

## Peer Review File

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Reviewer A:

Comment 1: The authors present a comprehensive, well-illustrated overview of the literature relating to medical thoracoscopy.

Reply 1: We thank the reviewer for the time dedicated to reading this paper and her/his considerations. Below is the point-by-point response to the observations made.

Comment 2: It is important to recognize that thoracoscopy is a surgical procedure, and that « medical thoracoscopy » refers to thoracoscopy performed by non-surgeons, in the absence of monitoring by an anesthesiologist.

Reply 2: Thoracoscopy itself is a visualization modality of the pleural cavity that can accompany a variety of surgical procedures. It is currently the most commonly used operating method to access the thorax. There are two different methods for thoracoscopy: video-assisted thoracoscopic surgery (VATS) and medical thoracoscopy (MT). MT can be performed by both surgeons and internists (Shojaee 2015, see references below).

MT can be performed according to different operational and anesthetic assistance profiles: the first descriptions envisaged the need for just local anesthesia, two operators and nursing staff. MTs carried out with the support of an anesthetist are currently well described (Sikachi 2023) and for example at our facility every single MT is conducted with sedation administered by the anesthetist (monitored anesthesia care, MAC).

Ref.

1. Shojaee S, Lee HJ. Thoracoscopy: medical versus surgical-in the management of pleural diseases. *J Thorac Dis.* 2015 Dec;7(Suppl 4):S339-51. doi: 10.3978/j.issn.2072-1439.2015.11.66. PMID: 26807282; PMCID: PMC4700382.
2. Sikachi RR, Chaddha U, Agrawal A. Anesthetic considerations for medical pleuroscopy. *Respir Med.* 2023 Jul;213:107225. doi: 10.1016/j.rmed.2023.107225. Epub 2023 Apr 5. PMID: 37028564.

Comment 3: Otherwise, there is really no conceptual difference between « VATS » and thoracoscopy.

VATS simply refers to thoracoscopy performed with a video screen. VATS also implies the use of additional incisions for the insertion of instruments dictated by the exact procedure being performed, but in reality, there is no reason why an additional small incision could not be used in « medical thoracoscopy » as well. Actually, one could go even further and assert that thoracoscopy only refers to the type of access to the pleural space, and not to any specific procedure being performed via that access. In fact, there are increasing reports of VATS complex lung resections being performed on spontaneously breathing, non-intubated patients.

And so the real difference between « medical » thoracoscopy and « VATS » lies in who is performing the procedures, and in what kind of environment. If thoracoscopy (even complex procedures on spontaneously breathing patients) can be performed safely by thoracic surgeons in the operating room, then what motivates medical thoracoscopy?

Reply 3:

- i. The authors agree that in terms of sole consideration of the visualization of the pleural cavity the conceptual difference is minimal. However, the difference should not be considered only in the context of the performance of thoracoscopy alone but of the following variables: size and variability of the operating room team, occupation time of the operating room, cost of the overall procedure and pre- and post-care procedural (e.g. hospital stay), morbidity and mortality following procedural stress. The authors acknowledge that the evidence comparing MT and VATS for several variables is still developing.
- ii. The first descriptions of MT by the Marseille school (Boutin and Astoul) also described the use of two ports, a technique which however has fallen into disuse in most centers, leading to the simplification of the procedure.
- iii. The evolution of the thoracic surgical specialty is evident from clinical practice and literature even if the general procedural safety and airway management profile is not well defined (Janik 2021). The geographical distribution of uniportal non-intubated VATS is currently very limited although evolving. One of the future alternatives is that thoracic surgery can replace TM, however in areas with a high prevalence of pleural diseases the increase in operating theater activity may be difficult in light of limited operating room access and increased costs (McDonald 2018).
- iv. The arguments in favor of permanence of MT in the thoracic management pathway are:
  - a. The more widespread diffusion of internal medicine and pneumology structures compared to thoracic or general surgeries that carry out operations on the thoracic area. Speaking from the point of view of the experience of the authors' state of origin (Italy) (all employed in academic hub hospitals), TM is also practiced in non-hub centers in order to accelerate the therapeutic and diagnostic path of pleural pathologies. Patients managed directly at the peripheral hospital are patients who are either not easily transferable or who would have long waiting times to be operated on at the nearest hub hospital. The authors agree that the safety profile of a MT in a peripheral hospital should be further explored in the literature, however it is a procedure that is widely practiced in both Italian and English territory.
  - b. The shortest learning curve with respect to developing skills in all thoracic surgery procedures. The authors do not underestimate the possible complications that can develop during MT, and the need to have the appropriate skills to deal with them, however the procedures performed using MT and described in the paper are highly selective and minimally invasive.

Ref.

1. Thoracoscopy for Pulmonologists - A Didactic Approach. <https://link.springer.com/book/10.1007/978-3-642-38351-9>
2. Janík M, Juhos P, Lučenič M, Tarabová K. Non-intubated Thoracoscopic Surgery-Pros and Cons. *Front Surg.* 2021 Dec 6;8:801718. doi: 10.3389/fsurg.2021.801718. PMID: 34938770; PMCID: PMC8687085.
3. McDonald CM, Pierre C, de Perrot M, Darling G, Cypel M, Pierre A, Waddell T, Keshavjee S, Yasufuku K, Czarnecka-Kujawa K. Efficacy and Cost of Awake Thoracoscopy and Video-Assisted Thoracoscopic Surgery in the Undiagnosed Pleural Effusion. *Ann Thorac Surg.* 2018 Aug;106(2):361-367. doi: 10.1016/j.athoracsur.2018.02.044. Epub 2018 Mar 22. PMID: 29577922.

Comment 4: On multiple occasions the authors mention patient « inoperability » as an indication for « medical thoracoscopy » rather than VATS, but can one really make such an argument? I rather think that resource allocation (considering the scarcity of operating room access) is the real (and, in an increasingly resource-conscious healthcare environment, valid) argument in favour of medical thoracoscopy.

Reply 4:

- I. The inoperability of a patient can be defined based on the clinical status at a given time condition. What can make a patient inoperable is both his presentation condition during hospitalization which therefore allows the patient to be subjected to only minimal therapeutic stress. In this case, intraoperative ventilation by intubation and general anesthesia may be contraindicated, while mild sedation may be feasible. Another condition often encountered is the patient who presents himself in hospital for a progressively worsening subacute condition and who, due to the lack of availability of a time slot in the operating room, has to wait several days to undergo surgery. In the authors' experience this frequently happens for a massive pneumothorax with a persistent air leak already subjected to chest drainage which is stabilized but may require several days if not weeks of waiting to undergo surgery. In this case, management using MT can speed up therapeutic management times and reduce the risk of hospital infection and LOS.
- II. The text (lines 89-91) highlights the points that are motivating the geographical expansion of MT: reduction of invasiveness (especially compared to historical procedures e.g. thoracotomy), reduction of complications associated with the procedures, reduction of LOS and favorable cost-profile effectiveness compared to traditional VATS.

Comment 5: If we accept that argument, then these important questions follow: what training is required of the « medical thoracoscopist » in order to insure competency; how is case selection performed in order to insure safety; what kind of surgical support is required, and what are the fallback options in case something goes wrong.

Reply 5: The training required for MT varies according to the operator's country of origin in different forms of university or post-university courses:

- USA: MD -> residency -> interventional pulmonology fellowship -> board certification

(see. AABIP site)

- UK: MD -> residency -> interventional pulmonology / pleural fellowship (See Northumbria and Oxford)
- Europe: MD -> residency -> university master's degree (e.g. Florence or Ancona) or postgraduate course
- Australia: MD -> residency -> pleural-fellowship (e.g. Clinical Pleural Fellowship - Western Australia)

The operator must be trained in a high operating volume center and must annually maintain his own personal operating volume in the facility where he operates.

The authors believe adding a paragraph on the training of medical thoracoscopists to the text is misleading with respect to the focus of the paper and the foreseeable cultural origin of the reader who will in any case be able to find relevant bibliographic sources of interest.

The selection of cases varies based on the experience of the individual center in managing the various clinical entities of pleural relevance and the feasible management volume for the operating rooms of the center where the operator works. There may be centers where all oncological pleural pathologies and pneumothorax are taken care of by the pulmonologist or vice versa by the thoracic surgeon.

Complications are inevitable in invasive procedures and for each patient, based on the geographical setting in which it is managed, the following must be established:

- Need for transfer to hub hospital
- Anticipate the necessary management times in order to minimize the LOS
- Anticipate procedural risks
- Adequately inform the patient of possible adverse events

Comment 6: This paper goes some ways in its attempt to answer the second question, but does nothing address the others. These other questions are critical, and I think that they are inescapable in any review of medical thoracoscopy. Therefore, this is an important shortcoming of this paper that needs to be addressed. A corollary of the preceding questions is the issue of credentialing, both at the individual and institutional levels, and I think this also should be addressed.

Reply 6: In producing the paper we considered examples from our clinical practice which nevertheless follow the experience of other national and international institutions, as supported by the literature cited. The areas where the authors' experience has been mostly cited are pneumothorax and chylothorax, two fields where the scientific evidence is still primordial and the experience of the various centers can certainly be discordant.

Comment 7: The authors describe various diagnoses for which « medical thoracoscopy » can be used successfully, and I think that in that sense their literature review is indeed useful, because it gives the reader an idea of the scope of potential applications. However, it is important to recognize that each of these diagnostic categories belies a heterogenous group of situations, some of which may be safely approached using medical thoracoscopy, but also very probably, some of which

cannot and should not. Anyone who has operated empyema, dense pleural adhesions, and secondary pneumothorax in patients with advanced COPD knows how fraught with « traps » and pitfalls » these cases can be; a torn apical adhesion can result in massive hemorrhage; emphysematous lungs can tear in spite of the utmost care, etc.,. Once again, I think that the importance of case selection cannot be overemphasized. Astute case selection requires proper training, adequate experience, and an acute awareness of one's hospital environment; but most of all it requires awareness of one's limitations and excellent clinical judgement. Randomized trials are limited in their capacity to answer such questions.

Reply 7: The authors completely agree with the reviewer on the fact that the adequate selection of cases and the success described in our clinical practice and some clinical trials is inevitably the indirect representation of a selection bias (cherry picking induced by the experience and culture of the operator).

According to the reviewer's indications, the "Future trends" section has been modified as follows: "The procedure should not aim to replace surgical alternatives for the pathological entities in which it is applied, but should find its role in highly selected cases as a low-cost, safe, and highly effective therapeutic choice in the hands of the interventional pulmonologist."

Comment 8: I am quite skeptical of any surgical procedures being performed « at the bedside ». Anyone who has inserted a chest tube at the bedside knows that even such a « simple » procedure is not always a straightforward task. Performing thoracoscopy at the bedside where sterility is questionable, on a ward where staff are not necessarily trained in such a procedure, where some instruments may not be readily available and where, in case of an unforeseen « intraoperative event » no remedial options are available, seems to me quite problematic. The same goes for medical throacoscopy performed in the ICU. The ICU patient that the authors describe as a potential candidate for medical thoracoscopy is de facto already under « general anesthesia ». I think any such procedure would therefore be carried out much more safely and effectively in an actual operating room where all required technical and human resources are available. In my opinion, the « safety » argument here points to the operating room rather than the bedside. Perhaps such a patient may not tolerate one lung ventilation or lateral decubitus, but this is not an argument against general anesthesia itself. If the patient is too unstable to even be moved down the hall to the operating room, in my opinion « medical thoracoscopy » is most certainly contraindicated.

Reply 8: The reviewer's observation derives from high clinical acumen and well-founded experience in clinical practice. The experience described by Ooi et. al is highly questionable in the context of clinical practice and none of the authors would carry out the procedure described in the cited document at the patient's bedside. However, in the context of even a non-systematic review, it is debatable whether omitting bibliographic entries based on one's own experience is ethical or whether it is better to include them so that the reader can interpret the use he can best make of them once he has been made aware of the existence of this practice. From the point of view of sterility and microbiological air quality, there are significant differences between operating rooms and the endoscopic room per se which have not yet been addressed in the literature but which for now have no real evidence. From another point of view, in exceptional conditions, the availability of access to endoscopic or surgical operating rooms at the exact moment in which the patient needs the procedure must also be considered. In order to maintain a paragraph that we are sure can generate

debate, we have modified the text to accommodate the reviewer notes: *“MT is a safe procedure with low mortality, major and minor complications reported in the current literature (10–12). Its application has also been described in patients admitted to the intensive care unit, where, in highly selected cases, it may represent a valuable therapeutic alternative in critically ill patients (13,14).”*

Ref.

1. Ooi H. Bedside pleuroscopy in the Intensive Care Unit. *Ci Ji Yi Xue Za Zhi*. 2018;30(2):97–101

Comment 9: I certainly think that any medical thoracoscopy program should be developed with the active involvement of thoracic surgery and anesthesia who can aid with program development, case selection, and the availability of backup in the case of intra-procedural adverse events.

Reply 9: We agree in the need for high collaboration between the various teams both in the selection of cases who undergo MT and in the management of complications. These collaborative projects will certainly be more fluid and feasible in large hospital facilities, while facilities that practice MT in non-hub centers will have to carry out considerable procedural risk planning.

So in conclusion the authors did a very good job in reviewing the literature relating to medical thoracoscopy, but in my opinion several critical issues are lacking.

Miscellaneous comments :

Comment 10: p.7 line 152 : contraindications to medical thoracoscopy include « tract metastasis » or « rib fracture » around the port insertion site : these seem more like adverse outcomes than contraindications; please explain.

Reply 10: Tract metastasis is an entity that the pulmonologist may encounter before carrying out thoracoscopy, as a result of multiple thoracentesis or a previous chest tube. It should not be chosen as the port entry site as it is usually highly vascularized (often visualized during color Doppler ultrasound when choosing the entry site) and at high risk of bleeding.

Rib fracture is also a phenomenon that the pulmonologist may encounter before performing MT as it is a manifestation of a pathological fracture due to neoplastic bone involvement. The patient usually has a pleural effusion that is diagnosed and treated with talcum powder during the same procedure. Using the area near the rib fracture for the entrance of the port entails the need to administer greater doses of analgesic therapy and sedation, as well as to increase the dosage of the local anesthetic. This condition represents a contraindication if the “easy” entry sites into the pleural cavity are few and the procedure is conducted only under local anesthesia and mild sedation.

The paragraph (line 151-157) has been modified as follows to make it better understandable: *“Absolute contraindications to performing medical thoracoscopy include an uncorrectable bleeding disorder, significant pulmonary hypertension, cardiovascular instability, acute uncorrectable type 1 respiratory failure, ongoing type 2 respiratory failure, and absence of the possibility of generating an adequate pleural space (10,18,24) Conditions that may require*

changing the entry site into the pleural cavity are the presence of cutaneous infection, tract metastasis or rib fracture around the port insertion site.”

Comment 11: p.7 line 156: tension pneumothorax is an indication for immediate drainage; I do not think medical thoracoscopy is appropriate in this context

Reply 11: The reviewer's note is correct. The paragraph (line 158-161) has been changed to: *“Of note, if the procedure is therapeutic, such as in the setting of massive pleural effusion or pneumothorax, and clinical improvement may be expected, MT may be performed even in the presence of hypercapnia, considering adequate post-procedural assistance and monitoring (7,34).”*

Comment 12: P.10 lines 219, 226: « bronchopleural fistula » : strictly speaking, this refers to a hole in an actual bronchus; if the authors are referring to a tear in the visceral pleura, they should use terms that refer to such tears, or « air leaks », or prolonged air leaks.

Reply 12: The reviewer's note is correct. The inherent paragraphs (line 221-236) has been changed to:

*“Complications in MT can be divided in major and minor adverse events. Significant complications include empyema, hemorrhage, prolonged air leak, periprocedural pneumothorax, pneumonia, and port site tumor growth, and have a cumulative rate of 1.8% (52,53,55). Minor complications include subcutaneous emphysema, minor hemorrhage, operative skin site infection, procedural hypotension, atrial fibrillation, and increased body temperature, with a cumulative rate of 7.3% (10,55). While these rates refer to MT performed typically in an endoscopy suite, similar numbers were reported in its use in the ICU and when performed at the patient's bedside (14). Procedural risks are influenced by the underlying pathology with visceral pleural tears more frequently reported when obtaining biopsy samples of honey-comb lung in end-stage pulmonary fibrosis and lung laceration during trocar insertion in the presence of extensive pleural adhesions (53). Precautions may be considered to reduce the risk of complications, such as postponing MT in the presence of severe cough, maintenance of chest tube until no air leakage is detected, and gradual lung re-expansion to prevent re-expansion pulmonary edema. In addition, in the setting of suspected mesothelioma, it is possible to administer radiation therapy to the incision area to prevent port site tumor growth (56,57).”*

Comment 13: I was unable to view video 1. The video quality of 2 and 3 is average at best; however, the idea of including videos is welcome.

Reply 13: The photographic material comes from the new equipment at our disposal and is therefore characterized by a better resolution. The videographic material derives from historical instruments, however it represents in a figuratively adequate way the therapeutic intent that the authors want to represent.

**We thank the reviewer enormously for the accuracy of his observations which reveal the high level of knowledge and clinical skill developed within institutions that manage a high clinical complexity.**

Reviewer B:

Comment 1: In general, the paper lacks in structure and needs some language revision (ex: please check verbs and their concordance)

Reply 1: A complete rereading and grammatical revision of the text was carried out by all authors.

Reply 2: Abstract: "result" session is missing

Reply 2: as per JTD authors' guideline the abstract has been structured with the sections:

- Background and Objective: describe relevant background, reasons for conducting this review, and primary objectives of this review.
- Methods: briefly describe the search strategy, including databases, time frame, and language considerations. Key Content and Findings: describe what the literature review will mainly contain and any key findings.
- Conclusions: describe the main conclusions and how the review may potentially impact future research, clinical practice, and policy making.

The section "Key content and findings" has been updated: *"Medical thoracoscopy has mostly been described and is currently used globally in the diagnostic approach to exudative pleural effusion of undetermined origin. Carefully evaluating the literature, it is clear that there is initial evidence to support the use of medical thoracoscopy in the therapeutic approach of malignant pleural effusion, pneumothorax, empyema, and less frequently hemothorax and foreign body retrieval."*

Reply 3: Introduction:

-- line 80-81: about mechanical pleurodesis and adhesiolysis, these indications are on the edge of surgical thoracoscopy. You should specify somewhere in the text, possibly in a dedicated paragraph, when a medical thoracoscopy could be attempted and when a surgical approach is better as first therapeutic option. What, in your opinion, leans toward surgical or medical thoracoscopy in adhesiolysis?

Reply 3: line 91-92 The following paragraph has been added: *"The decision to perform MT rather than VATS should be carefully made based on patient-related factors, the underlying pathology and the operator's experience in MT."*

The selection of cases varies based on the experience of the individual center in managing the various clinical entities of pleural relevance and the feasible management volume for the operating rooms of the center where the operator works. There may be centers where all oncological pleural pathologies and pneumothorax are taken care of by the pulmonologist or vice versa by the thoracic surgeon. Empyema with the need for thoracoscopy in almost all global centers is the responsibility of the thoracic surgeon.

Based on the phases of the pathology and the patient's conditions, MT or something else may be proposed in theoretical terms, but it is always the operator's experience that ultimately leads to the decision whether to do the procedure or not.



Reply 4: line 85: what is the added value of TM compared to a chest drain? Further in the text (page 17), you have written the role of MT in CPPE and the sparse literature on it, so that guidelines do not recommend it. But, despite guidelines, you state that it is used in PI, suggesting it as "useful alternative approach". I would make a more precise distinction about clear and recognized indications for MT and "conditional" indications since by putting all the indications on the same level we risk not distinguishing those that are well recognized and those that are burdened by personal experience (ex: small case series).

Reply 4: line 88-91 The following paragraph has been added: *"The additional benefits of performing a MT instead of just placing a chest drain are the possibility of carrying out a direct endoscopic evaluation of the pleural cavity, performing adhesiolysis and carrying out a biopsy sampling if necessary."*

Reply 5: line 86-88: I would remove the last sentence since seems to give an advice that should not be given. Would you perform a MT to an unstable patient? How you define an "unstable" patient? Are there any evidences on that apart from Thakore paper? One paper describing few cases does not make an evidence.

Reply 5: line 98-100: The paragraph has been removed.

Reply 6: Equipment: pictures could better explain the differences b/w rigid and flex thoracoscope

Reply 6: An image (Figure 1) has been added with the relative description of the instrumentation necessary for rigid thoracoscopy. Flexible thoracoscopy is only performed in one center in our state, and obtaining an original image without contacting the provider may take longer.

Reply 7: Contraindications: here you talk about unstable patients (see comments in the introduction). Moreover, in massive pleural effusion the first therapeutic option is a chest drain not MT; the same for tension pneumothorax. I would change the sentence.

Reply 7: line 169-171: The paragraph has been modified according to the reviewer's observation.

Reply 8: Why you do not have included more technical notes in the "equipment" section? ex: forceps biopsy, cryobiopsy?

Reply 8: line 139-140: the relevant paragraph has been integrated, table 2 reports further information on the methods.

Reply 9: "rationale and knowledge gap": you have stated that MT is done in daily practice in several situation despite the guidelines do not suggest its use. I would be careful in similar statements: first of all, my fear is that MT is not done in "daily practice", especially in cases where the indication is blurred. Moreover, why guidelines do not suggest MT, for example, in PI but you still consider it as a valid therapeutic option? What is your opinion on the different topic you have mentioned (pnx, pleurodesis, etc)? Should guidelines be revised in the view of more recent studies?

Reply 9: Current global scientific knowledge is mainly based on the evaluation of the comparison between minimally invasive treatments (conservative, intravenous therapies, chest drainage, fibrinolysis) compared to thoracic surgical treatment. It is conceivable that the centers that currently perform MT will introduce randomized studies in the future that evaluate three arms: drainage ( $\pm$ other treatments) vs. medical thoracoscopy vs. VATS (uniportal/other; with or without intubation;

with various levels of sedation).

The scientific field is indeed blurry and lends itself to comparison between schools of thought that usually carry out different procedures. The pool of authors of this document is all Italian and in our state interventional pulmonologists working in academic centers with high procedural volumes have been practicing MT for CPPE/empyema for at least two generations of proceduralists. In centers where thoracic surgery has an inherently high workload, the management of pneumothorax very often passes to pulmonologists, which also happens for the French thoracoscopic school (Boutin, Astoul, Tshopp).

The guidelines currently suggest a correct message, it is the centers that carry out MT for broader indications that must make an effort to propose clinical studies that lead to the updating of the guidelines themselves.

Reviewer C:

Comment: Thank you to all the authors for an interesting review article. The topic of medical thoracoscopy is important in general thoracic surgery. The authors screened thoroughly all indications possible for this surgical procedure.

Reply: We thank the reviewer for the time dedicated to reading and analyzing our article. We consider the procedure to be invasive but also possible to be carried out by adequately trained medical personnel and in a highly experienced setting.

Reviewer D:

Comment: The review considers population studies, meta-analyses, case series, and case reports, which may provide insights into the potential limitations and challenges of this procedure.

The paper does not explicitly state a problem with bronchoscopy. However, it does mention that thoracoscopy represents one of the main endoscopic procedures, along with bronchoscopy in interventional pulmonology. This suggests that both thoracoscopy and bronchoscopy are important procedures in the field of interventional pulmonology, each with its own specific applications and considerations.

Reply: We thank the reviewer for the time he dedicated to reading and analyzing our article. Many of the pulmonology departments located in large university centers in Europe perform bronchoscopy, much fewer facilities perform medical thoracoscopy or local anaesthetic thoracoscopy. We believe that being able to perform both is an added value in patient care.

Reviewer E:

Comment: Thank you to the authors for this comprehensive narrative review on an important topic. The review is very detailed and well written. The reference list is up to date and complete with > 100 references. The most important works regarding this subject have been included. The images

are fitting, and the flowchart for the management of pneumothorax is well structured and informative.

Reply: We thank the reviewer for the time he dedicated to reading and analyzing our article and for the positive opinion.

Reviewer F:

Comment: Congratulation for this comprehensive review.

In the chapter on pleural infection, I would have been interested in a few more details on how the intracavitary fibrinolysis is performed: mechanical fibrinolysis using biopsy forceps or argon plasma or other methods?

Similar to the chapter of retained hemothorax, where you describe different options.

Reply: We thank the reviewer for the attention dedicated to our article. Currently the evidence on medical thoracoscopy and in particular on the management of pleural infection is limited to practicing mechanical adhesiolysis, using the forceps of the thoracoscope (see modification made to the text on line 368), the drainage of the pleural fluid both in its free flowing component and that present at the level of organized sacs. In addition, the irrigation of the pleural cavity with saline solution or fibrinolytics is described in the literature. Many academic authors and specialists in describe the prosecution of fibrinolysis even after thoracoscopy; however, in light of the focus of this paper on medical thoracoscopy we have refrained from describing what is pursued in the post-procedural phase. The use of argon plasma in the context of medical thoracoscopy, to the best of the authors' knowledge (see references below), has been implemented in the majority of cases with the aim of obtaining pleurodesis or closure of pulmonary breaches in patients with pneumothorax; in addition, it has been described as a method aimed at pleurodesis in the setting of malignant pleural effusion. The evidence regarding the use of APC in the context of pleural infection is therefore absent/deficient and probably deserves in-depth studies. Currently in the clinical practice of the authors, APC is applied only in the bronchoscopic field and in rare cases of medical thoracoscopy.

The management of retained hemothorax has little scientific evidence in the literature which we report in full in the text. The lysis of adhesions practiced by the authors is mechanical using the thoracoscope forceps. In the literature, as described in the text, the use of the cryoprobe to assist in the lysis of adhesions has been described. The use of APC in this setting is mainly aimed at controlling small foci of bleeding (see text and reference in the manuscript)

Refs:

1. Guo HY, Pan XQ, Hu M, Liang YF, Qiu XC, Chen ZH. Medical Thoracoscopy-Assisted Argon Plasma Coagulation Combined with Electrosurgical Unit for the Treatment of Refractory Pneumothorax in Elderly Patients. *Ann Thorac Cardiovasc Surg.* 2019 Oct 20;25(5):237-245. doi: 10.5761/atcs.oa.19-00017. Epub 2019 Jul 4. PMID: 31270297; PMCID: PMC6823171.
2. Hua Zhang, Changsheng Ge, Guangwei Xue, Lei Wang, Cunling Duan, Xiaoli Liu, Weiwei

Xu, Zongtao Liu, Mengyao Wang, Xiancong Bu, Wei Zhang European Respiratory Journal Sep 2019, 54 (suppl 63) PA3396; DOI: 10.1183/13993003.congress-2019.PA3396

3. Zhang L, Xie T, Fu Y, Wu H. Assessment and review of treatment for secondary spontaneous pneumothorax using medical thoracoscopy-assisted argon plasma coagulation in association with autologous blood pleurodesis. *Therapeutic Advances in Respiratory Disease*. 2021;15. doi:10.1177/1753466620986390
4. Mai Z, Feng B, He Q, Feng Q. Medical Thoracoscopic Thermal Ablation Therapy for Metastatic Pleural Tumors with Malignant Effusion: An Exploratory Retrospective Study. *Int J Gen Med*. 2021 Dec 4;14:9349-9360. doi: 10.2147/IJGM.S339596. PMID: 34898999; PMCID: PMC8654692.
5. <https://www.ers-education.org/lr/show-details/?idP=9791>

Reviewer G:

Thank you for giving me an opportunity to review the manuscript “Beyond diagnosis: a review of the evolving therapeutic role of medical thoracoscopy in the management of pleural diseases”. I appreciate the authors’ extensive time and efforts for the narrative review.

Comment 1: The manuscript was well-summarized, but I could not find the role and novelty of this review article. The manuscript is too long and only based on overviews of previous studies and describing the authors' expert opinions. Although I agree with most of their descriptions and the manuscript reflects the current situation, I cannot accept it as a publication.

Reply 1: We thank the reviewer for taking the time to read and analyze the article. Below is the point-by-point answer.

The article aims to summarize the new evidence on medical thoracoscopy applied in therapeutic mode. The length of the manuscript reflects the guidelines for authors (no more than 6000 words excluding title page, abstract, tables, figures, legends and references) and is divided into sections that allow the reader to jump to areas of personal interest.

Comment 2: I was also concerned about the unclear aim of this review.

Reply 2: The Objective section, in addition to adding details regarding the quality scale used in the constitution of the narrative review, describes the purpose of the review: "to perform an overview of new clinical contexts in which the use of MT has the potential to bring further alternative therapeutic benefits to patient care". This area is currently underestimated by the literature and clinical practice, as most centers that practice medical thoracoscopy use it mainly for diagnostic purposes.

Comment 3: They can summarize the results and the limitations of previous studies in tables and figures so that readers can understand them at a glance.

Reply 3: The addition of a table listing the various studies, their respective characteristics and

limitations should be carefully evaluated on our part, however we feel we should ask the editor to consider the final layout of the possible paper:

- a. The tabulation should be carried out for each individual topic covered or at least for the most relevant ones, thus generating different tabulations at least for the following topics: comparison of the available instrumentation (in this regard we have already prepared the short table 2), malignant pleural effusion, pneumothorax, pleural infection. In depth tables would be generated for each topic which would take up approximately 1 page each.
- b. In light of the current word count (5043), only partially reducible in the future with the use of tables in order to maintain the appropriate text flow, there is a risk of having to include much of the tabulations in supplementary materials.
- c. The authors collectively believe that, should the editor agree to our production of these tables, we would need more than the three weeks currently allowed for this peer review and that actual usefulness to the reader should be assessed first.

**Comment 4:** The authors should describe what were the limitations of each study from clinical and methodological perspectives.

**Reply 4:** We agree with the reviewer that the description of the cited studies should be as in-depth as possible, however within a narrative and non-systematic review the flow of the text is inevitably focused on simplicity of reading and maintaining a high reader interest with the aim of evoking variations in daily clinical practice and new research questions. The studies cited in the review were described in their study design, number of patients recruited and results obtained, and were then compared with other original studies. In light of the vastness of the references that it was necessary to contemplate in the paper, each single subchapter of the review would require a separate paper to allow the limitations of each study to be clarified and to best compare all the evidence in a pragmatic manner.

**Comment 5:** Finally, the authors should illustrate the study selection flow, that is the number of studies they found during the literature search and those excluded, etc.

**Reply 5:** The article is associated with the tabulation (see Table 1. Summary of the search strategy) created according to the instructions for the authors regarding the description of the data search aimed at establishing the narrative review. The table shows the time frame considered for the publications, the inclusion and exclusion criteria and the selection process. As per SANRA quality scale (reference at the end of the text. See point 3 of the scale) no PRISMA Flow Diagram is needed for narrative reviews.

We remain at your disposal for any clarification and await updates from the editor and the reviewer to make the requested changes in order to improve the quality of this paper as much as possible.

**References:**

Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev.* 2019 Mar 26;4:5. doi: 10.1186/s41073-019-0064-8. PMID: 30962953; PMCID: PMC6434870.

