Journal of *Respiration*

MDPI

*Review*

# A Review of Medical Thoracoscopy and Its Role in Management of Malignant Pleural Effusion

**Michael Gioia and Rosa L. Arancibia ***

Division of Pulmonary and Critical Care, SUNY Downstate Health Sciences University, Brooklyn, NY 11203, USA; michael.gioia@downstate.edu

* Correspondence: rosa.arancibia@downstate.edu

**Abstract:** Pleural effusion is the most common disease among all pleural diseases and affects 1.5 million patients per year in the United States. Different interventions can be performed when dealing with pleural effusions. In this review, we present medical thoracoscopy as a minimally invasive procedure with both diagnostic and therapeutic utility in the management of pleural disease. It has a higher diagnostic yield than commonly performed percutaneous procedures (thoracentesis, closed pleural biopsy) and simultaneously offers many of the therapeutic benefits of more invasive procedures, such as video-assisted thoracoscopic surgery, with a lower risk profile. The role of medical thoracoscopy is evolving and will likely continue to expand as more centers start performing the procedure nationwide.

**Keywords:** pleural effusion; medical thoracoscopy; lung cancer



**Citation:** Gioia, M.; Arancibia, R.L. A Review of Medical Thoracoscopy and Its Role in Management of Malignant Pleural Effusion. *J. Respir.* **2024**, *4*, 35–49. https://doi.org/10.3390/jor4010004

Academic Editor: Bruce Fernando Sabath

Received: 11 November 2023
Revised: 29 January 2024
Accepted: 6 February 2024
Published: 26 February 2024



## 1. Introduction

Medical thoracoscopy (also known as pleuroscopy) is a minimally invasive procedure in which an endoscope is passed through the chest wall to allow for direct visualization of the pleural space [1]. It allows for both diagnostic and therapeutic procedures to be performed at the same time. It differs from video-assisted thoracoscopic surgery (VATS) in that medical thoracoscopy uses a single port of entry. The thoracoscope is inserted, with instruments then being passed through the working channel. VATS utilizes multiple entry ports (one for the thoracoscope and an additional port or ports for instruments). Also, when performing a rigid medical thoracoscopy, a second port might be necessary for better visualization, to drain complex loculated fluid collections, to facilitate adhesion lysis and to control bleeding. Another difference is that, due to the extra required space to have multiple ports, VATS typically requires single lung ventilation but has the advantage of allowing for complete visualization of the hemithorax and can facilitate more advanced therapeutic modalities such as lobectomy and decortication. Medical thoracoscopy has the advantage of not requiring single lung ventilation and therefore it can be safely performed on spontaneously breathing patients (under moderate sedation) [2].

## 2. History

Thoracoscopy as a diagnostic and therapeutic procedure has been around for more than a century. Haus-Christian Jacobaeus first wrote on the technique of thoracoscopy in 1910.

In 1915 [3], in a case of cavitary pulmonary tuberculosis, he performed a thoracoscopy under local anesthesia with two separate entry ports, one for the optic and one for the cautery, in the fifth and third intercostal spaces, respectively. He saw a false adherence which joined the parenchyma to the diaphragm and a true one located on the upper right lobe, the size of a little finger. He cauterized it, causing the instant collapse of the lung. In subsequent years, his clinical studies of patients treated with thoracoscopic lysis of

adherences which prevented pneumothorax (later to be known as the Jacobaeus operation) became more numerous. Later, he utilized this in the treatment of pleural tuberculosis.

Jacobaeus also worked closely with the thoracic surgeon at his hospital, Einar Key, which enabled an appropriate and complete response to intrathoracic pathologies. In 1922, he published an article which gives an account of five cases of thoracoscopy prior to thoracotomy [4]. In these patients, Jacobaeus induced a pneumothorax and examined the pleural cavity, identifying the endothoracic tumor and providing useful information for the subsequent thoracotomy (therefore doing something similar to what today is defined as staging).

In the 1950s, with the advent of anti-tuberculous chemotherapy, surgical collapse therapy was abandoned. Thoracoscopy also declined, except in continental Europe, where various centers developed it for the diagnosis of many pleuropulmonary diseases under the leadership of pulmonologists such as Brandt in Germany, Sattler in Austria, Swieringa in Holland, Alcozer in Italy and Boutin in France, to mention the most important.

Two meetings were of fundamental importance for the rebirth of thoracoscopy: in 1980 Boutin organized the first International Symposium on Thoracoscopy in Marseille [5], and in 1987 Loddenkemper organized the second Thoracoscopy Symposium in Berlin [6]. Two books represented the pinnacle in the period of the rebirth of thoracoscopy: the Atlas of Diagnostic Thoracoscopy published by Brandt, Loddenkemper and Mai [7], and Practical Thoracoscopy published in 1991 by Boutin in collaboration with Viallat and Aelony [8].

## 3. Indications

As medical thoracoscopy becomes more widely available, its role as both a diagnostic and therapeutic procedure continues to expand. Some of the most common indications for medical thoracoscopy include malignant pleural effusion, unexplained pleural effusion, tuberculous pleural effusion, talc pleurodesis and lysis of adhesion.

## 4. Diagnostic Yield of Medical Thoracoscopy

Medical thoracoscopy is increasingly being used in the diagnosis of unexplained pleural effusion. When compared to closed pleural biopsy (CPB) for the diagnosis of unexplained exudative pleural effusion, medical thoracoscopy had a higher diagnostic yield (93.2% vs. 84.5%, $p = 0.02$), with similar overall morbidity and mortality (8.3% morbidity and 0.0% mortality for CPB; 5.6% morbidity and 0.37% mortality for MT) [9]. In an analysis by Maturu et al., when ultrasound guidance was used for trocar placement in MT, the diagnostic yield improved to 98.7% [10]. Another study found MT had a pooled sensitivity of 97% and a specificity of 100% in the diagnosis of unexplained pleural effusion. Another randomized control trial found the diagnostic yield of MT for unexplained pleural effusion to be 86% and the total complication rate to be 10%, compared to a diagnostic yield of 62% and a complication rate of 17% for CPB [11]. With regards to the specific type of thoracoscope used for MT in the diagnosis of unexplained pleural effusion, Dhooria et al. found in a randomized control trial that rigid thoracoscopy was associated with a higher overall diagnostic yield (97.8% vs. 73.3% with a semi-rigid thoracoscope). This difference was not seen, however, when only comparing cases where biopsies were successfully obtained [11].

MT also has a high diagnostic yield in the diagnosis of malignant pleural effusion, ranging from about 86–100% in several studies [12–14]. One of the advantages of MT which helps explain the high diagnostic yield is that MT allows for the direct visualization of the visceral pleura, parietal pleura and diaphragmatic pleura, allowing the proceduralist to obtain tissue samples from areas of pleural irregularity/nodularity [12]. Another advantage is that pleurodesis can be performed at the time of the diagnostic procedure, as opposed to undergoing multiple procedures, and the success rate for talc poudrage pleurodesis during MT has been reported to range from ~78–93% [15,16]. Thoracoscopic talc pleurodesis remains the preferred technique for pleurodesis for malignant pleural effusion in patients with superior performance status [16].

Thoracoscopy can also have a significant role in the diagnosis and management of mesothelioma. Malignant pleural mesothelioma has traditionally posed a diagnostic challenge. In a retrospective analysis by Renshaw et al., the sensitivity of cytologic examination of pleural fluid for a diagnosis of malignant mesothelioma was only 32% [17]. In a study by Arranoos and Gibbs, the sensitivity and specificity of closed pleural biopsy in the diagnosis of malignant mesothelioma was 16% and 94%, respectively; in comparison, they found the sensitivity and specificity of open pleural biopsy to be 95% and 100%, respectively [18]. MT has a sensitivity approaching 98% and allows for the simultaneous performance of talc pleurodesis and/or placement of a tunneled pleural catheter [16]. Another study found a sensitivity of ~90% for early-stage mesothelioma and its specificity to approach 100% [19]. Another indication where thoracoscopy provides both improved diagnostic yield and therapeutic benefits is in the management of tuberculous effusion. AFB smears and cultures of pleural fluid have been reported in multiple studies to have very poor sensitivity (<10% and <30%, respectively) in diagnosing TB pleural effusion [20,21]. Adenosine deaminase (ADA) sent from pleural fluid sample can increase the sensitivity of diagnosing TB effusion to 86% if there is a high pre-test probability of TB. MT has a sensitivity in diagnosing TB effusion of 93% in developed countries and a 98% sensitivity in endemic countries. MT also offers the benefit of allowing for therapeutic procedures such as lysis of adhesions in loculated effusion [16]. Other studies have also reported similarly high diagnostic yields of MT in pleural effusion due to TB. One Chinese study found a diagnostic accuracy of 87.5% for TB pleural effusion in patients undergoing MT [22].

## 5. Therapeutic Procedures Performed during Thoracoscopy

The pleural disease in which the therapeutic role of MT has been most extensively studied is malignant pleural effusion. The role of MT in MPE will be discussed in further detail in a separate section in this review. There are other therapeutic interventions utilized by interventional pulmonologists, as described below.

Pneumothorax is another problem commonly encountered by interventional pulmonologists where the role of MT has been explored. In patients with primary spontaneous pneumothorax who underwent MT with talc poudrage there was a lower recurrence rate (5%) compared to a 34% recurrence rate in patients who underwent pleural drainage alone [23]. In PSP (primary spontaneous pneumothorax) patients, MT offers an additional benefit of direct visualization of any subpleural blebs or bullae under white light MT and pleural porosity under fluorescein-enhanced autofluorescence MT.

Secondary spontaneous pneumothorax has a higher rate of recurrence after the 1st episode due to the presence of underlying lung disease, which therefore carries a significantly greater risk to the patient than PSP. Therefore, guidelines recommend more invasive procedures, such as VATS with pleurectomy or bullectomy, but require general anesthesia with single lung ventilation. This carries a significant risk of morbidity and mortality for patients deemed unfit for general anesthesia, while medical thoracoscopy–talc poudrage is a safe and effective alternative. This has been shown in a study evaluating the safety and efficacy of MT–TP for patients with moderate to severe COPD (mean FEV1 0.88l). The long-term success rate was a 95% success rate at 35 months in COPD patients [16]. However, this study revealed a significant 30-day mortality rate of 10%. This early mortality was directly related to severe underlying lung disease, low BMI and associated ischemic heart disease. These risks should be discussed with individual patients and weighed up against the significant risk of pneumothorax recurrence after the first episode. When performing MT for pneumothorax, a single port is inserted into the third or fourth intercostal space after checking that the lung is properly collapsed. After the inspection, 1–2 g of graded talc is gently insufflated into the pleural space, paying attention to achieving a spread of talc diffusely over the pleura and diaphragm.

The role of MT in the management of complex parapneumonic effusions and empyema has not been studied as well as the role of MT in the diagnosis and management of malignancy. One small prospective randomized control trial comparing intrapleural fibrinolytic

therapy to early medical thoracoscopy found no statistically significant difference in median length of stay after intervention, treatment failure rates, mortality or adverse events [24]. Lysis of adhesions and drainage of pleural fluid can be performed, and some small studies have suggested that MT can be quite effective in the treatment of complex parapneumonic effusion (up to 100% of cases in which fluid is free-flowing) and empyema (91.7% of cases), although the diagnostic benefit was not as robust (positive cultures in 47% of patients in one study) [9].

## 6. Complications

Medical thoracoscopy is considered a safe procedure and is usually well tolerated by patients; however, complications can and do occur. Complications of MT can be divided into major and minor complications. According to a comprehensive study, major complications (pneumonia, hemorrhage, empyema, bronchopleural fistula, port site tumor growth, postoperative pneumothorax or air leak) occurred in 86/4736 cases (1.8%). Minor complications (fever, minor hemorrhage, subcutaneous emphysema, operative skin site infection, atrial fibrillation or hypotension during the procedure) occurred in 177/2411 procedures (7.3%) [25].

In a study by Wan et al. [26], the authors looked at the complications of medical thoracoscopy in the management of different pleural diseases including malignancies and pleural infections (Tables 1 and 2). The distribution of complications differed based on the indication for the procedure. Pain and fever were the most frequent complications in the pleurodesis group, whereas cutaneous infection in the entry site was the most frequently reported complication in pleural decortication in the empyema group.

**Table 1.** Safety and complications of medical thoracoscopy in the management of pleural diseases. Complications of medical thoracoscopy. Reprinted/adapted with permission from reference [26].

| Complication | Diagnostic Thoracoscopy (n = 662) | Therapeutic Thoracoscopy (n = 1264) | *p*-Values |
|---|---|---|---|
| **Major complications** | | | |
| Mortality | 0 | 1 (0.1) | 1.0 |
| Lung laceration | 1 (0.2) | 5 (0.4) | 0.628 |
| Bleeding | 1 (0.2) | 5 (0.5) | 0.47 |
| Pulmonary reexpansion oedema | 1 (0.2) | 1 (0.1) | 1.0 |
| Prolonged air leak | 1 (0.2) | 8 (0.6) | 0.262 |
| Mediastinal emphysema | 0 | 2 (0.2) | 0.549 |
| **Minor complications** | | | |
| Subcutaneous emphysema | 20 (3.0) | 42 (3.3) | 0.722 |
| Pain | 132 (19.9) | 617 (48.8) | <0.001 |
| Fever | 3 (0.5) | 398 (31.5) | <0.001 |
| Cutaneous infection in entry site | 14 (2.1) | 123 (9.7) | <0.001 |

**Table 2.** Safety and complications of medical thoracoscopy in the management of pleural diseases Complications of therapeutic thoracoscopy based on therapeutic indication Reprinted/adapted with permission from reference [26].

| Complications | Pleurodesis (n = 358) | Adhesiolysis (n = 517) | Pleural Decortication of Empyema (n = 125) | Bulla Electrocoagulation (n = 264) | *p*-Values |
|---|---|---|---|---|---|
| **Major complications** | | | | | |
| Mortality | 0 | 0 | 1 (0.8) | 0 | 0.099 |
| Lung laceration | 0 | 4 (0.8) | 1 (0.8) | 0 | 0.158 |
| Bleeding | 0 | 3 (0.6) | 0 | 3 (1.1) | 0.185 |

**Table 2.** *Cont.*

| Complications | Pleurodesis (n = 358) | Adhesiolysis (n = 517) | Pleural Decortication of Empyema (n = 125) | Bulla Electrocoagulation (n = 264) | *p*-Values |
|---|---|---|---|---|---|
| Pulmonary re-expansion oedema | 0 | 1 (0.2) | 0 | 0 | 1.0 |
| Prolonged air leak | 0 | 1 (0.2) | 1 (0.8) | 6 (2.3) | 0.002 |
| Mediastinal emphysema | 0 | 2 (0.4) | 0 | 0 | 0.597 |
| **Minor complications** | | | | | |
| Subcutaneous emphysema | 0 | 28 (5.4) | 0 | 14 (5.3) | <0.001 |
| Pain | 244 (68.2) | 203 (39.3) | 28 (22.4) | 142 (53.8) | <0.001 |
| Fever | 218 (60.9) | 109 (21.1) | 54 (43.2) | 17 (6.4) | <0.001 |
| Cutaneous infection in entry site | 16 (4.5) | 20 (3.9) | 82 (65.6) | 5 (1.9) | <0.001 |

In the same study, when all therapeutic thoracoscopies were grouped together and their complication rate was compared to diagnostic thoracoscopies, there was no statistically significant difference in any major complication. There was, however, a statistically significant increase in the minor complications of fever, pain and cutaneous infections in those who underwent therapeutic procedures as opposed to diagnostic procedures. Fever and pain were more common among patients who underwent talc pleurodesis than in those undergoing MT for any other indication. Cutaneous infections were most commonly seen in those undergoing decortication/adhesion lysis for empyema. When looking at specific therapeutic indications, major complications tended to occur more frequently in the group undergoing adhesion lysis when compared to other diagnostic/therapeutic indications (although this association did not reach the level of statistical significance). Of all the patients included in the study, there was one patient with empyema who died when artificial pneumothorax was being established during insufflation [26]. We must keep in mind that extensive adhesions in the pleural cavity increase the risk of lung laceration when introducing a trocar, especially when the space is less than 1 cm in depth. Despite no statistical significance for complications when performing adhesion lysis being found, the study raises the following questions: What degree of adhesions is insufficient for MT? What is the selection for patients with extensive adhesions, VATS or other pleural procedures? These crucial issues should be resolved in future studies.

Based on the study, prolonged air leak was more common in the bulla electrocoagulation group. It is probably related to destruction of emphysematous bullae, and it is advised that bulla electrocoagulation combined with pleurodesis would reduce incidence of prolonged air leak [26]. However, bulla electrocoagulation is more commonly performed in VATS, and it is rarely performed during medical thoracoscopy.

Overall, therapeutic MT is a safe procedure when the interventional pulmonologist is aware of all the complications.

## 7. Equipment and Technique

Beyond knowing the indications and risks of medical thoracoscopy, it is important for the interventional pulmonologist to be familiar with the equipment needed for MT and the technique involved in performing the procedure. The procedure is typically performed under moderate sedation without the patient being intubated; however, in special circumstances, intubation and general anesthesia may be preferable, such as with uncooperative patients [16].

The rigid thoracoscopy equipment consists essentially of a light source (usually xenon arc lamps), trocars and obturators, a rigid telescope with a camera, and biopsy forceps. Trocars and telescopes range in size from 3 to 13 mm in external diameter. A larger trocar allows the introduction of a larger telescope, improving the quality of the exploration. How-

ever, the manipulation of a large trocar within the intercostal space can be painful and less suitable for a procedure with local anesthesia. The optimal size of the trocar and telescope depends on patient's considerations and operator's preferences, but a 7 mm diameter is considered a good compromise [27,28]. The angle of vision of the rigid telescopes varies according to the utilized optics: direct view (0-degree optic), oblique view (30 or 50 degree optic) and 'periscope' view (90 degree optic). The availability of different optics allows a more accurate exploration of the pleural cavity. Biopsy of the parietal pleura performed with a 5 mm optical forceps allows the use of the single-puncture technique [29]. Smaller-diameter telescopes (2–3 mm) have been used in the so-called 'Mini thoracoscopy'. Tassi and Marchetti [30] reported a high yield of 93.4% in the diagnosis of pleural effusions using a 3 mm thoracoscope to perform pleural biopsies under local anesthesia. A comparison of the standard thoracoscope of 7 mm diameter with a 2 mm and a 3.5 mm thoracoscope was carried out by Janssen et al. [31]. The 3.5 mm thoracoscope had a diagnostic yield of 100%, equal to the 7 mm set. However, the yield of the 2 mm thoracoscopy set was only 40%.

The semi-rigid thoracoscope (model LTF 160 or 240, Olympus, Tokyo, Japan) is similar in design and handling to a bronchoscope, making it more attractive to general pulmonologists. It is commonly introduced into the pleural space through a dedicated 8–10 mm disposable plastic trocar (Olympus, Tokyo, Japan). The thoracoscope consists of a handle and a shaft with an outer diameter of 7 mm and a total length of 27 cm. The distal 5 cm of the shaft can be flexed by moving the lever on the handle, allowing a two-way angulation capability of 160° up and 130° down. It has a 2.8 mm working channel through which a variety of endoscopic instruments can be passed (biopsy forceps, needles, electrocautery probes) [32]. There are no absolute advantages to semi-rigid instruments over rigid thoracoscopes. Although the semi-rigid thoracoscope is handled very similarly to a bronchoscope, a learning curve is still required. The biopsy forceps used through the semi-rigid thoracoscope obtain small samples of about 2 mm, which may limit the diagnostic yield, especially in the case of mesothelioma [28,29,33].

These are the types of thoracoscopes (Figure 1):

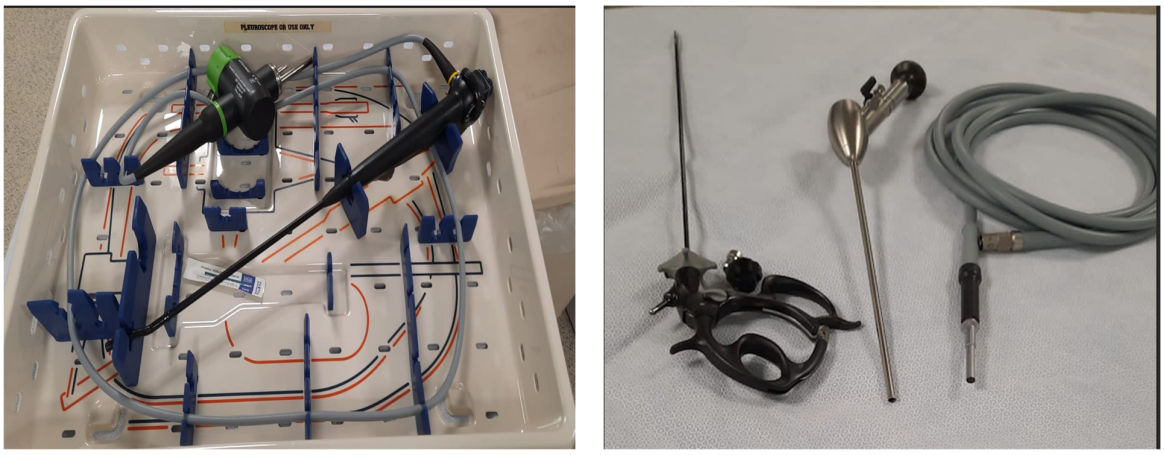

**Figure 1.** Semi-rigid thoracoscope (Olympus, Tokyo, Japan) (**left**) and rigid thoracoscope (Richard Wolf Medical Instruments Corporation, Vernon Hills, IL, USA) (**right**).

The procedure is performed with the patient in the lateral decubitus position (Figure 2). The ipsilateral arm is positioned either over the head or is supported in a sling to elevate the arm. The operator is typically positioned facing the patient to allow for optimal exposure once the thoracoscope is inserted.

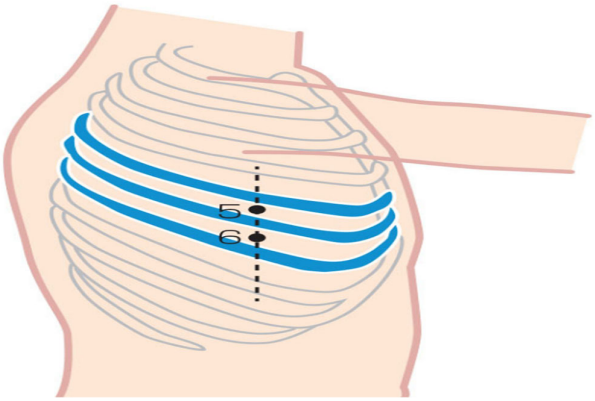


**Figure 2.** Position and point of entry for thoracoscopy(adapted from textbook thoracoscopy for pulmonologist).

It is recommended that trocar insertion be performed in the "triangle of safety"). The triangle of safety is formed by the borders of the pectoralis major muscle anteriorly, latissimus dorsi muscle posteriorly, and the nipple line (in men) or infra-mammillary fold (in women). This will typically lead to trocar placement in the fourth or fifth intercostal space in the lateral thorax; however, ultrasound guidance should be used to identify the most appropriate site for trocar insertion and to avoid any areas of lung adhesion. Once the insertion site has been identified, the skin over the entire hemithorax should then be cleansed with an alcohol-based skin sterilizing solution, then a sterile drape is placed over the hemithorax with only a small opening that allows for access to the operative site. The skin should then be cleansed again prior to the administration of local anesthetic. The skin is then infiltrated with local anesthetic (typically lidocaine 0.5% or 1%). Subsequently, the subcutaneous tissue and muscular layer should be anesthetized as well. If there is a pleural effusion, aspiration of pleural fluid should be confirmed [16].

Then, a ~1 cm horizontal skin incision is made through the skin and subcutaneous tissue. The incision should be in the middle of the selected intercostal space. Blunt dissection is then performed with a blunt dissecting forceps to dissect through the chest wall and parietal pleural. Once adequate blunt dissection has been performed, the trocar should then be inserted into the pleural space using a corkscrew motion. At this point, the pleural fluid can be suctioned out. As the pleural fluid is suctioned out, air will enter the pleural space from around the suction catheter to create a pneumothorax. Once the trocar is in place and the pleural effusion has been evacuated, the thoracoscope is inserted via the inner channel of the trocar. Once the thoracoscope has entered the pleural space, thorough visual inspection of the parietal pleural, visceral pleura and lung should be performed. Biopsy forceps (Figure 3) can then be introduced via the working channel of the thoracoscope. The pleural biopsy should be performed over a rib which can be touched and felt with biopsy forceps. A lateral "lift and peel" technique is utilized to obtain large, 1–2 cm pleural tissue biopsies. With this technique, the edge of the pleural surface is lifted and gently pulled sideways to obtain biopsies [16]. Cryoprobes are used to perform pleural biopsies as well. They work on the Joule–Thompson principle, wherein the sudden expansion of a gas from a high- to low-pressure region results in cooling [17,18]. The flexible cryoprobe is passed through the working channel, and the tip of the probe is placed in the parietal pleura where the abnormality is present. This freezes the tissue around the tip of the probe. The frozen tissue is extracted by gently pulling. The probe with the attached biopsy sample is removed through the thoracoscope [34]. Then, each biopsy sample is released from the probe by thawing in saline. A cryoprobe activation time of 3 s is generally used for cryobiopsy [35].

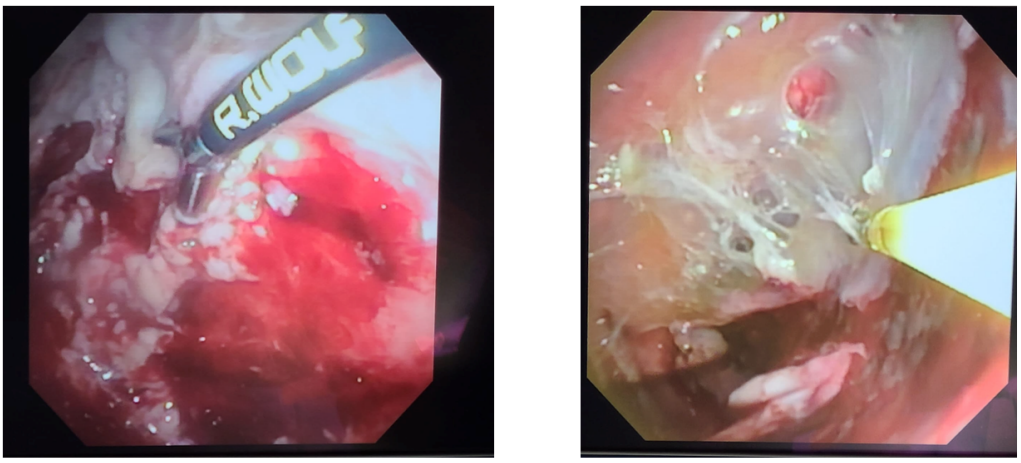

**Figure 3.** Forceps biopsy of parietal pleura using rigid forceps (**left**) and flexible forceps (**right**).

Cryobiopsy specimens are larger than forceps biopsy specimens, with no difference in diagnostic yield. The cryotechnique proved to be beneficial in cases of thin highly vascular pleura, allowing easier biopsies with a lesser risk of bleeding [36]. Maturu and Sehgal [37] reported that cryobiopsy was larger with better preserved cellular architecture and tissue integrity than flexible forceps biopsy.

There also have been small case reports of the use of the hybrid knife to obtain punch pleural biopsies. Obtaining adequate samples from thickened pleura is the most important limitation of semi-rigid thoracoscopy with flexible forceps, especially in patients with mesothelioma or benign fibrothorax. The hybrid knife (HK) is an innovative design fusing high-pressure water injection and a conventional diathermic knife that can allow for the safe resection of a larger lesion during gastrointestinal endoscopic dissection. This tool has been utilized as a new pleural biopsy device in semi-rigid thoracoscopy when pleural lesions are difficult to biopsy using flexible forceps.

The tip of the hybrid knife is inserted, and an electrosurgical circular incision is made around the pleural lesion [34,38].

At the end of the procedure, a chest tube is inserted. It should be the same caliber as the trocar or larger (generally at least 20 French). The chest tube can be removed once full lung re-expansion has occurred. If biopsies or pleurodesis are performed, then the patient can be hospitalized post-procedure. There will still be severe pain that cannot be controlled with NSAIDs and acetaminophen [16].

In our institution, all our thoracoscopies are performed under moderate sedation. However, we have to keep in mind that lung laceration can occur when placing a trocar, and sometimes the bleeding cannot be controlled. In this scenario, a conversion to video assisted thoracoscopic surgery (VATS) should start promptly.

## 8. Role in Management of Malignant Pleural Effusion

Malignant pleural effusions (MPE) are estimated to affect more than 200,000 patients in the United States annually. Of all thoracenteses performed, 36% are performed for malignant pleural effusions. The malignancies most associated with MPE are lung cancer (adenocarcinoma being the most likely type of lung cancer to be associated with MPE), followed by breast cancer and lymphomas. In 5–10% of cases, the primary malignancy is never identified. The prognosis in patients with MPE is poor, generally ranging from 3–12 months, depending on the underlying primary malignancy [39].

Malignant pleural effusion is considered a quite common cause of exudative pleural effusion. The overall diagnostic sensitivity of thoracentesis is around 60% [40]. The yield of pleural fluid cytology from the first specimen is 51%, which increases by an additional 7% from the second specimen and by only 2% from the third [41]. The sensitivity of pleural fluid cytology also varies by the specific primary malignancy. One study found an overall

sensitivity of pleural fluid cytologic analysis to be 46%, with primary malignancy-related sensitivities of 6% for mesothelioma, 40% for hematologic malignancies, 79% for lung adenocarcinoma and up to 95% when ovarian cancer is the primary malignancy [42]. Also, thoracentesis has a diagnostic role in patients with metastatic malignancy that presents with a pleural effusion. In a study by Grosu et al., 725 patients were examined, 63% had pleural fluid cytology positive for malignancy. The sensitivity of thoracentesis varied according to the type of solid tumors. Low sensitivity was seen in sarcomas, head and neck malignancies, and renal cell cancers. The highest was seen in breast cancer and pancreatic cancer. In the study, the factors associated with an increased risk of MPE included a larger amount of fluid drained and higher pleural fluid protein [43]. Thus, additional investigation is clearly needed in such a situation of a non-diagnostic thoracentesis in which MPE is a consideration (or is suspected). Medical Thoracoscopy (MT or VATS) is successful in achieving diagnosis when pleural fluid cytology is nondiagnostic as well as in treating MPE through loculation breakdown, chemical pleurodesis and/or tunneled pleural catheter (TPC) insertion. The sensitivity of thoracoscopy ranges from 92 to 97%, and its specificity is 99–100% for patients with a malignant pleural effusion [44]. The diagnostic sensitivity of thoracoscopy does not alter according to the origin of the malignant pleural effusion: it is 96% for lung carcinomas, 92% for mesotheliomas and 96% for extra-thoracic metastatic malignancies [45]. On inspection, the endoscopic appearance of pleural lesions during medical thoracoscopy is suggestive of malignancy in 86% of cases [8]. The lesions seen during thoracoscopy may vary from polypoid tumors, masses, "candle wax drops", to nodules and/or pleural thickening—diffuse or localized with associated islands of metastatic invasion from uninvolved pleura. In the latest series in the *European Respiratory Review*, leading pleural specialists have provided reviews on the latest advances in pleural medicine. Psallidas et al. [46] provide a state-of-the-art review of malignant pleural effusion from bench-to-bedside focusing on the pathogenesis, novel treatments and future directions (Figure 4).

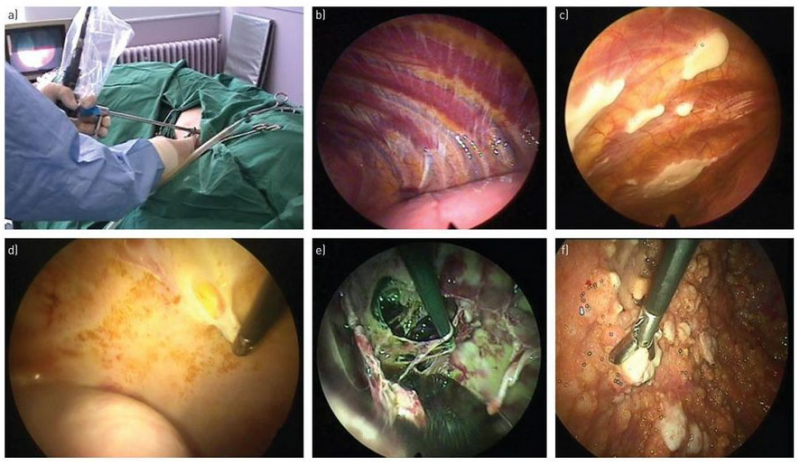


**Figure 4.** Medical thoracoscopy. (**a**) Example of procedural room set-up for rigid thoracoscopy. (**b**) Normal parietal pleura with clearly defined anatomy. (**c**) Pleural plaque disease with typical "fried-egg" appearance overlying ribs. (**d**) Diffuse parietal and visceral pleural thickening secondary to mesothelioma with two-port strip biopsy technique. (**e**) Heavily septated pleural space using two-port technique to divide septations in context of intercurrent malignancy and infection. (**f**) Widespread malignant pleural nodularity with two-port biopsy technique (reprinted from *Pleural diseases ERR* [46]).

However, there are malignancies which may resemble nonspecific inflammation and, conversely, certain inflammatory lesions can mimic tumors. To improve the diagnostic accuracy of thoracoscopy, autofluorescence has been assessed in combination with the conventional method, as the effectiveness of autofluorescence techniques has been proven in both the accurate detection of early malignant or invasive lesions and appropriate sampling

of tissue during bronchoscopy. This has also been evaluated during the thoracoscopy procedure. In a study by Chrysanthidis et al., normal areas in the pleural surface appeared white or white/pink in both white light thoracoscopy (WLT) and autofluorescence thoracoscopy (AFT) (Figure 5). Areas with fat on the pleural layer appeared yellow under the conventional mode, but orange under the autofluorescence mode. In all cases of histologically proven malignant pleural disease, the color of the affected area of the pleura changed from white/pink to red in a darker or slighter attenuation [47].

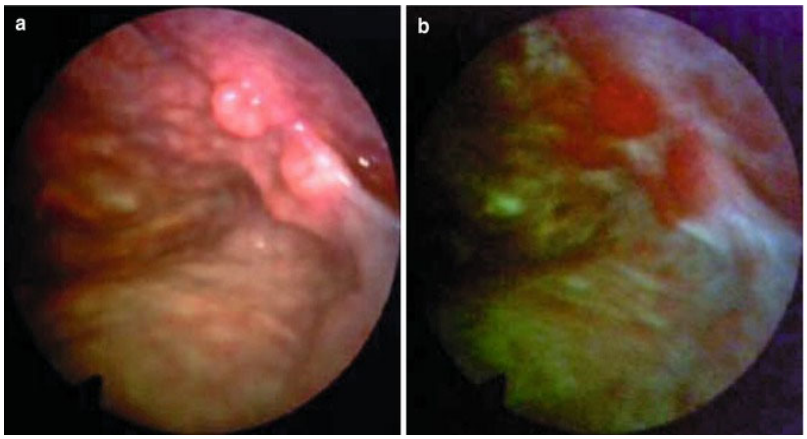


**Figure 5.** Malignant pleural mesothelioma detected in occupational asbestos-exposed patient by white-light source (**a**) and autofluorescence thoracoscopy (**b**) (reprinted from Thoracic Key Engine) [48].

Lung cancer remains the most common fatal malignancy, and it is the most common cause of malignant pleural effusion. The incidence of pleural effusion in patients with lung carcinoma ranges between 7–23% [49]. The presence of pleural effusion typically signals an advanced stage of disease and is therefore associated with poor prognosis. In some cases, however, the pleura itself is not involved in tumor growth. These accompanying para-malignant effusions are due to post obstructive pneumonia or atelectasis, venous obstruction by tumor compression or lymphatic obstruction by mediastinal lymph nodes and are not associated with direct pleural involvement. Such patients are few in number, but, if pleural cytology is negative, the clinician should explore additional diagnostic avenues, medical thoracoscopy or surgical procedures (VATS/open biopsy) [50]. Therefore, thoracoscopy can be performed to further assess the pleural cavity and to detect localized or diffuse pleural infiltration and, in so doing, determine—in cases of non-small cell lung carcinoma (NSCLC)—the unresectable character of the tumor (M1a), which is imperative given the multimodality treatment for NSCLC, including immunotherapy and targeted therapy based on NSG mutations. In our practice, we perform inspection of apical, anterior mediastinal, parietal and diaphragmatic with semi-rigid thoracoscope since this allows a two-way angulation capability of 160° up and 130° down that allows us to reach areas that could not be easily accessible by rigid thoracoscope when we are dealing with malignant loculated pleural effusions. Once we identify the abnormal gross appearance, then we switch to a rigid thoracoscope to perform parietal pleural biopsies and, in some cases, biopsies on diaphragmatic pleura when nodules are seen on its surface.

In small cell lung carcinoma (SCLC), disease free and overall survival of patients with ipsilateral malignant pleural effusion appears to be worse than in patients with limited stage (LD) without pleural effusion, but better than those with extensive stage disease (ED) [51].

Medical thoracoscopy is considered a less invasive procedure compared to VATS, requires moderate sedation, requires a single port of entry and can be performed in the endoscopy suite. Although rigid MT can obtain a larger specimen, the diagnostic yield of rigid and flex–rigid is similar in malignant pleural disease [16,35]. However, there is

an exception when malignant mesothelioma is suspected; larger biopsies are needed for accurate histological subtyping in this case, and rigid thoracoscopy is more advantageous.

As more treatment options for advanced malignancies become available, there is an increasing role for the histopathologic diagnosis of cancer and genetic analysis of malignancy. In non-small cell lung cancer, approximately 10–30% of tumors harbor activating mutations in the tyrosine kinase domain of the EGFR gene, with the prevalence even higher in specific populations (up to 60% in Asians). Patients who are found to have EGFR-mutated lung cancer can be treated with tyrosine kinase inhibitors (osimertinib, dacomitinib, afatinib, erlotinib, gefitinib). Another potential therapeutic target is ALK gene rearrangements. Approximately 5% of NSCLC harbors ALK mutations, for which targeted treatment options include alectinib, brigatiinib, crizotinib, certinib and lorlatinib. Several other potential genetic mutations seen in ~1–3% of NSCLC that have targeted treatments include ROS1 (ceritinib, crizotinib, entrectinib), RET (selpercatinib, cabozantinib) and BRAF V600E (dabrafenib with trametinib). In patients with no targetable genetic mutations, PD-1/PD-L1 inhibitors have become front-line therapy [52].

Given the important role of tumor genetic analysis in guiding cancer treatment, every effort should be made to obtain sufficient tumor/tissue for analysis. One review of confirmed MPE cases due to primary NSCLC found that cytology-based MPE samples made into formalin-fixed, paraffin-embedded cell blocks had similar success rates to surgical pleural biopsies (95% vs. 100%) for EGFR mutation analysis [53]. Another study looked at the characteristics of pleural fluid samples that were associated with successful molecular analysis. Overall cellularity of the fluid and tumor cell percentage were more important factors in determining whether a sample would be suitable for genetic analysis than the volume of the sample [5]. These studies indicate that when pleural fluid cytology is positive, those samples are also typically sufficient for molecular analysis; however, as stated previously, pleural fluid cytology alone has a sensitivity of ~46–60%. In cases where pleural fluid cytology does not yield a diagnosis and/or cases where the pleural fluid sample is not sufficient to perform full genetic analysis, the ability to obtain tissue biopsies with MT can provide sufficient samples for diagnosis and genetic analysis.

Patients with malignant pleural effusion have limited life expectancy and typically have limited functional status, so the ability to make a definitive diagnosis in a timely manner and in the least invasive manner possible is of the utmost importance. Medical thoracoscopy was able in one study of 833 patients with unexplained pleural effusion to establish a definitive diagnosis in 92.6% of cases, including all 342 who were diagnosed with MPE in the cohort [54].

Another benefit of performing thoracoscopy is that therapeutic procedures can be performed to address recurrent malignant pleural effusion. The rate of recurrence of malignant pleural effusions largely depends on the type of cancer. Current ATS guidelines for recurrent malignant pleural effusions (MPEs) recommend definitive procedures, such as indwelling pleural catheters (IPCs) or pleurodesis, over repeat thoracentesis. Unfortunately, patients with recurrent malignant effusion are not receiving definitive treatment. In a study by Ost et al., thoracentesis for MPE was performed in 23,431 patients. In this study, a second pleural procedure was needed because of recurrence seen in 12,967 (55%). Recurrence was rapid in 7565 (58%) of the 12,967 patients that had a recurrence. Of the 7565 patients with rapid recurrence, 1811 (24%) received guideline consistent care. Definitive pleural procedures compared with repeat thoracentesis resulted in fewer subsequent pleural procedures, fewer pneumothoraces and fewer ED procedures. Repeat thoracentesis and IPCs resulted in fewer inpatient days compared with chest tube or thoracoscopic pleurodesis [55]. Therefore, when performing thoracoscopy for a malignant effusion, a pleurex catheter, either with or without talc poudrage, can be performed in one single session to provide definitive treatment for a recurrent malignant pleural effusion.

The diagnostic yield of MT has been well established [15,32,43,56]. However, the talc poudrage's pleurodesis success varies in different studies between ~78–93% [15,32]. A 2014 meta-analysis found that Thoracoscopic talc poudrage was more effective than bedside

talc slurry [57]. This finding has recently come into question, as the TAPPS trial found no statistically significant difference in the 90-day failure rate of talc poudrage when compared to talc slurry administered via thoracostomy tube [58].

In regards the sclerosing agent to perform pleurodesis. A Cochrane review [50] and a systematic review on the effectiveness of management of MPE [27] concluded that 'talc' had the highest efficacy for preventing MPE recurrence when compared with other commonly used sclerosants. Talc can be introduced into the pleural space in two different ways: instillation through a thoracostomy tube—also known as 'talc slurry'—and thoracoscopic talc poudrage or insufflation (TTI). Whereas the first one has the main advantage of being performed at the bedside, TTI allows complete fluid evacuation, adhesion lysis and even distribution of talc during insufflation. The two previously mentioned reviews favor the use of TTI over talc slurry due to a reduction in recurrence of MPE [59,60]. However, this was based on the results of two small randomized controlled trials [61,62]. Subsequent to these reviews, Dresler et al. [32] conducted the largest randomized trial, which had a primary endpoint of 30-day freedom from radiographic recurrence of MPE. There were no differences in the primary endpoint between the two study arms (TTI, 78%; talc slurry, 71%). However, ad hoc subgroup analysis revealed that patients with primary lung or breast cancer had a higher success rate with TTI (82%) than with talc slurry (67%). However, the TAPPS trial found no statistically significant difference in the 90-day failure rate of talc poudrage when compared to talc slurry administered, which included lung and breast cancer patients [58]. If thoracoscopy is readily available, for patients with adequate performance status and clinically suitability for medical thoracoscopy, talc poudrage should be considered so that diagnosis, staging and therapeutic measures can be performed in one procedure and on an outpatient basis.

Another advantage during thoracoscopy is the visual assessment of the lung; if the lung re-expands, talc poudrage can be performed for more definitive management of the MPE [54]. In other instances, if the lung is not expandable due to entrapment/trapped lung, then an indwelling pleural catheter placement can be performed.

## 9. Summary

Pleural effusion is the most common disease of the pleura, and for patients with pleural effusion it can be debilitating. Management of pleural effusion depends on the accurate diagnosis of the underlying etiology of the effusion and treatment of the underlying disease. As procedural techniques and medical technology advance, the interventional pulmonologist has a variety of options to diagnose and treat pleural effusion. Medical thoracoscopy has emerged as both a highly effective diagnostic tool and safe treatment option in the management of pleural effusions. The role of medical thoracoscopy will continue to expand as it becomes more widely available.

## 10. Future Direction

Medical thoracoscopy has not yet been considered as the first-line investigation in malignant pleural effusion. However, this review provides enough evidence that medical thoracoscopy offers the opportunity for both diagnosis and therapy in a single setting and to prevent multiple future pleural procedures often necessitating further hospital admissions or a surgical referral. This represents an extra burden to both the patient and the healthcare service in terms of waiting time, days spent in hospital and invasive procedures for our patients. In patients in whom accurate histology will change treatment (e.g., small cell lung cancer, breast cancer or differentiating adenocarcinoma from mesothelioma), medical thoracoscopy may be indicated and should be considered as the first-line investigation.

We have found in our practice that medical thoracoscopy is more sensitive than thoracentesis +/− closed pleural biopsy in the diagnosis of malignant effusion. We have also found several cases where, on MT, parietal pleural and visceral pleural nodules are seen that were not readily seen on ultrasound or CT imaging. The pleural biopsy specimens obtained have consistently been sufficient to establish the diagnosis, as well as to send for

NSG and PDL1 markers when dealing with non-small cell lung cancer. In many cases, we have also been able to perform pleurodesis or place an indwelling pleural catheter during MT, so our patients have their cancer diagnosed and staged and receive a definitive management of their malignant pleural effusions all in one procedure.

The interventional pulmonologist should have the facility to discuss selected cases with cardiothoracic centers to establish whether a surgical procedure (VATS/thoracotomy) or a local medical thoracoscopy is the optimal treatment strategy for each individual case.

The British Thoracic Society recently published guidelines on the management of pleural disease that give a conditional recommendation for medical thoracoscopy in the initial diagnostic work-up of MPE [63]. We are hoping that in the future our guidelines continue to change and medical thoracoscopy will become the first-line investigation when there is a high suspicion of malignancy.

**Author Contributions:** The authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Written informed consent has been obtained from the patient to publish this paper.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Medical Thoracoscopy/Pleuroscopy. *Chest J.* **2003**, *123*, 1712–1713. [CrossRef]
2. Loddenkemper, R.; Lee, P.; Noppen, M.; Mathur, P.N. Medical Thoracoscopy/Pleuroscopy: Step by Step. *Breathe* **2011**, *8*, 156–167. [CrossRef]
3. Marchetti, G.P.; Pinelli, V.; Tassi, G.F. 100 Years of Thoracoscopy: Historical Notes. *Respiration* **2011**, *82*, 187–192. [CrossRef] [PubMed]
4. Jacobaeus, H.C. The practical importance of thoracoscopy in surgery of the chest. *Surg. Gyn. Obstet.* **1922**, *34*, 289–296.
5. Boutin, C. Symposium sur la thoracoscopie dans les maladies pleuro-pulmonaires. *Poumon. Coeur.* **1981**, *37*, 62.
6. Thoracoscopy Symposium 1987. *Pneumologie* **1989**, *43*, 45–125. (In German)
7. Brandt, H.J.; Loddenkemper, R.; Mai, J. *Atlas of Diagnostic Thoracoscopy: Indications–Technique*; Thieme: New York, NY, USA, 1985.
8. Boutin, C.; Viallat, J.R.; Aelony, Y. (Eds.) Diagnostic thoracoscopy for pleural effusions. In *Practical Thoracoscopy*; Springer: Berlin/Heidelberg, Germany, 1991.
9. Murthy, V.; Bessich, J. Medical thoracoscopy and its evolving role in the diagnosis and treatment of pleural disease. *J. Thorac. Dis.* **2017**, *9* (Suppl. S10), S1011–S1021. [CrossRef]
10. Maturu, V.N.; Dhooria, S.; Bal, A.; Singh, N.; Aggarwal, A.N.; Gupta, D.; Behera, D.; Agarwal, R. Role of medical thoracoscopy and closed-blind pleural biopsy in undiagnosed exudative pleural effusions: A single-center experience of 348 patients. *J. Bronchol. Interv. Pulmonol.* **2015**, *22*, 121–129. [CrossRef] [PubMed]
11. Dhooria, S.; Singh, N.; Aggarwal, A.; Gupta, D.; Agarwal, R. A Randomized Trial Comparing the Diagnostic Yield of Rigid and Semirigid Thoracoscopy in Undiagnosed Pleural Effusions. *Respir. Care* **2014**, *59*, 756–764. [CrossRef]
12. Haridas, N.; Suraj, K.P.; James, P.T.; Chetambath, R. Medical Thoracoscopy vs Closed Pleural Biopsy in Pleural Effusions: A Randomized Controlled Study. *J. Clin. Diagn. Res.* **2014**, *8*, MC01–MC04. [CrossRef]
13. Diacon, A.H.; Van de Wal, B.W.; Wyser, C.; Smedema, J.P.; Bezuidenhout, J.; Bolliger, C.T.; Walzl, G. Diagnostic tools in tuberculous pleurisy: A direct comparative study. *Eur. Respir. J.* **2003**, *22*, 589–591. [CrossRef] [PubMed]
14. Loddenkemper, R.; Grosser, H.; Gabler, A.; Mai, J.; Preussler, H.; Brandt, H.J. Prospective evaluation of biopsy methods in the diagnosis of malignant pleural effusions-intrapatient comparison between pleural fluid cytology, blind needle-biopsy and thoracoscopy. *Am. Rev. Respir. Dis.* **1983**, *127*, 114.
15. De Campos, J.R.M.; Cardoso, P.; Cargas, F.S.; Teixeira, L.R.; Jatene, F.B.; Light, R.W. Thoracoscopy Talc Poudrage A 15-Year Experience. *Chest* **2001**, *119*, 801–806. [CrossRef] [PubMed]
16. Alraiyes, A.H.; Dhillon, S.S.; Harris, K.; Kaphle, U.; Kheir, F. Medical Thoracoscopy: Technique and Application. *Pleura* **2016**, *3*, 1–11. [CrossRef]
17. Morgan, A.E.R.K. Cryosurgery. *Eur. Respir. Monogr.* **2010**, *48*, 161–172.
18. Bonniot, J.P.A.; Homasson, J.P.D.; Roden, S.L.; Angebault, M.L.; Renault, P.C. Pleural and lung cryobiopsies during thoracoscopy. *Chest* **1989**, *95*, 492–493. [CrossRef] [PubMed]

19. Renshaw, A.; Dean, B.; Antman, K.; Sugarbaker, D.; Cibas, E. The Role of Cytologic Evaluation of Pleural Fluid in the Management of Malignant Mesothelioma. *Chest* **1997**, *111*, 106–109. [CrossRef]
20. Attanoos, R.L.; Gibbs, A.R. The comparative accuracy of different pleural biopsy techniques in the diagnosis of malignant mesothelioma. *Histopathology* **2008**, *53*, 340–344. [CrossRef]
21. Metintas, M. Medical Thoracocscopy at 105. Anniversary. *Eurasian J. Pulmonol.* **2015**, *17*, 129–135. [CrossRef]
22. Sharma, S.K.; Mohan, A. Extrapulmonary tuberculosis. *Indian J. Med. Res.* **2004**, *120*, 316–353.
23. Epstein, D.M.; Kline, L.R.; Albelda, S.M.; Miller, W.T. Tuberculous pleural effusions. *Chest* **1987**, *91*, 106–109. [CrossRef] [PubMed]
24. Liu, X.; Dong, X.; Zhang, Y.; Fang, P.; Shi, H.; Ming, Z. Diagnostic Value and Safety of Medical Thoracoscopy for Pleural Effusion of Different Causes. *World J. Clin. Cases* **2022**, *10*, 3088–3100. [CrossRef]
25. Tschopp, J.M.; Boutin, C.; Astoul, P.; Janssen, J.P.; Grandin, S.; Bolliger, C.T.; Delaunois, L.; Driesen, P.; Tassi, G.; Perruchoud, A.P. Talcage by medical thoracoscopy for primary spontaneous pneumothorax is more cost-effective than drainage: A randomised study. *Eur. Respir. J.* **2002**, *20*, 1003–1009. [CrossRef]
26. Wan, Y.Y.; Zhai, C.C.; Lin, X.S.; Yao, Z.H.; Liu, Q.H.; Zhu, L.; Li, D.Z.; Li, X.L.; Wang, N.; Lin, D.J. Safety and complications of medical thoracoscopy in the management of pleural diseases. *BMC Pulm. Med.* **2019**, *19*, 125. [CrossRef]
27. Rodriguez-Panadero, F. Medical thoracoscopy. *Respiration* **2008**, *76*, 363–372. [CrossRef]
28. Rodriguez-Panadero, F.; Janssen, J.P.; Astoul, P. Thoracoscopy: General overview and place in the diagnosis and management of pleural effusion. *Eur. Respir. J.* **2006**, *28*, 409–422. [CrossRef]
29. Lee, P.; Colt, H.G. State of the art: Pleuroscopy. *J. Thorac. Oncol.* **2007**, *2*, 663–670. [CrossRef]
30. Tassi, G.; Marchetti, G. Minithoracoscopy: A less invasive approach to thoracoscopy. *Chest* **2003**, *124*, 1975–1977. [CrossRef]
31. Janssen, J.P.; Thunnissen, F.; Visser, F. Comparison of the 2.0 mm and the 3.5 mm minithoracoscopy set to standard equipment for medical thoracoscopy. *Eur. Respir. J.* **2003**, *22* (Suppl. S45), S451.
32. Dresler, C.M.; Olak, J.; Herndon, J.E.; Richards, W.G.; Scalzetti, E.; Fleishman, S.B.; Kernstine, K.H.; Demmy, T.; Jablons, D.; Kohman, L.; et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* **2005**, *127*, 909–915. [CrossRef] [PubMed]
33. Lee, P.; Colt, H.G. Rigid and semirigid pleuroscopy: The future is bright. *Respirology* **2005**, *10*, 418–425. [CrossRef]
34. Yin, Y.; Eberhardt, R.; Wang, X.-B.; Wang, Q.-Y.; Kang, J.; Herth, F.J.F.; Hou, G. Semi-Rigid Thoracoscopic Punch Biopsy Using a Hybrid Knife with a High-Pressure Water Jet for the Diagnosis of Pleural Effusions. *Respiration* **2016**, *92*, 192–196. [CrossRef]
35. Dhooria, S.; Bal, A.; Sehgal, I.S.; Prasad, K.T.; Muthu, V.; Aggarwal, A.N. Pleural Cryobiopsy versus Flexible Forceps Biopsy in Subjects with Undiagnosed Exudative Pleural Effusions Undergoing Semirigid Thoracoscopy: A Crossover Randomized Trial (COFFEE Trial). *Respiration* **2019**, *98*, 133–141. [CrossRef]
36. Ahmed, M.M.; AlSharkawy, S.H.; Shoukri, A.M.; AbouBakr, Y.T. Evaluation of safety and diagnostic yield of pleural cryobiopsies during thoracoscopy. *Egypt. J. Bronchol.* **2019**, *13*, 63–66. [CrossRef]
37. Maturu, V.N.; Sehgal, I.S. Pleuroscopic cryobiopsy: Case series and systematic review. *J. Bronchol. Interv. Pulmonol.* **2015**, *22*, e11–e13. [CrossRef] [PubMed]
38. Sasada, S.; Kawahara, K.; Iwasaki, T.; Hirashima, T.; Miyazawa, T. An Electrocautery Pleural Biopsy for the Diagnosis of Desmoplastic Malignant Mesothelioma During Semirigid Thoracoscopy. *J. Thorac. Oncol.* **2008**, *3*, 803–804. [CrossRef]
39. Lat, T.; Paul, M. *Malignant Effusion*; StatPearls: St. Petersburg, FL, USA, 2023.
40. Shojaee, S.; Lee, H.J. Thoracoscopy: Medical versus Surgical—In the Management of Pleural Diseases. *J. Thorac. Dis.* **2015**, *7* (Suppl. S4), S339–S351. [CrossRef]
41. Light, R.W. Clinical practice. Pleural effusion. *N. Engl. J. Med.* **2002**, *346*, 1971–1977. [CrossRef] [PubMed]
42. Arnold, D.T.; De Fonseka, D.; Perry, S.; Morley, A.; Harvey, J.E.; Medford, A.; Brett, M.; Maskell, N.A. Investigating unilateral pleural effusions: The role of cytology. *Eur. Respir. J.* **2018**, *52*, 1801254. [CrossRef]
43. Grosu, H.B.; Kazzaz, F.; Vakil, E.; Molina, S.; Ost, D. Sensitivity of Initial Thoracentesis for Malignant Pleural Effusion Stratified by Tumor Type in Patients with Strong Evidence of Metastatic Disease. *Respiration* **2018**, *96*, 363–369. [CrossRef]
44. Boutin, C.; Viallat, J.R.; Cargnino, P.; Farisse, P. Thoracoscopy in malignant pleural effusions. *Am. Rev. Respir. Dis.* **1981**, *124*, 588–592. [PubMed]
45. Antony, V.B.; Loddenkemper, R.; Astoul, P.; Boutin, C.; Goldstraw, P.; Hott, J.; Panadero, F.R.; Sahn, S.A. Management of malignant pleural effusion. *ERS J.* **2001**, *18*, 402–419. [CrossRef] [PubMed]
46. Rahman, N.; Psallidas, I. Pleural Diseases. *Eur. Respir. Rev.* **2016**, *25*, 199–213.
47. Chrysanthidis, M.G.; Janssen, J.P. Autofluorescence videothoracoscopy in exudative pleural effusions: Preliminary results. *Eur. Respir. J.* **2005**, *26*, 989–992. [CrossRef] [PubMed]
48. Thoracic Key—Fastest Thoracic Engine Insight Engine, courtesy D Fielding, Department of Thoracic Medicine, Royal Brisbane and Womens' Hospital, Brisbane, Queensland, Australia. Available online: https://thoracickey.com/autofluorescence-and-thoracoscopy (accessed on 22 November 2023).
49. Froudakaris, M.E. Diagnosis and management of pleural effusion in lung cancer. In *Pleural Diseases*; Bouros, D., Ed.; CRC Press: Boca Raton, FL, USA, 2009.
50. Decker, D.A.; Dines, D.E.; Payne, W.S.; Bernatz, P.E.; Pairolero, P.C. The significance of cytologically negative pleural effusion in bronchogenic carcinoma. *Chest* **1978**, *74*, 640–642. [CrossRef]

51. Livingston, R.B.; McCracken, J.D.; Trauth, C.J.; Chen, T. Isolated pleural effusion in small cell lung carcinoma. A review of the southwest Oncology Group Experience. *Chest* **1982**, *81*, 208–211. [CrossRef]
52. Alexander, M.; Kim, S.Y.; Cheng, H. Update 2020: Management of Non-Small Cell Lung Cancer. *Lung* **2020**, *198*, 897–907. [CrossRef]
53. Folch, E.; Majid, A.; CanderLaan, P.; Yamaguchi, N.; Gangadharan, S.; Kent, M.; Whyte, R.; Kocher, O.; Boucher, D.; Huberman, M.; et al. Adequacy of Pleural Fluid Cytology and Pleural Biopsies for Multiple Tumor Genotyping Techniques in Non-Small Cell Lung Cancer. *Chest* **2014**, *146* (Suppl. S2), 609A. [CrossRef]
54. Wu, Y.B.; Xu, L.L.; Wang, X.J.; Wang, Z.; Zhang, J.; Tong, Z.H.; Shi, H.Z. Diagnostic value of medical thoracoscopy in malignant pleural effusion. *BMC Pulm. Med.* **2017**, *17*, 109. [CrossRef]
55. Ost, D.E.; Niu, J.; Zhao, H.; Grosu, H.B.; Giordano, S.H. Quality Gaps and Comparative Effectiveness of Management Strategies for Recurrent Malignant Pleural Effusions. *Chest* **2018**, *153*, 438–452. [CrossRef]
56. Dalvi, S.D.; Chau, K.; Sajjan, S.; Chakraborty, B.; Karam, P.; Khutti, S.; Gimenez, C.; Das, K. Adequacy of pleural fluid cytology for comprehensive molecular analysis of lung adenocarcinoma: Experience of a large health-care system. *Cytojournal* **2022**, *4*, 7. [CrossRef] [PubMed]
57. Xia, H.; Wang, X.J.; Zhou, Q.; Shi, H.Z.; Tong, Z.H. Efficacy and Safety of Talc Pleurodesis for Malignant Pleural Effusion: A Meta-Analysis. *PLoS ONE* **2014**, *9*, e87060. [CrossRef] [PubMed]
58. Bhatnagar, R.; Piotrowska, H.E.G.; Laskawiec-Szkonter, M.; Kahan, B.C.; Luengo-Fernandez, R.; Pepperell, J.C.T.; Evison, M.D.; Holme, J.; Al-Aloul, M.; Psallidas, I.; et al. Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate among Patients with Malignant Pleural Effusions: A Randomized Clinical Trial. *JAMA* **2020**, *323*, 60–69. [CrossRef] [PubMed]
59. Tan, C.; Sedrakyan, A.; Browne, J.; Swift, S.; Treasure, T. The evidence on the effectiveness of management for malignant pleural effusion: A systematic review. *Eur. J. Cardio-Thoracic Surg.* **2006**, *29*, 829–838. [CrossRef] [PubMed]
60. Shaw, P.; Agarwal, R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst. Rev.* **2004**. [CrossRef]
61. Yim, A.P.; Chan, A.T.; Lee, T.W.; Wan, I.Y.; Ho, J.K. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. *Ann. Thorac. Surg.* **1996**, *62*, 1655–1658. [CrossRef]
62. Manes, N.; Rodriguez-Panadero, F.; Bravo, J.L.; Hernandez, H.; Alix, A. Talc pleurodesis. Prospective and randomized study. Clinical follow-up. *Chest* **2000**, *118*, 131S.
63. Roberts, M.E.; Rahman, N.M.; Maskell, N.A.; Bibby, A.C.; Blyth, K.G.; Corcoran, J.P.; Edey, A.; Evison, M.; de Fonseka, D.; Hallifax, R.; et al. British Thoracic Society Guideline for Pleural Disease. *Thorax* **2023**, *78*, s1–s42. [CrossRef]