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REVIEW ARTICLE

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Advances in pleuroscopy

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Abstract

Objectives: To describe the technique of pleuroscopy, its clinical uses such as diagnosis of exudative pleural effusion, treatment of pleural infection, treatment of pneumothorax, and diagnosis and pleurodesis of malignant pleural mesothelioma. Also to describe the newer techniques developed such as minothoracoscopy, semirigid thoracoscopy, narrow band imaging pleuroscopy, infrared pleuroscopy, autofluorescence pleuroscopy.

Data source: We searched the pubmed the last decade for publications with the key words pleuroscopy, medical thoracoscopy, pneumothorax and pleuroscopy, malignant pleural mesothelioma, minothoracoscopy, semirigid thoracoscopy, autofluorescence pleuroscopy.

Conclusion: Medical thoracoscopy is the method of choice for investigation of the undiagnosed exudative pleural effusions. Newer techniques, such as narrow band imaging thoracoscopy, infrared thoracoscopy, autofluorescence thoracoscopy are offering a promising future for medical thoracoscopy.

KEYWORDS

advanced techniques, malignant pleural mesothelioma, medical thoracoscopy, pleurodesis, pleuroscopy, pneumothorax

1 | INTRODUCTION

Medical thoracoscopy, a method with more than 100 years history, was first used by a Swedish physician named Hans-Christian Jacobaeous, in order to explore the pleural cavity of a patient with pleural tuberculosis and lyse the pleural adhesions obtaining therapeutic pneumothorax in patients with pleural tuberculosis.[1] Nowadays, is the gold standard for the diagnosis of pleural effusions.[2] Currently, the diagnostic yield in patients with malignant pleural disease is reaching 95%.[3,4] As a therapeutic method, it is used for pleurodesis of malignant pleural effusions and pneumothorax with a success rate up to 90%[5] and 95%,[6] respectively. In recent years, besides its diagnostic and therapeutic utility, thoracoscopy has become an important tool in the research of pleural pathophysiology and molecular biology, with the development of new devices and the combination to novel molecular techniques and concepts.

The authors contributed equally in searching the bibliography and writing the review.

2 | TECHNICAL AND DIAGNOSTIC ASPECTS

Pleuroscopy is a simple, safe method of exploration of the pleural cavity.[7] It is a minimally invasive procedure that is performed by a pulmonologist in the endoscopy suite, under local anesthesia or mild conscious sedation with cardiovascular and respiratory monitoring. Thoracoscopy can be done either with a rigid or with a semi-rigid instrument, by a single port of entry or with two ports of entry. The diameter of trocar ranges from 7 to 11 mm, while the diameter of the optics ranges from 6 to 10 mm and that of the biopsy forceps from 4 to 6 mm.

Its sensitivity ranges from 92 to 97%[8] and its specificity from 99% to 100%[9] in patients with malignant pleural effusion. Biopsies may be taken not only from the parietal, but

also from the visceral and diaphragmatic pleura, since during thoracoscopy the whole pleural cavity is inspected under direct view.[9] When adhesions are found during the exploration of the pleural cavity, adhesionlysis can be performed in order to explore the whole pleural space.[10,11]

Efforts regarding patients' selection for thoracoscopy have been done. Martensson[12] performed logistic analysis using seven variables to discriminate malignant from nonmalignant disease in 334 patients with undiagnosed pleural effusion, in order to select patients for diagnostic thoracoscopy. They correctly predicted in 79% of the effusion cases, with strongest positive predicted value variable for malignancy the presence of bloody effusion. In the contrary, the variables with the strongest negative predictive value for malignancy were the presence of eosinophils >30% in the pleural fluid as well as age younger than 50 years.[12]

Recently, we published a study[13] designed to identify prognostic variables in patients presenting initially with undiagnosed pleural effusion proven to be malignant after diagnostic pleuroscopy. We found that the primary tumor, the ECOG performance status, the number of white blood cells, and the neutrophil/lymphocyte ratio (N/L ratio) were predictors of survival. These factors may help physicians select patients for treatment and/or interventional procedures such as thoracoscopy.

Janssen et al.[14] have followed their 208 patients with inconclusive thoracoscopy out of 709 patients who underwent thoracoscopy for undiagnosed pleural effusion; 391 of them (55%) had malignant pleural disease and 183 (26%) a true benign pleural effusion. Therefore, after long-term follow-up the sensitivity of diagnostic thoracoscopy was 91% and the specificity 100%. They suggested a wait and see approach, in such patient population, unless repeated thoracentesis suggests a progressive pleural disease.[14]

We also published our experience with patients with undiagnosed pleural effusion who underwent thoracoscopy for diagnostic reasons.[15] From the 175 patients with undiagnosed pleural effusion who underwent thoracoscopy for diagnostic purposes, finally 129 were diagnosed with malignancy (including 9 patients with eosinophilic pleural effusion), 36 have shown a true benign disease, and 10 patients had to be followed for idiopathic eosinophilic pleural effusion. Usually these effusions have a benign course with resolution within a year as has been shown by our extensive follow-up period (60 months).[15] We can conclude that when a non-specific pleuritis is diagnosed histologically, after initial thoracoscopy for pleural effusion, a follow-up must be undertaken, considering that there are few probabilities of a secondary malignant evolution.

Thoracoscopy in pleural disease without pleural effusion is another "gray zone" for respiratory physicians. Before the chest ultrasound (U/S) application in pleural disease, recognition of computed tomography features such as pachypleuritis and/or retraction of the hemithorax, together with the age of the disease were (and still are) key factors to choose entering or not into the pleural cavity when pleural fluid is absent. Chest U/S has changed definitely the approach in pleural disease, since from the simple pleural tap to the minimally invasive pleuroscopy, its use provides higher diagnostic accuracy and comfort for both patient and physician.[16] It is highly indicated in medical thoracoscopy in order to choose the right spot for trocar introduction, especially when empyema is suspected.[17]

The study of Marchetti et al.[18] opens a new horizon in pleuroscopy, changing the approach of patients without pleural effusion by using chest U/S. Indeed, the presence of the "sliding sign," defining the unrestricted movement of the visceral over the parietal pleura, support the decision for performing diagnostic thoracoscopy, regardless the amount of adhesions. The study by Marchetti et al. definitely shifts the indication of pleuroscopy in patients with pleural disease without effusion, from the "gray zone" to the "green zone" of practice for respiratory physicians.[19]

3 | THORACOSCOPY AND MALIGNANT PLEURAL MESOTHELIOMA

Malignant pleural mesothelioma (MPM) is a neoplasm with increasing incidence and poor prognosis, since median survival is 12 months with death resulting from respiratory failure. In the United States MPM occurs in about 2500 individuals every year, while 72 000 cases are expected to occur in the next 20 years. In Western Europe 5000 patients die of the disease each year.[20] Thoracoscopy is the best method to obtain the diagnosis of MPM when suspected on clinical or radiological data.[21] Thoracoscopy gives the advantage of obtaining multiple and deep biopsies making the diagnosis of mesothelioma easier. Differential diagnosis from other primaries, such as adenocarcinoma or sarcoma, as well as mesothelial hyperplasia is important and need specific pathologic training[22] (Table 1).

The diagnostic yield of thoracoscopy in MPM is >90%. Boutin and Rey[23] analyzed prospectively the records of 188 patients with MPM in order to compare the diagnostic value of thoracoscopic biopsy, fluid cytology, and closed needle biopsy. They achieved a diagnosis by fluid cytology in 26%, needle biopsy in 21%, combined fluid cytology and needle biopsy in 39%, and thoracoscopy in 98%. Thoracoscopy reduces the need for thoracotomy as it provides equally quantity and quality pleural biopsies for diagnosis.[24]

Mesothelioma is a malignant tumor of the pleural cavity which first develops on the parietal pleura and then spreads to the visceral pleura (Figure 1). The involvement of the visceral pleura has been found to be associated with a worse

TABLE 1 Important immunohistochemistry markers for differentiating malignant mesothelioma from lung and metastatic cancers

Malignant mesothelioma	Squamous cell lung carcinoma	Lung adenocarcinoma	Thyroid Carcinoma	Breast carcinoma	Matastaic adenocarcinoma
Mesothelin	p63	CEA	TTF-1	Mammoglobin	CK7
Calretinin	Ber-Ep4	TTF-1	Thyroglobulin	GCDFP-15	CK20
Thrombomodulin	CK 5/6	Napsin A		ER	PSA
CK 5/6				PR	

prognosis and therefore is considered an important prognostic factor.[25] The diagnostic yield of cytological examination for the diagnosis of MPM varies from 4 to 77%.[25] Pinelli et al. reported that the diagnostic yield of cytological examination was significantly higher in patients with MPM and visceral pleural invasion.[26] In 82% of patients with visceral pleura invasion, the cytological examination was positive, while 30% of patients with visceral pleura invasion had negative cytological examination.

In a recent study by Levallet et al.,[27] c-mesenchymal–epithelial transition (c-MET) has been found to be a potential prognostic biomarker in MPM. In 157 patients with MPM, positive expression of c-MET was found in 119 samples. In patients in whom the localization of c-MET was exclusively to plasma membrane the median overall survival was 25 months compared to 13 months for the rest of the patients. Whether c-MET targeted therapies will help patients with positive c-MET plasma membrane immunostaining will be answered in the future trials.

Markers with negative prognostic value have been reported such as serum SMRP, elevated levels of VEGF in pleural effusion and overexertion of VEGF in immunohistochemistry, and increased microvessel density.[28] More studies are needed in order to confirm or not the prognostic value of these markers.

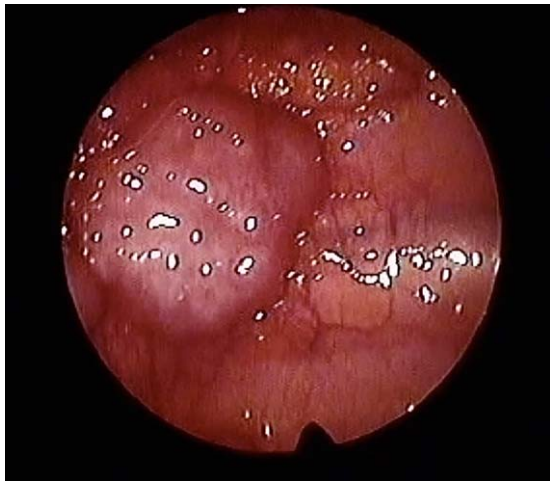

FIGURE 1 Thoracoscopic view of a patient with mesothelioma. Mass on the parietal pleura proven by biopsy to be epithelioid mesothelioma

4 | THORACOSCOPIC SYMPATHECTOMY

Utilizing thoracoscopic techniques in order to anatomically interrupt the thoracic sympathetic chain is a current standard approach for sympathectomy. Facial flushing, vascular disorders of the upper limbs (Raynaud's phenomenon, acrocyanosis, arterial insufficiency, Buerger's disease), causalgia, thoracic outlet syndrome, cardiac disorders, such as long QT syndrome and chronic pancreatic pain syndromes are all indications for thoracoscopic sympathectomy.[29] Open surgical interventions have been abandoned while the percutaneous ablation approach is not used frequently due to higher adverse event rate and lower efficacy.[30]

In a series of 138 patients who underwent bilateral thoracoscopic ablation of the sympathetic chain, 91% of the patients were very satisfied and 80% of them showed an increased quality of life.[31] Recently, the semi-flexible thoracoscope has been used in order to make sympathectomy for palmar hyperhidrosis.[32] All 32 patients were operated with local anesthesia, with no complications, and no symptoms during the follow-up.

5 | THORACOSCOPY AND PLEURAL INFECTION

When managing patients with pleural infection, the goal is to provide treatment to the patient, with the less morbidity and mortality, less hospital stay, and to avoid the need for surgical treatment and debridement.[33] The treatment of pleural infection depends on the stage of the disease and compromises antibiotics with or without chest tube drainage, use of fibrinolytics, medical thoracoscopy management, or surgical management. The use of fibrinolytics in the management of pleural infections has been under a lot of criticism. There are studies that have shown good results with the use of intrapleural fibrinolytics especially in complicated parapneumonic

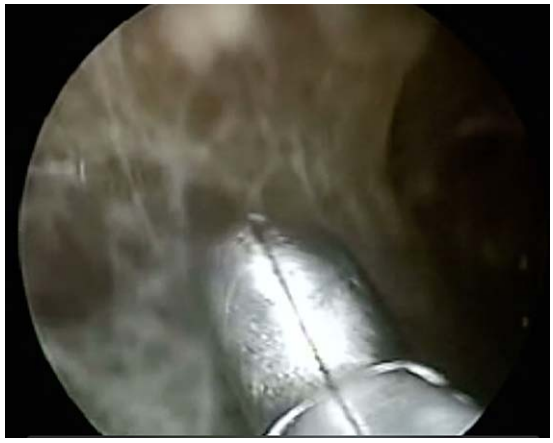

FIGURE 2 Thoracoscopic view of a multiloculated complicated parapneumonic pleural effusion

pleural effusions.[34] This good outcome was not the case with the MIST 1 study by Maskell et al.[35] Many methodological parts of this study have received a lot of criticism. Probably the use of intrapleural fibrinolytics in the earlier stages of the parapneumonic effusions has better results than using them in empyema.

Medical thoracoscopy in the treatment of pleural infection is used in order to mechanically remove the infected material, to lyse the adhesions which are present, and to allow the re-expansion of the lung (Figure 2). Before the entry into the pleural cavity, an ultrasound of the hemithorax must be done in order to choose the correct point of entry. In a study by Brutsche et al., 127 patients with multiloculated, complicated parapneumonic pleural effusions were treated with medical thoracoscopy and about half of them with intrapleural fibrinolytics as an adjuvant therapy. The success rate was 91% with only 9% complications.[36]

Although, it seems that the use of medical thoracoscopy in the treatment of complicated parapneumonic effusions must be done early in the infectious course offering less pain, lower cost, few complications, and avoiding surgical thoracoscopy under general anesthesia especially in patients unfit for surgical management, a good coordination between surgical and medical teams is the cornerstone to lower mortality rates in this patient population.[37,38] The success rate of medical thoracoscopy and Video Assisted Thoracoscopic Surgery in patients with complicated parapneumonic pleural effusions and empyema are described in Table 2.[36,39–44]

What is needed are prospective, well stratified on the stage of parapneumonic pleural effusion and empyema, multicenter studies with many patients in order to confirm the role of medical thoracoscopy in parapneumonic effusions and empyema.

6 | THORACOSCOPIC TALC POUDRAGE

Thoracoscopic talc poudrage, using the French (Luzenac) large particle size calibrated asbestos-free talc, is consider as the gold standard of pleurodesis in patients with malignant pleural effusion as its efficacy is over 90% achieving a long lasting result with low cost.[46] Thoracoscopic talc poudrage induces also systemic inflammatory reaction with increase in temperature, in the number of white blood cells, in the number of neutrophils, and in the level of C-reactive protein as has been shown by Froudarakis et al.[45]

Pleurodesis is indicated in patients experiencing a second episode of primary spontaneous pneumothorax, or when there is persistent air leak more than 3-5 days, or when there is a bilateral pneumothorax or the patient is diver or an aircraft personnel.[52] It is proposed by the 2015 ERS guidelines on managing primary spontaneous pneumothorax as a safe and most cost-effective method for obtaining diffuse chemical pleurodesis preventing recurrence of primary spontaneous pneuthorax (PSP).

A European randomized study of medical thoracoscopic talc pleurodesis vs. chest tube drainage showed significant lower recurrences, lower duration of hospitalization, and

TABLE 2 Medical and surgical thoracoscopy for pleural empyema

Intervention	Number of patients	Success rate (%)	References	Year
Medical thoracscopy	41	85	[45]	2013
Medical thoracscopy	127	91	[46]	2005
Medical thoracscopy	5	72	[47]	2004
VATS	120	92	[48]	2007
VATS	130	91	[49]	2006
VATS	234	86	[50]	2005
VATS	67	72	[51]	1998

Abbreviation: VATS: Video Assisted Thoracoscopic Surgery.

finally, lower costs in the group of patients with primary spontaneous pneumothorax included in the arm of medical thoracoscopy talc pleurodesis.[53] Rational for the non-surgical resection of blebs and/or bullae (and therefore for the efficacy of thoracoscopy talc pleurodesis) is that the presence or size of blebs and/or bullae, have never been proved to be a real risk factor of PSP occurrence.[50,51] In sight of these considerations, the need for a phase III randomized study comparing surgical procedure and thoracoscopy talc pleurodesis is warranted to definitively select the best management of patients with recurrent spontaneous pneumothorax.[49]

7 | ADVANCES IN INSTRUMENTATION

7.1 | Semi-rigid pleuroscopy

The semi-rigid pleuroscope (model LTF 160 or 240; Olympus, Tokyo, Japan) is working like the flexible bronchoscope. It consists of a handle and a shaft that measures 7 mm in outer diameter and 27 cm in length. The flexible tip is movable by a lever on the handle, which allows 2-way angulation 160° up and 130° down. It has a 2.8-mm working channel that accommodates biopsy forceps, needles and other accessories, and is compatible with various electrosurgical and laser procedures.[48] In a meta-analysis by Agarwal et al.,[47] which included 17 studies with a total number of 755 patients, the semirigid pleuroscope showed a sensitivity of 91% and a specificity of 100% in diagnosing exudative pleural effusions. Although the average sample size is double with rigid pleuroscopy compared with that of semi-rigid, the diagnostic accuracy is about the same.[54]

One of the problems of the use of semi-rigid pleuroscope is the biopsy of thickened pleura. In order to overcome this problem, Sasada et al.[55] proposed the use of a new electrocautery technique using an insulated-tip knife through the working channel of the semi-rigid pleuroscope. They reported their experience in 20 patients, and with the use of the insulated-tip knife they could get full thickness parietal pleura biopsies with a diagnostic yield higher (85%) compared with the standard flexible forceps (60%).

Another limitation of semi-rigid pleuroscopy is the size of the pleural biopsies and that usually are of insufficient depth (Figure 3). To overcome this limitation, Thomas et al.[56] used flexible cryoprobe biopsies of the parietal pleura through the working channel of the semirigid pleuroscope. In this feasibility and safety study which included twenty-two patients with pleural effusion, the sampling of parietal pleura with flexible cryoprobe was feasible and safe. The cryoprobe pleural samples were significantly larger than the samples obtained with the flexible forceps, deeper, and of better quality with less crash artifacts. The diagnostic yield was 90%, comparable with the diagnostic yield of the conventional biopsies.

FIGURE 3 Thoracoscopic view of biopsing the parietal pleura with the semi-rigid thoracoscope

7.2 | Minithoracoscopy

The minithoracoscopy technique is the same as the conventional medical thoracoscopy technique with two entry points. Two trocars, one for the telescope and one for biopsy forceps or accessory instruments, are positioned in two adjacent intercostal spaces or in the same intercostal space at a distance of 4 cm apart. The minithoracoscope is composed of two 3.8-mm trocars, one 3.3-mm telescope, and one 3.0-mm biopsy forceps. The telescope is 25 cm in length and has viewing angles of 0° and 45°.[57] The advantages of minothoracoscopy are less pain due to the smaller trocar, and examination of smaller loculated effusions not accessible to classic thoracoscopy. On the other hand, more time is needed for the mini thoracoscopic procedure and the biopsy specimen size is small, a problem that can be overcome by taking more samples.[58] It is ideal for patients with small effusions and narrow intercostal spaces (Figure 4).

7.3 | Infrared thoracoscopy

A technique used to investigate bullous or emphysematous lesions of the lung and assist in their excision is infrared thoracoscopy. Infrared thoracoscopy that can detect two different wave-lengths of infrared light can display indocyanine green (ICG) with an absorption peak in the infrared light region (805 nm) as blue. The normal lung is imaged as blue while the lung lesions are imaged as white due to less blood flow. Emphysematous lesions that are not detectable with conventional white light are better seen with infrared thoracoscopy. The decreased blood flow of bullous lesions is detected by a decreased indocyanine green intensity.[59] Gotoh et al.[59] reported their experience with infrared thoracoscopy in eight patients with spontaneous pneumothorax. Infrared throacoscopy helped them identify small bullous lesions that were undetectable with white light. Because the blue-white contrast lasts about 3-5 min and you cannot inject more ICG, there is no enough time to explore the whole lung surface.

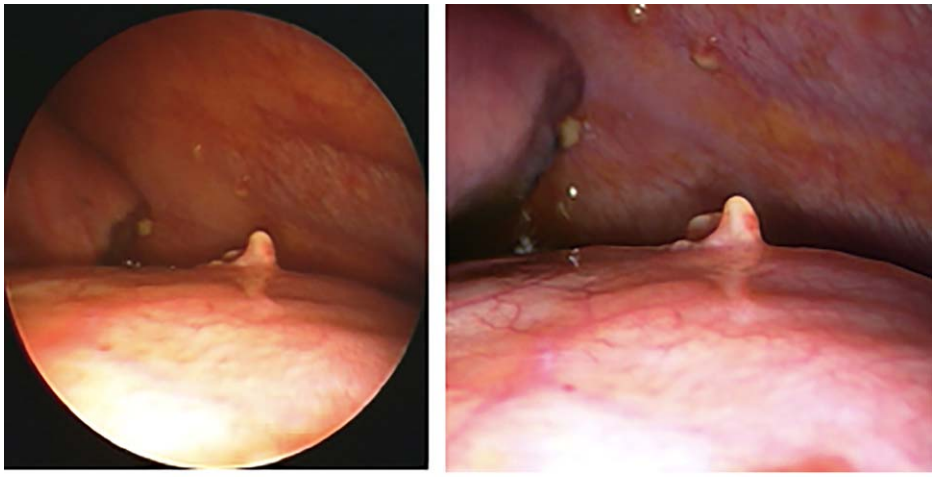

FIGURE 4 Thoracoscopic view of the parietal pleura with (A) minithoracoscope and (B) standard thoracoscope (pictures courtesy of Prof G. Tassi)

This is one of the problems of the infrared thoracoscopy but otherwise is a rapid and safe method for identifying small bullous lesions.

7.4 | Autofluorescence thoracoscopy

Autofluorescence thoracoscopy was introduced in order to increase the diagnostic accuracy of conventional thoracoscopy. Fluorescein-enhanced autofluorescence thoracoscopy is thoracoscopy performed after inhalation of aerosolized fluorescein. The visualization in the blue light excitation mode reveals much larger areas of parenchymal abnormality compared to the inspection with the white light. In addition, satellite areas of fluorescein accumulation can be identified with autofluorescence. These areas cannot be identified as lesions with conventional white light thoracoscopy. Noppen et al.[60] have reported their experience with fluorescein enhanced autofluorescence thoracoscopy (FEAT) in 12 patients with primary spontaneous pneumothorax and in 17 controls. High-grade FEAT lesions were exclusively present in patients with pneumothorax, and predominantly at lung zones that appeared normal at white light inspection. These findings suggest that significant parenchymal abnormalities are not limited to lesions visible during white light thoracoscopy, such as blebs and bullae. Chrysanthidis et al.[61] tested the diagnostic accuracy of autofluorescence thoracoscopy in 24 patients with exudative pleural effusion. The sensitivity was 100% for detecting malignant lesions, while the specificity was 75% and the positive predictive value was 92%.

7.5 | Narrow band imaging thoracoscopy

Narrow band imaging (NBI) is used in endoscopy in order to enhance the endoscopic image highlighting blood vessels. Wavelengths of light in the visible spectrum are filtered from the illumination source, with the exception of narrow bands in the blue and green spectrum centered at 415 nm and 540 nm, coinciding with the peak absorption spectrum of oxyhemoglobin, making blood vessels more pronounced when viewed in NBI mode.[62] Myazawa and coworkers reported their experience with narrow band imaging applied to pleuroscopy in patients with undiagnosed pleural effusion.[63] The accuracy, sensitivity, and specificity of NBI in detecting irregular patterns indicative of malignancy was superior and statistically significant in comparison with white light (60.3%, 76.5%, and 55.4% in white light and 80.8%, 85.3%, and 76.9% in NBI, respectively).

7.6 | Tridimensional medical thoracoscopy

The use of a 3D camera videoscope (Endoeye 3D, Olympus) to perform medical thoracoscopy has been reported recently.[64] It utilizes a tridimensional articulating videoscope which offers an inspection of the whole pleural cavity and better perception of the depth. The limitations of this technique are the use of a thoracoscope of 10 mm diameter which is larger than the thoracoscopes used in conventional medical thoracoscopy, the use of special glasses for the 3D visualization, the absence of working channel which necessitates the use of a second port for biopsies, and the increase cost of the system. In the future, more data and studies about the use of this system will be needed.

8 | CONCLUSION

Medical thoracoscopy is the method of choice for investigation the undiagnosed exudative pleural effusions. Pleural biopsies are easily performed with a high diagnostic yield. Treatment of recurrent pleural effusions can be achieved with pleurodesis, as well as the treatment of recurrent

pneumothorax. Sympathectomy, treatment of pleural infections is the other therapeutic option with medical thoracoscopy. Newer techniques, such as narrow band imaging thoracoscopy, infrared thoracoscopy, autofluorescence thoracoscopy are offering a promising future for medical thoracoscopy.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this work.

CONFLICT OF INTEREST

The authors state no conflict to disclose.

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