

## Peer Review File

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### Reviewer A

I read with interest the review of Migliore and colleagues on the role of minimally invasive surgery followed by an intracavitary treatment in the management of Malignant pleural Mesothelioma (MPM).

Authors summarized the available evidence on the modern role of HITHOC that is mostly limited to prospective and retrospective, single center, experience.

The article is overall well written, complete, and clear with minimal issues and concerns.

Authors reported the following sentence (line 33) “debulking surgery in the form of extrapleural pneumonectomy or pleurectomy/decortication”. It could be better modify “debulking” with Macroscopic Complete Resection (MCR) that is the aim of this kind of surgery (PMID: 29507798).

**This has been changed line 66 and Paper PMID: 29507798 added line 314**

Authors stated that Uniportal VATS is nowadays preferred to perform talc pleurodesis. Please add eventual references

**Added Line 106 and references 12,13,14**

Surgery and HITHOC are just a part of a multimodal treatment that usually include chemo (Immuno)therapy and radiation. Pleurectomy and decortication are very invasive operation that may impair the quality of life, despite the approach; have the authors any data on the patient’s rate underwent VATS and HITHOC who are able to start an adjuvant treatment?

**All our patients undergo adjuvant treatment. Added in line 118.**

Discussion could be improved with the following manuscript: PMID: 34501249

**Paper PMID: 34501249 has been added in the discussion reference 40**

### Reviewer B

1. Lines 34-35, "Despite the number of available treatments, the approach to MPM is considered tricky and there is the need for a global effort to approach this rare cancer." It would be useful for authors to give a detailed description of why the approach to MPM is considered tricky, for example, authors can cite references and specify the limitations and shortcomings of these treatments.

**Thank you for your comment this has been expanded now line 69-72 and references added (6-9)**

2. Lines 41-42, This sentence may lead to misunderstanding as this review focuses on VATS. The authors could consider rewording it, e.g., video-assisted thoracic

surgery has recently been increasingly used for decortication (pleurectomy/decortication), although many centers still perform open or double thoracotomy. Moreover, the authors should add citations to substantiate this statement-"Video Assisted Thoracic Surgery has also been used recently for debulking surgery (pleurectomy/decortication) for MPM", and more information about VATS can be given.

**This has been modified, more information regarding VATS given and references added.**

**(Line 70-74) references 6-10**

3. Since similar reviews in this field have already been published, e.g., PMID34501249, the authors should cite similar reviews for comparison and give a clarification on what this review adds to existing knowledge. We recommend that authors use a structured introduction to further increase the readability:

**Thank you so much. We followed the suggested template and the paper looks now different. Line 62-101**

4. Lines 67-69, "Larish et al. showed that decortication at 42 °C increased the cisplatin concentration in the lung in significantly when compared to non-decorticated tissue samples ( $p < 0.05$ ) with an overall maximum penetration depth of 7.5 mm (8)". The reference is wrong. The study by Larish et al. is ref.9 and their conclusions do not correspond to the benefits of hyperthermic conditions. Please check other references are cited correctly.

**Yes thank you this has been done. Line 169-171 reference 27.**

5. "In one previous publication we have reported an evidence table which shows that HITHOC improve survival and should not be forgotten when guidelines for malignant pleural mesothelioma are written (7,8)". It's suggested to revise "we" to "G M Hahn et al", and "improve" should correct to "improves".

Besides, the authors mentioned "in one previous publication", why do two references appear?

**This sentence have been modified.**

6. In Line 73, relevant references also need to be given to support "several guidelines"; The same applies to Line 96, "Extended extirpative surgery has been demonstrated that is not effective to prolong survival in MPM", "surgery in conjunction with chemotherapy and radiotherapy (multimodality treatment), has favorable outcome with less mortality"...

Please check the Full TEXT to ensure each statement is evidence-based.

**The comments 5 and 6 are correct. Thank you. We reworted from line 175-180 and appropriated references added.**

7. In this part-"When HITHOC is offered to patients?", except this sentence-"HITHOC is used to treat the first stages of MPM, in all other cases it is used when

the pleura is a metastatic site and therefore the cancer is advanced (10,11,12)", more is general information description. Although guidelines for MPM do not include HITHOC, we would like authors to provide more studies and describe their patient's clinical characteristics and therapeutic effects. For example, one of the authors' previous publications (PMID: 26638918), showed low morbidity and no perioperative mortality when intrapleural cisplatin was administered to young patients with good performance status, early disease, and predominantly epithelioid histology.

**This paragraph has been changed and modified. Your comment has been added (line 193-196).**

8. Line 117, Please ensure whether the abbreviation of extended pleurectomy/decortication is eP/D, EPD, or EP/D. In addition, please define 'SMD' when it is first used (line 128).

**Yes this has been modified in all the manuscript Line 204.**

9. Line 95, "Indication for surgical management, and how and when to do it is still debated". It would be nice for authors to provide their enriching experiences. For example, the authors could share when they chose P/D or EPP, which would be valuable for young surgeons.

**Thank you we Added line 143-149.**

10. Line 133, "P/D was associated with less mortality 11% vs. 0%; P=0.031 (34)". Is P/D (0%) compared with EPP (11%)? Also, the data 11% was not found in the ref. 34. Please re-check it.

**You are right the reference is the following: now n° 45 in the paper you can read: Perioperative mortality was 6 (11%) for EPP and 0 for P/D patients (P ¼ .031).**

11. It is important to note that we require that the main body also contain a discussion on the main strengths and limitations of this review to inform the reader of a more objective understanding of the information in the review.

**This has been done in all chapter and subchapter. To give more strengths to the manuscript we added line 320-330**

12. In Fig 1, it's suggested to show this trend in one picture, authors can use Boolean search, e.g., ((HIOC) OR (HITOC)) OR (HITHOC).

**This has been done.**