostic sensitivity (50–60%) for MPE (3). Furthermore, in the current era of targeted oncological therapy, simply confirming malignancy on pleural fluid cytology is no longer adequate. There is now a need for "actionable" cytology which is defined as having obtained sufficient molecular profiling of various cancers to guide treatment. The need for "actionable" cytology further reduces the sensitivity of pleural fluid as a diagnostic test that yields enough information to make treatment decisions. In a retrospective study involving 230 patients with MPE, "actionable" pleural fluid cytology was reported in only 32.1% of patients (16). In another multicentre study, the yield of "actionable" pleural fluid cytology in patients with non-small cell lung cancer with MPE was only 32.4%, an almost identical percentage (17). In our cohort, lung cancer accounted for up to two-thirds of patients diagnosed with MPE. Most lung cancers were lung adenocarcinomas with the majority (73.9%) having one or more of tyrosine kinase mutations, consistent with the high prevalence of lung cancer targetable mutations in many East Asian countries (18,19).

The high yield of thoracoscopic biopsies for "actionable" histology is supported by recent evidence showing the superiority of thoracoscopic biopsies in achieving full molecular profiling, when compared to CT or ultrasound-guided pleural biopsies (17,20). These various considerations speak to the importance of MT as an option for patients with suspected MPE. In instances where thoracoscopy is unavailable or inappropriate due to lung adhesions or patient frailty, image guided pleural biopsy is an alternative, particularly if pleural thickening or nodularity is visualised and accessible. Real time ultrasound pleural biopsy, which traditionally has been performed by interventional radiologists, has been increasingly adopted by respiratory physicians in recent years, with reported diagnostic sensitivities of between 88–94% (21,22). However, there are limitations of image guided pleural biopsies, which include inability to visually inspect the pleural cavity, perform biopsies under direct visualisation, or administer talc poudrage. With the need to reduce time to both diagnosis and treatment of cancer, there is also a drive for pleural effusion diagnostic pathways to incorporate the option of proceeding directly to pleural biopsy in patients with suspected MPE, away from the traditional sampling of pleural fluid as a routine first line evaluation (9). This strategy is particularly relevant for mesothelioma, because of the very low sensitivity of pleural fluid cytology (3). Going straight to thoracoscopy without a prior diagnostic thoracentesis ("upfront" thoracoscopy) as an option for patients with suspected mesothelioma is a new update to the 2023 British Thoracic Guidelines for Pleural Disease (9). As performing a thoracoscopy also allows for concurrent therapeutic interventions such as talc poudrage or IPC insertion, modern pleural services are also now able to provide a one-stop shop approach to suspected MPE, performing both diagnostic and therapeutic interventions in one procedure. In our cohort, more than half (55.3%) of the patients had thoracoscopy performed without prior pleural aspiration or thoracentesis, and all patients with a malignant histopathological diagnosis made on MT had achieved full molecular profiling of their cancers without the need for further biopsy procedures. In addition, almost half (47.5%) of our patients had concurrent talc poudrage performed during thoracoscopy. We did not find any significant difference in patient demographics, pleural effusion size and outcomes between patients with and without upfront MT. In our cohort the decision for upfront was primarily based on the clinical pre-test probability of malignancy, shared decision making between patient and physician, and also determined by when these patients were referred to the pleural service in our hospital, where some patients already had thoracentesis performed during the time of referral. While this study adds to the growing literature on an upfront biopsy approach, well designed randomised studies are needed to evaluate the utility and role of upfront MT, particularly in regions with differing epidemiology in pleural diseases, such as mesothelioma or tuberculous pleuritis.

The limitations of the study are that this is a single centre study, and not all patients had follow-up reviews for a minimum period of 12–24 months, which is commonly practiced for patients with non-specific pleuritis (23). Non-specific pleuritis is defined as fibrinous or inflammatory pleuritis which cannot be attributed to a specific benign or malignant etiology. On further follow-up, a clinical diagnosis was made for seven patients. Only three patients had a diagnosis of idiopathic non-specific pleuritis, two patients had a minimum follow-up period of 12 and 15 months revealing no re-accumulation of pleural effusion, and one patient had passed away from pneumonia at 4 months. Studies describe 3–12% of patients with non-specific pleuritis being diagnosed to have cancer (most commonly mesothelioma) at a median follow-up time between 9–12 months (24-26). Hence, this is unlikely to significantly impact on our reported diagnostic accuracy. What is unique about our patient cohort is the relatively

low rate (10.6%) of non-specific pleuritis compared to a mean incidence of 40% in other studies (24). This may be a reflection of our centre's selection of patients, where thoracoscopy is offered for cases with a higher pre-test probability of MPE. Nevertheless, there was still a significant percentage (10%) of tuberculous pleuritis seen in our patient cohort, and this is consistent with a South East Asian population with a higher prevalence of tuberculosis (27).

Conclusions

In conclusion, semi-rigid thoracoscopy in our patient cohort has a high diagnostic accuracy and good safety profile. For patients presenting with an unexplained pleural effusion, MT not only performs with high diagnostic sensitivity but also allows for definitive therapeutic options such as talc poudrage or IPC insertion as part of a single procedure, making it an invaluable tool in any comprehensive pleural service. With unprecedented advances in pleural disease research in the past two decades, and a range of pleural procedures now available to the respiratory physician, the challenge will be to integrate these into diagnostic and therapeutic pathways with a focus on expeditious evaluation, individualised treatment and limiting the number of invasive procedures while maintaining effective control of symptoms.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-219/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-219/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was submitted to the institutional review board. The informed consent for this analysis was waived and the study was exempted from formal review, as it was an observational study with subsequent deidentification of data.

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Supplementary

Table S1 Final diagnosis of patients with non-malignant histology on thoracoscopy pleural biopsy (n=31)

Patient No.	Histopathological findings from MT	Microbiological diagnosis or additional biopsy performed	Final clinical diagnosis
1	Solitary fibrous tumour	None	Solitary fibrous tumour
2	Atypical mesothelial proliferation	VATS and pleural biopsy	Epithelioid mesothelioma
3	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
4	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
5	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
6	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
7	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
8	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
9	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
10	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
11	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
12	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
13	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
14	Granulomatous inflammation	M. tuberculosis isolated from pleural fluid/tissue	Tuberculous pleuritis
15	Granulomatous inflammation	None	Tuberculous pleuritis
16	Granulomatous inflammation	None	Tuberculous pleuritis
17	Non-specific pleuritis	Mediastinotomy and mediastinal mass biopsy	Diffuse large B cell lymphoma
18	Non-specific pleuritis	VATS and pleural biopsy	Diffuse large B cell lymphoma
19	Non-specific pleuritis	Image-guided biopsy of mediastinal mass	Diffuse large B cell lymphoma
20	Non-specific pleuritis	Transbronchial lung biopsy	Marginal zone lymphoma
21	Non-specific pleuritis	Image-guided lung biopsy	Small cell lung cancer
22	Non-specific pleuritis	None	Heart failure
23	Non-specific pleuritis	None	Cirrhosis and chronic kidney disease
24	Non-specific pleuritis	None	Uremic pleuritis
25	Non-specific pleuritis	None	Parapneumonic
26	Non-specific pleuritis	None	Dasatinib-induced pleural effusion
27	Non-specific pleuritis	None	Dasatinib-induced pleural effusion
28	Non-specific pleuritis	None	Chylothorax from sclerosing mesenteritis
29	Non-specific pleuritis	None	Idiopathic non-specific pleuritis
30	Non-specific pleuritis	None	Idiopathic non-specific pleuritis
31	Non-specific pleuritis	None	Idiopathic non-specific pleuritis

MT, medical thoracoscopy; VATS, video-assisted thoracoscopic surgery.

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