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REVIEW ARTICLE

Pleural effusion: diagnostic approach

Maribel Botana-Rial[1,2,3,*], Cristina Ramos-Hernández[1,2], and Alberto Fernández-Villar[1,2,3]

[1]Pulmonary Department, Hospital Álvaro Cunqueiro, EOXI Vigo, Spain; [2]PneumoVigoI+i Research Group, Sanitary Research Institute Galicia Sur (IISGS), Vigo, Spain; [3]CIBER de Enfermedades Respiratorias, Spain

ABSTRACT

Diagnosing pleural effusion (PE) can be complex and challenging. Due to the wide variety of possible clinical settings, proper management of pleural diseases should be tailored on a case-by-case basis and requires a multimodal approach. We provide an overview of the typical diagnostic approach. It is through a history, clinical assessment, evaluation of pretest probabilities, and careful selection of diagnostic tests, of which there are many, that a physician can be confident in their diagnosis. Radiological investigation of PE is key in diagnosing and determining management. Computed tomography is the modality of choice for the assessment of pleural disease. Thoracic ultrasound adds significant value in the identification of pleural fluid and pleural nodularity, guiding pleural procedures, and increasingly yielding diagnostic of pleural biopsy. Pleural biopsies are often necessary if a PE remains undiagnosed after radiological imaging and pleural fluid analysis. Thoracoscopic biopsies are the gold standard for investigating pleural disease. However, this service is not universally available and may be unsuitable for some patients. Image-guided biopsies are very useful in a wide patient population and have high diagnostic rates.

Keywords: Computed tomography. Diagnostic algorithm. Imaging techniques. Pleural biopsy. Medical thoracoscopy. Thoracic ultrasound.

***Correspondence to:**
Maribel Botana-Rial
E-mail: Maria.Isabel.Botana.Rial@sergas.es

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INTRODUCTION

Pleural effusion (PE) is a frequent manifestation in respiratory medicine and is a major diagnostic and therapeutic problem. Pleural disease is common, affecting more than 300 people per 100,000 population each year and leading to more than 150 admissions per 100,000 population[1]. There are over 50 known conditions resulting in pleural disease and with a clinical presentation that is often nonspecific. No single test is likely to provide the entire diagnosis. PE has a wide differential diagnosis, but the most common causes are congestive heart failure, cancer, pneumonia, and pulmonary embolism[2,3]. Congestive heart failure and infections account for approximately two-thirds of cases, and 20–55% of patients with pulmonary embolism have a PE.

Malignant PE is common in patients with cancer. Most malignant PEs are secondary to metastasis to the pleura. The most common neoplasm to spread to the pleura is lung cancer (40% of pleural metastases), followed by breast cancer (20%), lymphoma (10%), and other primary malignancies (30%)[2,3].

Mesothelioma is the primary neoplastic cause of pleural disease. Its maximum incidence was reached in 2020, reflecting previous asbestos exposure with a latency period of around 40 years. In most developing countries where the use of asbestos is yet banned or controlled, mesothelioma will remain a major public health issue for many years[2,4]. The most commonly encountered causes of PE are provided in Table 1.

Of note, the increasing burden of pleural diseases in the last decades has been coupled with an outstanding evolution in medical technologies related to the diagnosis and management of such conditions, no longer reserved only for thoracic surgeons or interventional radiologists, but now widely available in daily practice in interventional pulmonology centers, leading to the development of a dedicated subspecialty in respiratory medicine[6]. There is a need for effective diagnostics in this patient population, with key priorities for emergency and pleural physicians revolving around providing effective, specialized care earlier to minimize the need for hospital admissions and repeated pleural procedures[6].

If an exudate PE is identified, further investigations are necessary to identify the etiology. There are several guidelines that outline the investigatory pathway for PE[7,8]. Radiological imaging and biochemical analysis of pleural fluid (PF) provide initial diagnostic information, but histological confirmation is usually required, particularly if malignancy is suspected because cytological examination of PF has a low sensitivity for malignant cells (less than 60%)[7,8].

RADIOLOGICAL INVESTIGATION OF PLEURAL DISEASE

Conventional chest radiograph remains the initial investigation of choice for patients with suspected PE. When abnormalities are detected, thoracic ultrasound (TU), computed tomography (CT), and/or positron emission tomography (PET) can each play

Table 1. The main causes of PE

Transudate • Congestive heart failure • Cirrhosis • Nephrotic syndrome • Urinothorax • Hypothyroidism • Hypoalbuminemia • Cerebrospinal fluid leak
Exudate • Malignant disease: carcinoma of any origin but especially lung and breast; lymphoma; mesothelioma • Infections: parapneumonic effusion; tuberculous pleurisy; fungal, parasitic, or viral infections • Autoimmune inflammatory diseases: systemic lupus erythematosus and other connective tissue diseases; rheumatoid arthritis • Pulmonary embolism • Intra-abdominal processes: pancreatitis; subphrenic/hepatic abscess • Drugs: amiodarone, dasatinib, methotrexate, nitrofurantoin, and others • Miscellaneous: benign asbestos reactive effusion; traumatic hemothorax; chylothorax and pseudochylothorax; postcardiac bypass surgery; postcardiac injury syndrome (Dressler syndrome); postradiation therapy; familial Mediterranean fever

Adapted from Beaudoin S, et al. (2018)[8]. PE: pleural effusion.

important roles in further investigation. Some authors have begun to investigate the use of magnetic resonance imaging (MRI).

Thoracic ultrasound

TU adds significant value in the identification of PF, pleural nodularity, and guiding pleural procedures[9,10]. The use of TU in diagnostics of pleural disease has transformed the field over the past three to four decades[9]. TU has now become a reliable, portable, and relatively cheap imaging tool to diagnose. Its use is also recommended in international guidelines to reduce the risk of procedural complications[9,11].

The echogenicity and complexity of PF were traditionally thought to represent whether the fluid was exudate or transudate. The presence of a complex septated and complex homogenous PE has a high specificity (94%) and a positive predictive value (96%) for exudative, but the low predictive value (44%) of an anechoic PE for detection of transudative does not obviate the need for subsequent diagnostic thoracentesis with PF analysis[8,12].

Other studies have evaluated the echogenicity of PF as measured by the pixel density of the ultrasound image. Pixel density is higher in exudative PE and it correlates with the level of lactate dehydrogenase (LDH) and proteins for PF[13].

Exudative PEs with high protein content often form septations with the deposition of fibrin strands becoming thicker over time. They are associated with infected PE or malignant PE. Eventually, septations may be thick and profuse enough to give a honeycomb-like appearance[14].

Although benign diffuse pleural thickening alone can be difficult to visualize on TU, in the presence of a PE, pleural nodularity (parietal, visceral, or diaphragmatic) is

diagnostic of malignant PE. Qureshi et al.[15] found a sensitivity comparable with contrast-enhanced CT when combining the presence of pleural thickening >1 cm, pleural nodularity, and the presence of hepatic metastases[15]. A recent meta-analysis found that the presence of pleural nodularity alone was a sensitivity of 97%[16].

Computed tomography

CT is the gold standard investigation to diagnose PE[14,17]. It can provide a three-dimensional representation of the thoracic and pleural anatomy, including central structures. CT offers additional information on PE and can be used to assess pleural thickening, homogeneity of pleural masses, and areas of fatty attenuation or calcification.

It is important to note that for diagnostic algorithms, CT does not need to be performed following therapeutic thoracentesis. A retrospective study at a large tertiary hospital showed no significant additional diagnostic information when a CT was performed before and after pleural drainage[18].

CT is crucial in the evaluation of malignant PE and pleural infection. CT findings, such as pleural enhancement, pleural thickening, and attenuation of extra-pleural subcostal fat, raise suspicion of pleural infection[14,19]. Pleural thickening can help distinguish septic from aseptic pleural infections, as thickening is most significant in purulent effusions and is absent in simple parapneumonic effusions. In addition, the "split-pleura sign" can differentiate pleural infection from pulmonary abscess[14,19]. This can be described as enhancing the visceral and parietal pleural layers around PF, a finding only present in pleural infections. Furthermore, pleural infections often contain extrapleural fat stranding and smooth margins, characteristics not typically present in pulmonary abscesses. While these findings are useful in distinguishing pleural infection and lung abscesses, they cannot differentiate complicated parapneumonic effusions and empyema as they can be present in both[19]. However, the presence of gas within the PF on CT is highly suggestive of empyema[19].

The "split pleura" sign and the presence of >30 mm distance between the parietal and visceral pleura were shown to correctly identify a complex parapneumonic effusion from a simple PE with a sensitivity of 80% and a specificity of 81%[19-21].

CT can evidence a pleural thickening of >10 mm, pleural nodularity, mediastinal thickening, or circumferential thickening, and they are suggestive of malignant PE[14]. These characteristics have a high sensitivity but low specificity. One retrospective study showed that the positive predictive value of a CT was 80%, but the negative predictive value was only 65%[22]. Table 2 presents the features of CT that are more suggestive of malignant PE than benign.

Porcel et al.[23] proposed a simple CT scoring system for predicting malignant PE, based on selected radiological parameters, showing promising results for the assessment of the pretest probability of malignancies.

Table 2. Features of CT suggestive of malignant PE

Features	Sensitivity (%)	Specificity (%)
Nodular pleural thickening	38–53	87–100
Pleural thickening along mediastinal surfaces	14–74	83–97
Thickening of the parietal pleura >1 cm	36–57	64–94
Circumferential pleural thickening encasing the lung	8–54	63–100

CT imaging of the abdomen and pelvis should also be considered. A prospective study found clinically significant subdiaphragmatic findings in nearly a quarter of patients (24%) who were investigated for unilateral PE[24]. "Clinically significant" was defined as findings that either identified the primary diagnosis (primary tumor in 7%), upstaged any malignant disease (13%), or highlighted a favorable site for further investigation (alternative biopsy site in 2%)[24].

A significant proportion of patients presenting with unilateral effusion may incidentally have a pulmonary embolism, particularly those subsequently diagnosed with pleural malignancy[25].

Positron emission tomography

PET is commonly used as a noninvasive method of determining metastatic spread in patients with cancer. In addition, PET/CT has been proposed as an imaging technique to allow differentiation between benign and malignant PE, but there is variation in the reported sensitivity (88–100%) and specificity (35–100%)[26,27]. Clinicians should therefore be aware of the potential false-negative and false-positive findings. False positives include infection (pleural tuberculosis or pleural infection) or previous talc pleurodesis. False negatives could include tumors with low metabolic activity (low-grade epithelioid mesothelioma) and small tumor size.

The use of PET-CT may be useful in selected scenarios, such as guiding needle or thoracoscopic biopsy according to uptake levels[14,27]. TARGET study (TARGETed pleural biopsy vs. CT-guided pleural biopsy in suspected pleural malignancy) specifically assessed the role of PET-CT-guided biopsies in patients with ongoing suspicion of pleural malignancy despite a negative CT-guided biopsy[28]. PET/CT may provide additional information in malignant PE regarding prognosis and response to therapy.

Magnetic resonance imaging

MRI could be a potential diagnostic tool in the study of PE, but its clinical value has yet to be determined, and its use should be limited to highly selected cases. Pessoa et al.[29] described this modality to be useful for the evaluation of the pleural interface, characterization of complex PE, or identification of exudate and hemorrhage. In this review, the main objective was to present the main aspects of pleural diseases seen with conventional and advanced MRI techniques[29].

Currently, MRI for PE has not been standardized; it is not included in clinical practice

guidelines as a standard technique and is not used as an alternative to chest CT[7,8].

INITIAL DIAGNOSTIC ASSESSMENT

Thoracocentesis and cytobiochemical fluid analysis

Initial diagnostic assessment, including clinical history, details on occupational exposure and drug intake, and careful physical examination, can provide useful information for guiding the subsequent diagnostic algorithm. In the majority of cases, however, PF analysis is required to assess the spectrum of potential diagnoses and to determine the next steps in the diagnostic work-up[2,7,8].

Thoracocentesis should be performed in all patients with more than a minimal PE (i.e., larger than 1 cm in height on lateral decubitus radiography, TU, or CT) of unknown origin. A standard PF analysis should also include a biochemistry panel (protein, LDH, glucose, pH), differential cell counts, microscopy, cultures, and cytological examination[2,7,8]. Between 1 and 10% of malignant MPE are characterized as transudates, despite using Light's criteria[30]. Classic diagnosis based on PF analysis is presented in Table 3.

However, it is increasingly recognized that a significant proportion of patients presenting with a PE will have dual pathology driving their presentation, which bears consideration[32,33]. This situation complicates the classification of PE by conventional methods.

While PF biochemistry may be suggestive of pleural infection, the gold standard for diagnosing the condition is positive microbiological growth within the PF[34,35]. When pleural infection is suspected, microbiological culture is an essential diagnostic component to determine causative organisms in pleural infection and guide antibiotic treatment choice. Unfortunately, a systematic review in this area found the PF culture positivity rate to be only 56%[36].

In high-incidence countries, a non-interventional approach combining simple pleural tap with elevated adenosine deaminase levels and a high percentage of pleural lymphocytes seems to have high diagnostic accuracy. In low-incidence countries, a pleural biopsy is necessary, not only to confirm the diagnosis but also to rule out malignancy since this is the leading cause of exudative PE in low-prevalence areas[7,19]. Pleural biopsy has demonstrated a strong negative predictive value in excluding pleural tuberculous in low-incidence areas (99% when <30 IU/l)[7,8]. However, false positives in empyema, rheumatoid pleuritis, and malignancy are seen, and therefore, reserving its use for only lymphocytic PE may increase its positive predictive value.

The use of PF cytology has long been the initial step in diagnosing malignant PE, although many recent studies have brought into question the diagnostic utility of cytology alone. The diagnostic sensitivity of PF cytology is relatively low at 37–47% in patients with proven malignant PE[7,37]. Some factors can influence the diagnostic rate, including sample preparation, operator experience, tumor burden, and subtype.

Table 3. Diagnosis based on PF analysis

Diagnosis	Criteria
Cardiac failure	Low protein, low LDH, NT-proBNP high
Tuberculosis	Exudate, lymphocytic predominance, positive acid-fast bacillus smear or cultures, ADA >50 U/l
Empyema	Exudative with PMN predominance/pus, positive Gram stains or cultures, LDH >1,000, glucose <40 mg%, pH < 7.2
Malignancy	Exudate, lymphocytic predominance, positive cytology
Hemothorax	Hemorrhagic, hematocrit. 50% of blood
Esophageal rupture	pH < 7, high salivary amylase
Urinothorax	pH < 7, transudate, pleural fluid-to-serum creatinine ratio > 1
Chylothorax	Triglycerides >110 mg/dl, chylomicrons, cholesterol/triglyceride > 1
Pseudochylothorax	High cholesterol, cholesterol crystals
Rheumatoid pleurisy	Exudate, lymphocytic predominance, rheumatoid factor positive, 1:320, low glucose, 40 mg%, ADA > 50 U/l
Lupus pleuritis	Exudate with PMN predominance, LE cells positive, ANA positive >1:160
	Exudate with PMN predominance, plenty of red blood cells
Pancreatitis	Acute: increased serum and pleural amylase
	Chronic: increased pleural fluid amylase, serum amylase normal
Fungal infection	Black-colored, fungal smear, culture positive

Adapted from Karkhanis et al. 2020[81].
ADA: adenosine deaminase; ANA: antinuclear antibody; LDH: lactate dehydrogenase; LE: lupus erythematosus; PMN: polymorphonucleocytes; PF: pleural fluid; RBC: red blood cells.

Once malignant cells have been identified, additional immunochemistry – performed on cytology samples, cell blocks, or clots – is highly recommended to characterize tumor type and direct therapies. Recent data showed that cell blocks from malignant PE may be also suitable for molecular testing, as the mutation detection rate did not significantly differ from that obtained in tumor tissue samples. Cell block in combination with immunohistochemistry increases the diagnostic yield and helps detect malignancy at an unknown primary site in effusion fluids. Both of these techniques can thus enhance the sensitivity and specificity of the diagnosis of effusion cytology[38].

In addition, PF can be used to assess targetable mutations in patients with lung adenocarcinoma[37,39]. Mutation analysis on a PF cell block was performed on 56 patients. It was adequate for the complete analysis ordered, including EGFR, KRAS, BRAF, ALK, and ROS1 rearrangements on 40 (71%) samples. For individual mutations, EGFR testing was possible in 38 of 49 (78%); KRAS in 22 of 28 (79%); BRAF in 10 of 13 (77%), ALK gene rearrangement in 42 of 51 (82%), and ROS1 gene rearrangement in 21 of 28 (75%) PF specimens. The analysis was satisfactory in 13 of 19 (68%) samples with ≤100 ml vs. 27 of 37 (73%) with >100 ml of fluid tested ($p = 0.7$)[39].

Other diagnostic tests: pleural manometry

Pleural manometry is critical for the measurement of pleural elastance, diagnosis of an unexpandable lung, and differentiation between trapped lung and lung entrapment. This usually has significant clinical implications in terms of further management of patients with PE[40].

PLEURAL BIOPSY TECHNIQUES

Approximately 40% of exudative PE cannot be diagnosed by thoracentesis. Repeating thoracenteses unnecessarily may increase pleural space septations, making future diagnostic and therapeutic interventions difficult. As such, patients with unexplained exudative PE can be referred for pleuroscopy with pleural biopsies or image-guided pleural biopsies[7,8,19,41].

Closed-needle biopsies

Pleural biopsies typically form the gold standard in the diagnosis of malignant PE and can increase the microbiological yield in both pleural infection and tuberculous PE[7,8,37]. Tissue sampling for culture and sensitivity should be the preferred option for all patients with suspected tuberculous PE[7,42].

The AUDIO study (Pilot Feasibility Study in Establishing the Role of Ultrasound-Guided Pleural Biopsies in Pleural Infection), a pilot study with 20 patients, showed that ultrasound-guided cutting needle biopsy at the time of drainage in pleural infection can increase microbiological yield[43]. The overall diagnostic yield of the biopsy cultures was 45%. The addition of biopsies to blood and PF cultures increased the overall yield by 25%. TU-guided pleural biopsies are safe for pleural infection and improve microbiological yield when combined with blood and PF samples[42,43].

There are different options for obtaining pleural biopsies in undiagnosed PE. Medical thoracoscopic or image-guided pleural biopsy may be used depending on the clinical indication and local availability of techniques (including the need for control of PF)[7,8,11,44]. Blind (non-image-guided) pleural biopsies should not be conducted.

Medical thoracoscopy to obtain pleural biopsies is a well-established largely and effective diagnostic procedure[44]. However, medical thoracoscopy requires a degree of expertise and is not available in many hospitals. In addition, certain patients may not be fit to undergo the procedure because of medical conditions. Therefore, image-guided pleural biopsies are the preferred initial diagnostic procedure[41].

Blind pleural biopsy with reverse bevel closed needle was originally described by Abrams and Cope in 1950[45]. The use of TU-guided pleural biopsy with cutting needles (Tru-cut) has been increasingly adopted by interventional pulmonologists, as, in experienced hands, it offers the advantage of sampling pleura, peripheral lung lesions, and chest wall abnormalities under real-time visualization of both needle and target,

with reduced time, costs, and complication rate[4,9,11].

Recent studies have proposed that image guidance with either image significantly increases the yield of such biopsies and also decreases the risk of complications[46]. Mei et al.[46] performed a systematic review and meta-analysis to evaluate diagnostic yield and safety of CT- and TU-guided biopsies in the diagnosis of PE. Data showed that CT- and TU-guided biopsies in the diagnosis of pleural disease were both excellent procedures in diagnostic yield and safety. The yield diagnostic was 84% for TU-guided pleural biopsy and 93% for CT-guided biopsy[46].

The addition of CT guidance to the Abrams needle technique has been shown to improve sensitivity to 82%, increasing to 93% when pleural thickness exceeded 1 cm, across all cases of cytology-negative exudates in a randomized controlled trial[47].

Whether to undertake cutting needle biopsies preferentially under ultrasound or CT guidance is a question not fully answered. Different studies suggested that there was little difference in diagnostic accuracy between the two techniques[48,49]. The choice of modality is guided by availability and operator preference. However, given that TU is nonionizing and easily performed at the bedside, faster and less expensive in the practice, it should be the preferred approach when adequate expertise is available[49].

TU-guided pleural biopsy is an important diagnostic method for PE. Studies that have evaluated the overall diagnostic yield of TU-guided biopsies for diagnosing PE suggest that the overall sensitivity was over 80%, 77% for malignant PE and 80% for tuberculous pleurisy[11,44,48,50,51]. In areas where tuberculosis is endemic, its sensitivity seemed to be higher in this setting[7,42].

The reported sensitivities vary widely depending on the population studied, with a large retrospective study suggesting a diagnostic yield of 51% for malignancy and 69% for tuberculous pleuritis[52]. A recent meta-analysis of 10 studies evaluating closed pleural biopsies in the diagnosis of exudative PE suggested a sensitivity of 77%[53].

There are different needles for pleural biopsy. If there is a discrete pleural mass or area of pleural thickening, a cutting needle biopsy can be used to obtain a core sample. A recent meta-analysis found that ultrasound-guided needle biopsies in patients with a variety of diagnoses resulted in a pooled sensitivity of 83% and specificity of 100%[54].

However, recent TU findings in suspected pleural pathology may change the standard diagnostic procedure. TU-guided biopsy has been shown to be as cost-effective as thoracoscopic pleural biopsy in patients with exudative PE, and it is associated with a shorter procedure and hospital stay and fewer complications[53].

In some cases, however, the diagnostic yield of pleural biopsy with respect to malignant PE can be lower than that of only cytology. One possible reason for the low yield could be the patchy involvement of the pleura in malignant PE. This low yield does not occur in tuberculous PE, which has a diffuse

expression throughout the pleural surfaces, and for which sensitivity can reach 85%[42]. Theoretically, we would expect pleural metastases to be more frequent inferiorly in the thorax and ultrasound examination may be able to help identify a more suitable, lower location for sampling. Ultrasound-assisted pleural biopsy allows biopsies to be performed in the lower thoracic parietal pleura, where the secondary spread from pleural metastases is more likely to be initially found and may lead to improved diagnostics. One small study analyzed whether choosing the point of entry for pleural biopsy with TU influences the diagnostic yield. The diagnostic yield of a pleural biopsy with an Abrams needle increased by >17% in subjects with MPE[55].

Adopting a combination of a "first procedure" with TU-guided biopsy and therapeutic aspiration may allow for a middle ground between minimal service impact and increasing the chances of successful diagnosis[56].

In the field of malignant PE, one area with the potential to improve the diagnostic yield of TU-guided pleural biopsies is the use of intravenous contrast. Contrast-enhanced ultrasound has the potential to increase diagnostic yield in pleural biopsy, as it provides real-time information on microvascular perfusion, highlighting areas of high metabolic tumor activity that are most likely to provide a molecular diagnosis[57].

In another study, 63 patients with parietal pleural lesions were investigated using contrast-enhanced ultrasound. Marked enhancement was significantly more frequently associated with malignancy compared with benign lesions. However, some benign lesions, such as chronic inflammatory processes, may also show marked enhancement. Therefore, the interpretation of perfusion patterns in these lesions must always take into account the clinical background of the patient[58].

Ultrasound elastography is a promising new approach to optimize the diagnostic yield of pleural biopsy[59]. In this prospective, multicenter, observational trial, Deng et al.[60] examined 98 adults with unilateral PE of unknown origin after negative cytological examination. Enrolled participants were selected based on the absence of pleural nodularity on CT and a pleural thickness of 5 mm or less. All participants underwent ultrasound elastography-guided pleural biopsy. The reported diagnostic yield was 92% for all diagnoses, while for malignant PE, sensitivity was 88%[60]. Notably, there was adequate tissue for molecular studies of tumor cells in all cases. Nonmalignant diagnoses were followed up for a 12-month period to ensure that clinical behavior was consistent with the reported diagnosis. The diagnostic accuracy for tuberculous effusions was lower, with a sensitivity of 69%[60].

Koegelenberg et al.[61] proposed this diagnostic algorithm. Pleural disease is classified based on ultrasound appearance as well-circumscribed mass lesions, diffuse pleural thickening/nodularity, or insignificant/no pleural thickening. In patients with a mass, fine-needle aspiration with rapid onsite cytological evaluation was undertaken, followed by cutting needle biopsy if the initial diagnosis was nonmalignant. In the presence of

pleural thickening, biopsies were performed using an Abrams needle if the pleura measured 10–24 mm or a cutting needle if greater than 25 mm. If there was no obvious pleural thickening, Abrams biopsy was employed. This method increased the diagnostic yield for malignancy from 31 to 89% ($p < 0.001$) and for all diagnoses to 90%[61].

Diagnoses of exclusion such as benign asbestos-related PE and eosinophilic pleuritis also require pleural biopsy before they are finalized[7,19].

Medical thoracoscopy

Pleural biopsies under direct vision using a fiber-optic camera to assess the macroscopic appearance of the pleura, diaphragm, and lung and guide biopsy targets remain the gold standard investigation for diagnosing unexplained exudative PE in patients in good physical condition[9,44]. It has been shown to be an efficacious procedure in diagnosing unexplained exudative PE with excellent safety[44].

Medical thoracoscopy, or local anesthetic thoracoscopy, is typically undertaken by pleural or respiratory physicians, with conscious sedation in a spontaneously breathing patient. It usually occurs as a day case procedure, and it can be performed in the endoscopy suite[9,44].

The diagnostic yield of medical thoracoscopy for unexplained PE in the literature is between 91 and 95% with the most common diagnoses assessed being malignant PE and tuberculous PE[44,62]. A pooled analysis of 22 studies including 1,369 patients reported that a diagnostic sensitivity of medical thoracoscopy was 92%[63] comparable to video-assisted thoracoscopic surgery. Importantly, it has been proven to be a safe procedure with low morbidity (1.8%) and mortality (0.3%) rates[9,44].

The main objective of this study was to assess the diagnostic significance of thoracoscopy in the management of patients with malignant PE. The most common etiological causes were metastatic carcinomas (n = 272), mesothelioma (n = 35), and lymphoma (n = 10). It should be mentioned that we could not identify the original malignancies in 25 patients with malignant PE. Among metastatic malignancies that resulted in malignant PE, the most common cancer included lung cancer, followed by breast cancer, ovarian cancer, and pancreatic cancer[64].

Janssen et al.[65] followed patients with inconclusive thoracoscopy out of 709 patients who underwent thoracoscopy for undiagnosed PE; 391 of them (55%) had malignant PE and 183 (26%) a true benign PE. Therefore, after long-term follow-up, the sensitivity of diagnostic thoracoscopy was 91% and the specificity was 100%[65].

The role of medical thoracoscopy in tuberculous is beneficial. In some parts of the world, tuberculosis is a common etiology of undiagnosed lymphocytic exudates. In these cases, thoracoscopy continues to play an essential role in the management of this disease. A retrospective analysis of patients with

tuberculous pleurisy demonstrated safety of medical thoracoscopy and showed the presence of mycobacteria or characteristic granulomas in 99% of patients[66].

Medical thoracoscopy allows for various tools to be used to biopsy the parietal pleural. Generally, samples are obtained from abnormal-looking pleura. Flexible forceps can be used via a semirigid thoracoscope or rigid forceps can be used through a rigid thoracoscope[67]. There remains some debate over the use of rigid to semi-rigid thoracoscopes and, more recently, the rigid mini-thoracoscope[68].

However, there is no difference between the first two procedures[67]. A comparable diagnostic yield is achieved with the semi-rigid pleuroscope, even though pleural biopsies are smaller using flexible forceps as compared to rigid thoracoscopy. Semi-rigid pleuroscopy is extremely well tolerated and can be performed safely as an outpatient procedure[67,69].

However, in the MINT study (rigid mini-thoracoscopy vs. semirigid thoracoscopy in undiagnosed exudative PE), a single center comparing rigid mini-thoracoscope to semi-rigid thoracoscopes, the authors did find a greater diagnostic yield in the semi-rigid thoracoscopes group (81–69%)[68].

Grossu et al.[62] conducted a prospective observational multicenter cohort study of consecutive patients undergoing pleuroscopy with the main objective of creating a predictive model to estimate the probability of malignant PE. Logistic regression showed that a higher level of malignancy on visual assessment (odds ratio [OR] = 34.68), rapid on-site evaluation of touch preparation (OR = 11.63), and the presence of pleural nodules/masses on CT were associated with higher odds of malignant PE (OR = 6.61)[62].

In addition, biopsy quality can be further enhanced with accessories that are compatible with the semi-rigid pleuroscope such as the insulated tip knife and cryoprobe[69,70].

In the search for an improved diagnostic yield of medical thoracoscopy, pleural cryobiopsy (freezing pleural tissue with a cryoprobe via thoracoscope and removing it en bloc with the instrument) has been shown as an option for obtaining larger specimens with deeper tissue layers while avoiding crush artifact from traditional flexible biopsy forceps. Two systematic reviews and meta-analyses were published in the same year, and these yields were reproduced in both reviews[70,71].

Medical thoracoscopy should be viewed as a minimally invasive technique offered to patients for diagnosis of PE.

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CONFLICTS OF INTEREST

None.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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