Review Article

A narrative review of video-assisted debulking surgery and hyperthermic intraoperative thoracic chemotherapy (HITHOC) for malignant pleural mesothelioma

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Background and Objective: Malignant pleural mesothelioma (MPM) is a cancer that carries a dismal prognosis. At the present time the role of video-assisted thoracic surgery (VATS) as an approach to operate patients with MPM is becoming more common. Furthermore, an increase in the use of hyperthermic intraoperative thoracic chemotherapy (HITHOC) is visible in the medical literature. The main objective of this paper is to provide an overview of the key findings and debates of VATS and HITHOC for the treatment of MPM.

Methods: A review was conducted on studies pertaining to the use of VATS to treat MPM and the HITHOC. The search was performed using PubMed/MEDLINE, Web of Science, Scopus and Google Scholar. The studies were assessed to evaluate the perioperative and long-term outcomes.

Key Content and Findings: Most of the studies presented in the manuscript are very encouraging. Current literature suggests that the use of VATS is feasible and it can be proposed not only for talc pleurodesis but also to perform pleurectomy/decortication (P/D) to treat MPM. VATS also offers similar or better perioperative outcomes than open approaches. In addition, there is robust evidence based on published data suggesting that the use of HITHOC may be appropriate to prolong survival in patients with epitheliod MPM.

Conclusions: VATS is an appropriate approach for MPM. Nevertheless, more level 2 evidence is necessary to convince oncologists and thoracic surgeons to use HITHOC as an "adjuvant" treatment. Future prospective multi-institutional studies (a global trial) will be needed in order to fully evaluate the value of VATS and HITHOC in treating MPM.

Keywords: Hyperthermic intraoperative thoracic chemotherapy (HITHOC); mesothelioma; video-assisted thoracic surgery (VATS); debulking surgery; pleurectomy/decortication (P/D)

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive cancer that carries a dismal prognosis. The median survival rate in patients who do not undergo treatment is still limited to less than 1 year from the time of diagnosis (1). Various treatment modalities have been used to manage MPM including immunotherapy, chemotherapy, radiation therapy and macroscopic complete resection (MCR) in the form of extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D). 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. This is due to the divergent data that can be found in the medical literature regarding type of surgery and chemo or immunotherapy (2-4). Surprisingly, even the different available guidelines do not write any opinion on the use of video-assisted thoracic surgery (VATS) as an approach to treat MPM associated with hyperthermic intraoperative thoracic chemotherapy (HITHOC) as adjuvant treatment (5-8).

Although many centers still perform thoracotomy to perform P/D, VATS has been increasingly used for P/D for MPM in the past 20 years (9). Moreover, the use of HITHOC (10) is increasing in general oncological thoracic surgical practice as demonstrated by the surge of recent publications reported in PubMed when the term hyperthermic intrathoracic chemotherapy (HITOC) is searched (*Figure 1*).

There are three main unresolved questions that determine the utility of VATS and HITHOC in treating MPM:

(I) Is VATS a feasible approach to treat MPM?
(II) What is HITHOC, is it dangerous, and more importantly is it useful?
(III) Should we continue investigating on VATS and HITHOC for MPM?

This article will review the literature on these three questions to assist surgeons in determining the ideal surgical approach and treatment of MPM. Databases searched included PubMed/MEDLINE, Web of Science, Scopus and Google Scholar. We present this article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-22-62/rc).

Methods

In order to identify all studies evaluating the role of VATS and HITHOC, we performed a Boolean search using HITHOC or HITOC. Two authors (M.M., I.A.) reviewed the appropriate published manuscripts in English language using PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar (*Figure 1*). As a first step, studies were evaluated for inclusion based on title and abstract. As a second step, the authors (M.M., I.A.) performed a more detailed review of the full manuscript for inclusion. There is no years limit (*Table 1*). All studies were reviewed and results were summarized in order to answer the proposed three questions.

Is VATS a feasible approach to treat MPM?

Uniportal VATS is nowadays the preferred option to perform talc pleurodesis (11-13) in many circumstances even for malignant pleural effusion secondary to MPM. Although debulking surgery was previously performed only by large thoracotomy with or without removal of a rib or double thoracotomy, nowadays VATS can be performed with success as demonstrated by different authors (3,9). On the basis of our classification on VATS published in 2000, at the beginning of our experience with VATS and HITHOC, we performed a video-assisted mini-thoracotomy which consists of a small thoracic incision of 10–12 cm with the assistance of an optic (14,15). A small rib retractor was used to spread the ribs (*Figure 2A*) while nowadays we prefer a large Alexis rib spreader (*Figure 2B*). The optic can be inserted through the same or a different incision. The latter is our preferred option as two chest drains are always necessary at the end of the procedure to perform the HITHOC, and therefore we use the two optic port entries to insert the chest drains. Having performed many of these operations we confirm that video-assisted mini-thoracotomy (10–12 cm) is a very good approach even to perform extended pleurectomy/decortication (EPD) for MPM.

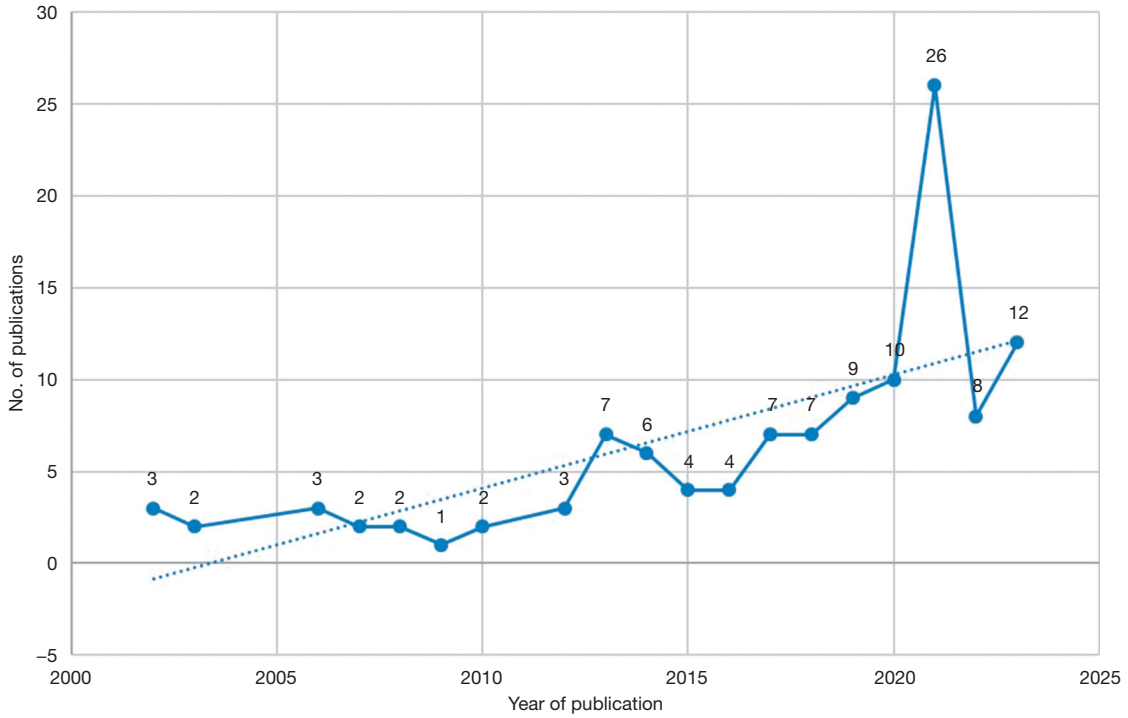


Figure 1 Evidence of the increased interest in HITHOC, HIOC, or HITOC publications reported on PubMed by the 29th July 2023. The dotted line represents the trendline. HITHOC, hyperthermic intraoperative thoracic chemotherapy; HIOC, heated intraoperative chemotherapy; HITOC, hyperthermic intrathoracic chemotherapy.

Table 1 Literature search strategy summary

Items	Specification
Date of search	28 May 2022, 29 July 2023
Databases and other sources searched	PubMed/MEDLINE, Web of Science, Scopus and Google Scholar
Search terms used	VATS, Uniportal VATS, mesothelioma, HITHOC, HIOC, HITOC, hyperthermic intrathoracic chemotherapy, talc Pleurodesis, pleurectomy decortication, debulking surgery
Timeframe	No limit
Inclusion criteria	English language only
Selection process	M.M. and I.A. reviewed selected studies

VATS, video-assisted thoracic surgery; HITHOC, hyperthermic intraoperative thoracic chemotherapy; HIOC, hyperthermic intraoperative chemotherapy; HITOC, hyperthermic intrathoracic chemotherapy.

VATS and P/D

Surgical treatment of MPM is still not uniform (2,16). The role of debulking surgery is to remove the macroscopic pathology of MPM which can be seen by the human eye. However, surgeons who treat MPM are aware of the challenges in obtaining a clear macroscopic resection margin (MCR). Unfortunately, recurrence or progression of MPM is not unusual.

Indication for surgical management, and how and when to do it is still debated. Extended extirpative surgery has been demonstrated that is not effective to prolong survival in MPM (2,16). Nevertheless, surgery in conjunction with chemotherapy and radiotherapy (multimodality treatment), has favorable outcome with less mortality (17).

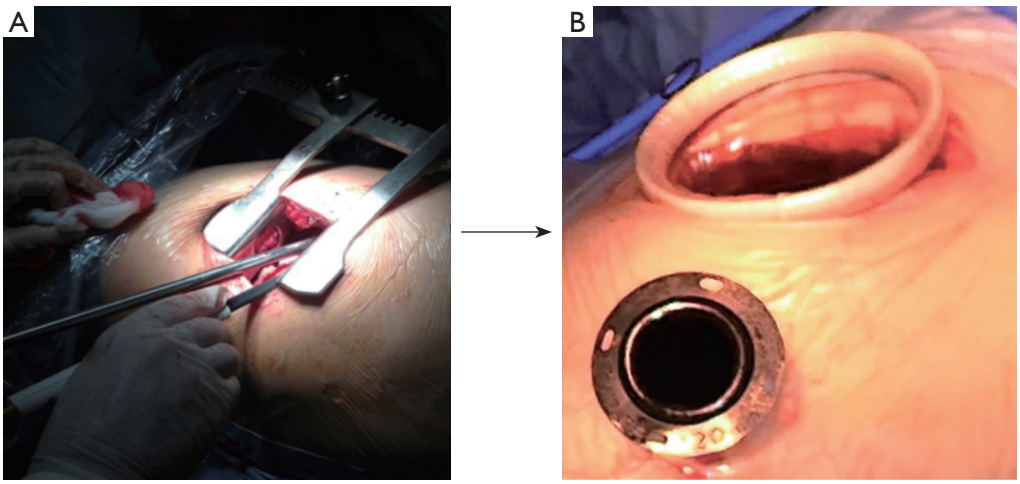
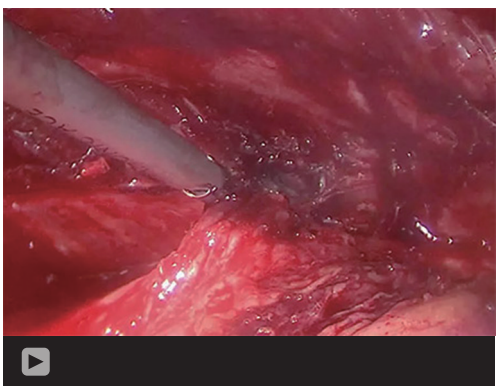


Figure 2 Minimally invasive approach for malignant pleural mesothelioma. (A) VATS with mini-thoracotomy. (B) VATS with no rib spreader. VATS, video-assisted thoracic surgery.



Video 1 Parietal pleurectomy.

Three surgical methods have been popularized to treat MPM such as P/D, EPD, on the contrary, more radical methods such as EPP is now less and less used.

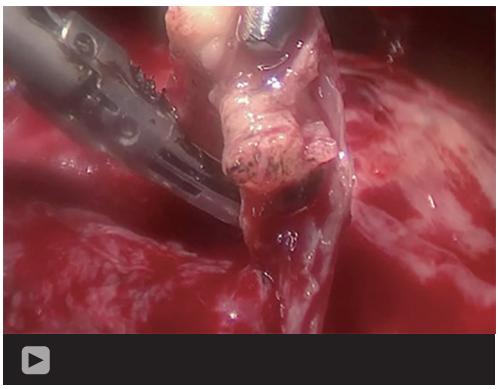
The milestone studies and experiences comparing P/D to EPP have been reported in 2008 and 2015 (18,19). A reanalysis of a large number of 1,512 patients treated with P/D versus 1,391 treated with EPP suggested that P/D is associated with better short-term mortality than EPP and survival at 2 years was not statistically significant between groups. The authors informed surgeons and researchers that P/D should therefore be favored when possible (20,21).

P/D is the removal of parietal and visceral pleura without including the hemi diaphragm and pericardium (*Video 1*). The recent use of ultracision devices decreases the risk of parietal bleeding. A variation is known as EPD where pericardium and the hemidiaphragm are removed. It has been reported that EPD decreased mortality and morbidity by 2.5 folds with survival benefit (20).

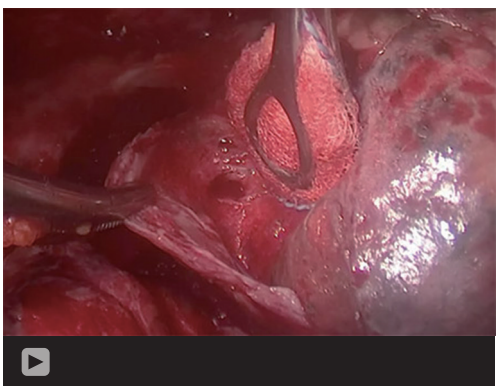
Nevertheless, other authors suggested that surgical complications of EPP are higher than the probable benefits and that VATS talc pleurodesis is less invasive and more effective method (2,16,21). Since we performed surgery for MPM 20 years ago, and although at the beginning we performed more often EPP, we gradually abandoned the operation for unpleasant surgical results and on the basis of the MARS trial. Nowadays in our unit, we only perform VATS P/D, while EPP is reserved only in case of participation in randomized trials. *Video 2* and *Video 3* show that when decortication is performed the risk of parenchymal air leak is higher, and prolonged air leak should be expected. Before the chest is closed we always protect the lung to avoid prolonged air leaks (*Video 4*).

What is HITHOC: rationale, indications, complications, and results

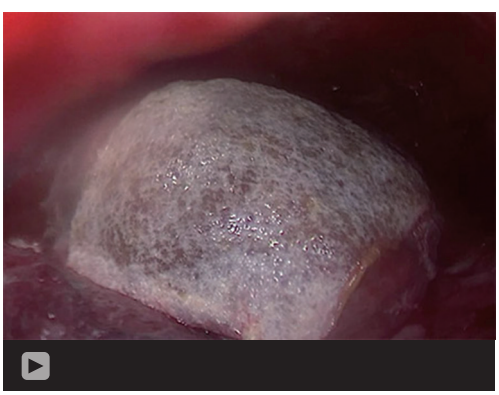
HITHOC is an adjuvant treatment which is performed in the operating room following P/D or debulking surgery for advanced thoracic tumors involving the pleura. The chemotherapeutic drug (most commonly cisplatinum) is introduced in a container of 2–3 L of 0.9% saline solution. When surgery is ended, the apical and basal drains and the thermometer are inserted in the chest and connected to the extracorporeal apparatus. The chest is then closed.



Video 2 Decortication of the lower lobe with evidence of air leaks.



Video 3 The risk of parenchymal air leak is higher than decortication for stage III empyema, and prolonged air leak should be expected as shown.



Video 4 To avoid prolonged air leaks the decorticated lung is protected. The video shows the full expansion of the decorticated lobes and the uncovered chest wall.

Immediately after the chest is filled with the normal saline, and when the intrathoracic temperature of 42 or 43 ℃ is reached, cisplatin (or another drug or a combination of two) perfusion is started for 60 min. Nevertheless, surgeons and oncologists perform the procedure using different drug concentrations and the duration of the perfusion is not standardized and ranges between 30–90 min.

Rationale for the use of HITHOC

The infusion of the drug into the pleural cavity acts on tumor cells lining its surface directly, furthermore, the hyperthermia confers toxicity to malignant cells while synergistically amplifying the toxicity of the chemotherapeutic agent (22,23). Further to that, under *ex vivo* hyperthermic conditions, cisplatin was found to better penetrate the human lung tissue to a depth of 3–4 mm (24). Luckily, the systemic concentrations levels remain low due to the limited absorption of the drug from the cavity and this allows for less adverse effects of the drug. To further support the benefits of hyperthermic conditions, Larisch *et al.* showed that decortication at 42 ℃ increased the cisplatin concentration in the lung significantly when compared to non-decorticated tissue samples ($P<0.05$) with an overall maximum penetration depth of 7.5 mm (25).

When HITHOC is offered to patients?

Several guidelines to provide guidance to appropriate treatment for MPM have been published (5-8). Nevertheless, none of them include HITHOC, which often causes misunderstanding about the procedures (26,27) as it could be considered still experimental. HITHOC is relatively new because it has been performed for the first time in more than 2 decades (10). In one previous publication, we have reported an evidence table which shows that HITHOC improves survival and should not be forgotten when guidelines for MPM are written (26). Although it is known that HITHOC is associated to surgery to treat the first stages of MPM, recently there has been an increase in its use when the pleura is the only metastatic site of advanced cancers (28-30).

The incidence of HITHOC renal complication

Renal toxicity was commonly associated with HITHOC in

the past, but it is now less reported. This can be attributed to the incorporation of preoperative hydration which was shown to be adequate to avoid the progression to renal failure (31-33). To note, a new study from the USA reports a high incidence of acute kidney injury. Having read the paper with attention it appears clear that renal toxicity and mortality develop when HITHOC is added to EPP, and not with P/D (34). A retrospective, multicenter study of 700 patients who underwent debulking surgery and HITOC using cisplatin was performed to demonstrate postoperative morbidity of HITHOC, particularly renal failure (32). It was found that renal toxicity developed in 12% of patients, and the risk for renal failure was associated with the cisplatin dosage (31).

HITHOC after P/D

The addition of HITHOC immediately after the P/D seems to achieve longer survival and good quality of life when compared to EPP or P/D alone (35-39). Recently, numerous meta-analyses and systematic reviews concluded that P/D associated with HITHOC demonstrated prolonged survival, less morbidity and mortality when compared with P/D or EPP alone (39-42).

A meta-analysis (41) was performed to compare 762 patients treated with HITHOC to a group treated without HITHOC. The study demonstrated a SMD of 0.24 (95% CI: 0.06–0.41) in favor of the HITHOC group. The survival outcome of HITHOC in epithelioid MPM showed a SMD of 0.79 (95% CI: 0.48–1.10) and supported this type of surgery for the epithelioid MPM. Another systematic review (42) of 15 studies including 598 patients found that higher survival rates were seen in patients who underwent HITHOC with debulking surgery when compared to those who have undergone surgery alone. To note, an important study showed that the type of operation has also an effect on mortality. In fact, it has been demonstrated that when comparing EPP and P/D, P/D was associated with less mortality 11% *vs.* 0% with a P=0.031 (43).

HITHOC and EPP

Extra-pleural pneumonectomy is the *en-bloc* resection of the parietal pleura, pericardium, and diaphragm including the lung. Recently based on the results of the MARS trial (2), several authors demonstrated that EPP should be used for MPM with caution and only within trials and in large units because of the higher risks and mortality associated with it (43).

Initial experience with HITHOC and EPP was reported by van Ruth *et al.* in 2003 (36). It was demonstrated that patients with EPP and HITHOC had a higher complication rate and no better survival than P/D (36). van Sandick *et al.* in 2008 reported a negative surgical experience (44). A group of 15 patients was treated with EPP and radiotherapy and compared to 20 patients who underwent P/D or EPP associated with HITHOC. The median overall survival was 29 months for EPP/radiation therapy (RT) patients while the survival in the HITHOC group was only 11 months. Although the number of patients was small, the unsatisfactory results led the authors to conclude that debulking surgery plus HITHOC should not be performed because survival is dismal and renal failure is common.

A follow-up retrospective study was performed of 132 patients undergoing EPP plus HITHOC followed by chemoradiation. The study showed an unsatisfactory recurrence rate of 75% (45), and the authors reported an untrustworthy therapeutic effect of HITHOC in MPM surgery.

Furthermore, a recent experience (34) showed that 48% of 501 patients with MPM who underwent EPP with 82% of them receiving cisplatin-based HITOC were more prone to develop kidney impairment. Moreover, the survival benefit was obtained only in patients who did not develop acute renal failure. It is evident that these results are in contrast to our personal experience and with those colleagues who performed HITHOC after less invasive extirpative surgery (32,33,46-48). Furthermore, it is important to note that different reviews and meta-analyses concluded that EPP was associated with more complication and mortality in comparison with P/D without any observed survival benefit (39-42).

We can therefore speculate that when the lung is completely removed as there is no absorption of the cisplatin via the lung parenchima, there will be more availability of the drug in the blood via the chest wall to cause kidney injury. Moreover, the high mortality of EPP even with HITHOC confirms the absence of usefulness of the EPP in Mesothelioma (2,34).

Reoperation for mesothelioma is extremely uncommon and only occasionally beneficial (49). However, other research claims that HITHOC can still be done repeatedly while the patient is awake (50). Three operations on one patient were performed without any HITHOC toxicity (51).

Should we continue investigating on VATS and HITHOC for MPM?

Very few trials have been performed to demonstrate the superiority or non-inferiority of debulking surgery and HITHOC versus EPP alone, P/D alone or talc pleurodesis (52-54). Burt *et al.* (52) have shown that HITHOC using cisplatin and gemcitabine can be administered safely and feasibly by EPP or P/D. In a phase 2 trial, Tilleman *et al.* reported that HITHOC using cisplatin perfusion following EPP might enhance local control in the chest (53).

Our data extrapolated from the pilot study (54) on 27 patients with MPM comparing P/D and HITHOC to talc pleurodesis alone are very promising. The HITHOC group showed a mean survival for the epithelioid type of 45 months compared to 18 months to the non-HITHOC group. Furthermore, we can speculate that the fact that we use a video-assisted mini-thoracotomy could enhance postoperative recovery and survival for a better immune response. In our experience, one patient who survived 8 years has been operated 3 times with debulking surgery and HITHOC (51).

Recently in Singapore at the IASLC (International Association for The Study of Lung Cancer, September 11, 2023), Dr. Lim reported the results of the MARS 2 trial. It has been showed that decortication and chemotherapy is associated with worse outcomes for patients with resectable mesothelioma (55) when compared to chemotherapy alone. He concluded that EPD should not be offered to patients with pleural mesothelioma and classified MPM as "unresectable". Pragmatically, while witnessing this sad result we still believe that there are signals that "new" intrathoracic local treatments after debulking surgery could prolong survival in MPM. There is no doubt, that future researches on large scale are essential and mandatory to prove that the signals are true.

Conclusions

The different acronyms HITHOC, HIOC (heated intraoperative chemotherapy), and HITOC describe the same procedure of hyperthermic intraoperative intrathoracic chemotherapy. It is therefore advisable to find general consent between scientific societies to choose the proper name and acronym. In this paper, we use the acronym HITHOC.

Although today the most common approach to MPM is the use of chemotherapy alone (56), multimodal therapy represents the most advanced archetype to treating MPM. We have demonstrated that HITHOC can add survival to patients with MPM, and this result should be sufficient to continue research on this topic. It is important to inform that there are other approaches which have shown some promising results (57-59). A single institute reported a 10-year experience on the use of povidone-iodine as an agent that can be combined with P/D (57). It kills MPM cells by the generation of reactive oxygen species causing cellular necrosis. Immunocytokines infusion is another agent that activates immune cells (LAK cells). The delivery options of the chemotherapeutic agent include a cisplatin-fibrin gel, hyaluronate cisplatin film, expansible nanoparticles and surface-fill hydrogel nanocomposite (58,59). Finally, photodynamic therapy is another adjuvant which utilizes a laser that targets a light-absorbing photosensitizing agent absorbed by tumor cells (60). All these adjuvant treatments must still intensely be studied via trials and observational studies.

Although most of the studies presented in this manuscript and our personal experience are very encouraging, it is evident that more level 2 evidence is necessary to convince oncologists and thoracic surgeons to use this type of "adjuvant" treatment. Nevertheless, decision-making process and the paradigm in the treatment of MPM is changing (61). A global effort is necessary to perform large trials.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://vats.amegroups.com/article/view/10.21037/vats-22-62/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patients for publication of this review article and accompanying videos. A copy of the written consent is available for review by the editorial office of this journal.

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