Review Article

A glimpse into the role of debulking surgery and hyperthermic intrathoracic chemotherapy (HITHOC) in the management of malignant pleural mesothelioma

Marcello Migliore[1]^, Ibrahem Albalkhi[2]^, Abdullah Alshammari[3]^, Hamsa Aldebakey[2], Omniyah Alashgar[4], Joaquín Calatayud Gastardi[5], Norberto Santana-Rodríguez[2,4,6]^

[1]Minimally Invasive Thoracic Surgery & New Technologies, University Hospital of Catania and Department of General Surgery and Medical Specialties, University of Catania, Catania, Italy; [2]Department of Surgery, College of Medicine, Alfaisal University, Riyadh, KSA; [3]Department of Thoracic Surgery, Royal Brompton Hospital, London, UK; [4]Thoracic Surgery & Lung Transplant, Lung Health Centre, Organ Transplant Center of Excellence (OTCoE), King Faisal Specialist Hospital & Research Center, Riyadh, KSA; [5]Department of Thoracic Surgery, Hospital Universitario San Carlos, Madrid, Spain; [6]Instituto Canario de Medicina Avanzada (ICMA), Las Palmas de Gran Canaria, Canary Islands, Spain

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Correspondence to: Marcello Migliore, MD, PhD. Department of General Surgery and Medical Specialties, University of Catania, Catania, Italy. Email: mmiglior@unict.it.

Abstract: Malignant pleural mesothelioma (MPM) is a devastating malignant disease with a poor prognosis due to the lack of effective treatment and the advanced stage evidenced at diagnosis. Multimodality treatment involving chemotherapy, surgery, and radiotherapy is currently the advised regimen to prolong survival. Recently, surgeons and oncologist increased their interest in new innovative treatments such as hyperthermic intrathoracic chemotherapy (HITHOC) and immunotherapy. The role played by surgery appears questionable due to the unattainability of radical resection in most cases and is based on the performance of different surgical techniques to achieve cytoreductive surgery ranging from aggressive extrapleural pneumonectomy to pleurectomy/decortication. HITHOC was introduced several decades ago where the anti-tumoral effects of chemotherapy work synergistically alongside the cytotoxic effect of high temperature on exposed tissue, hence, aiming to improve surgical radicalism. However, its role in the treatment of MPM is still controversial. Hereby, we present a literature review of the role of HITHOC following cytoreductive surgery in the management of patients with MPM. In most cases, an excellent local control was obtained as well as a better overall survival associated with a low rate of complication. HITHOC may be considered a feasible, safe, and highly effective procedure even though there is a high heterogeneity between the protocols adopted globally. There is a need for further structured research to arrive at a unanimous consensus on this technique.

Keywords: Hyperthermic intrathoracic chemotherapy (HITHOC); hyperthermic chemotherapy; cytoreductive surgery; pleurectomy; mesothelioma

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^ ORCID: Marcello Migliore, 0000-0002-6272-8983; Ibrahem Albalkhi, 0000-0002-2729-514X; Abdullah Alshammari, 0000-0002-4889-2605; Norberto Santana-Rodríguez, 0000-0003-3524-5991.

Introduction

Malignant pleural mesothelioma (MPM) is a devastating cancer. Survival of MPM changed a little in the last 20 years. In the last decade, the median overall survival reported in 12,168 patients with MPM improved only from 7.3 [1993–2003] to 8.9 [2004–2011] and 9.3 months from 2012 to 2018 (P<0.001). This unfortunate result confirms that the prognosis for MPM is still poor. Although the use of chemotherapy increased from 9.3% to 39.4%, most of the patients (62.2%) received no antitumor treatment due to poor performance status and patient preference (1).

Several surgical techniques which are considered radical have been popularized over the years. However, some randomized trials have repeatedly shown limited improvement in patient outcomes, with a considerable number of harmful postoperative consequences (2-5). In a few words, randomized clinical evidence to validate the different surgical approaches of extrapleural pneumonectomy (EPP), pleurectomy/decortication (P/D) and talc pleurodesis is very weak. Video-assisted thoracoscopic surgery (VATS) talc pleurodesis remains the most used treatment and is the only acceptable approach for many patients with MPM (3). Novel management approaches are necessary to prolong survival in these patients without devastating extirpative operations.

Although hyperthermic intraoperative thoracic chemotherapy (HITHOC) was introduced more than 20 years ago (6,7), it is still infrequently used and is not routinely performed in general thoracic surgical practice. Nevertheless, at present, the role of HITHOC in clinical practice is becoming more central, and its position in today's world of oncology and surgical oncology is increasing (8).

In this article, we summarize the evidence taken from the recent literature and our surgical experiences on the role of HITHOC following cytoreductive surgery for MPM.

What is HITHOC

HITHOC is a type of adjuvant treatment which is performed in the operating room immediately after debulking surgery for extended thoracic cancers. After surgery, two to four drains (apical and basal) and two thermometers are inserted in the chest. The drains are connected to the extracorporeal machine, while the chest is closed (*Figure 1*). The chemotherapeutic drug (cisplatinum most of the time although other drugs or a combination of two has been assayed) is introduced in a bag containing 2–3 L of normal saline and when the intrathoracic temperature of 42.5 ℃ is reached, intrapleural cisplatin perfusion is started for 60–90 min. Advanced cardiac and hemodynamic monitoring is mandatory during the procedure (*Figure 2*).

Rationale for using HITHOC

The infusion of the drug into the pleural cavity leads to the direct exposure of tumour cells lining its surface, furthermore, the hyperthermia itself confers toxicity to malignant cells and amplifies the toxicity of the chemotherapeutic agent (9,10). Moreover, under *ex vivo* hyperthermic conditions, it has been found that cisplatin penetrated the human lung tissue with a depth of 3–4 mm (11). Mercifully, the systemic concentrations remain below toxic levels due to the limited absorption of the drug from the cavity. The original article of Larish *et al.* (12) demonstrated that decortication at 42 ℃ significantly increased the cisplatin concentration in the lung in comparison to non-decorticated tissue samples (P=0.005) with an overall maximum penetration depth of 7.5 mm. The authors also demonstrated that a temperature rise showed no effect on the cisplatin concentration in decorticated tissue samples (P=0.985) (11).

Guidelines for the use of HITHOC

Guidelines for the use of HITHOC for MPM do not exist and its absence could create confusion for patients, oncologists and surgeons (8,13-16). Nevertheless, in 2020, an expert recommendation paper has been published in Germany (17). Some may erroneously conclude that the procedure is still experimental, while the reality says that, despite its current limited use, HITHOC is more than 20 years old. We have recently published a study which demonstrated that HITHOC should be taken into consideration to be included in the guidelines for MPM (13). It is important to comprehend that in MPM, HITHOC was used when the tumour is at the initial stage (stage I–II), while in all other thoracic cancers HITHOC is used when the tumour has reached an advanced stage, and the pleura is a metastatic site (18-23).

Renal toxicity

The reported renal toxicity which was common in the

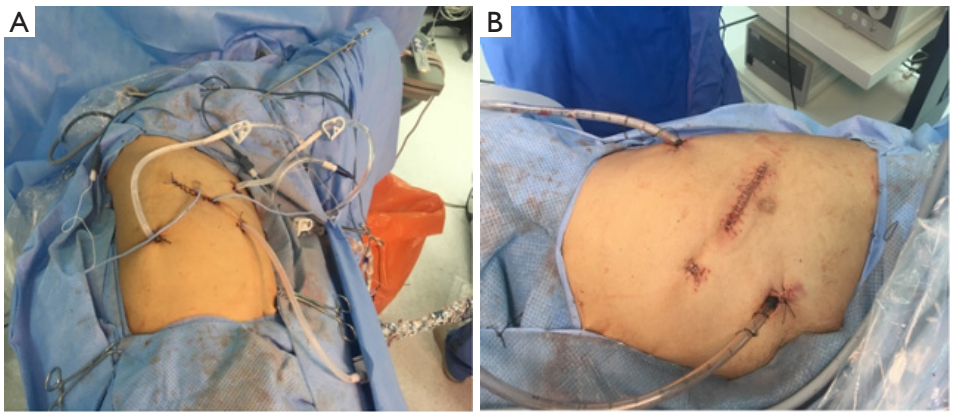


Figure 1 Position of thoracic drains and thermometers during HITHOC. (A) Drains and thermometer's placement for HITHOC after VATS P/D in a patient with stage III MPM. (B) Final aspect of the patient in surgical position after HITHOC. HITHOC, hyperthermic intrathoracic chemotherapy; VATS, video-assisted thoracoscopic surgery; P/D, pleurectomy/decortication; MPM, malignant pleural mesothelioma.

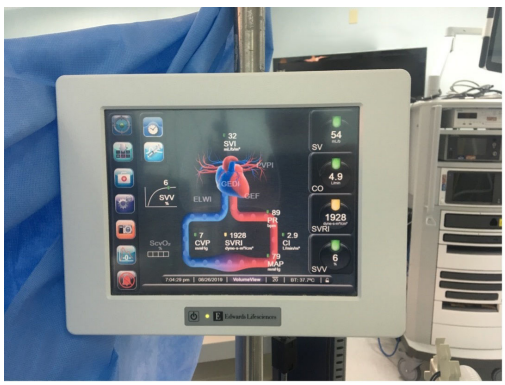


Figure 2 Cardiac and hemodynamic monitoring is advisable during HITHOC. HITHOC, hyperthermic intrathoracic chemotherapy.

early phase of use (24) is now rarely reported as it has been demonstrated that preoperative hydration is sufficient to avoid the development of renal failure. Although a recent paper from the United States (25) reported a high incidence of renal toxicity as acute kidney injury. It seems clear that renal toxicity and mortality developed in patients who underwent EPP, and not in those who underwent P/D (13-15). A retrospective, multicenter study of 700 patients who underwent cytoreductive surgery plus cisplatin based HITHOC reported significant postoperative morbidity related to HITHOC, particularly renal insufficiency (26,27) since it appeared in 41 patients (12%) and the risk for postoperative renal failure was dependent on the intrathoracic cisplatin dosage.

Debulking surgery

The treatment algorithm for MPM is still under constant development and adjustment. Surgical management, in particular, holds a huge controversy on how and when to do it. It is now accepted that implementing surgery alone will not be effective for the management of MPM. Surgery, alongside other modalities such as chemotherapy and radiation, has a more favourable outcome. Surgical management varies from performing minimally invasive excisions to more radical methods. Three surgical methods have been popular over the past decades to treat MPM such as P/D, extended pleurectomy/decortication (EPD), and extra-pleural pneumonectomy.

Pleurectomy/decortication involves total parietal and visceral pleurectomy that spares the pericardium and hemidiaphragm. It is usually recommended for the early stages of the disease; however, the risk of parenchymal air leak is high. EPD is the removal of parietal and visceral pleura as well as the pericardium and the hemidiaphragm (28-32). Extra-pleural pneumonectomy is the in-bloc resection of all the above tissue including the lung (33).

Several studies have concluded that EPP should no longer be used for MPM due to the rate of risks and high mortality associated with it (2,28,32). Several systematic reviews and meta-analyses have concluded that EPP was associated with more postoperative mortality and morbidity in comparison with P/D. It was also concluded that EPD decreased mortality and morbidity by 2.5 folds and that it improved survival (15,22,34-37).

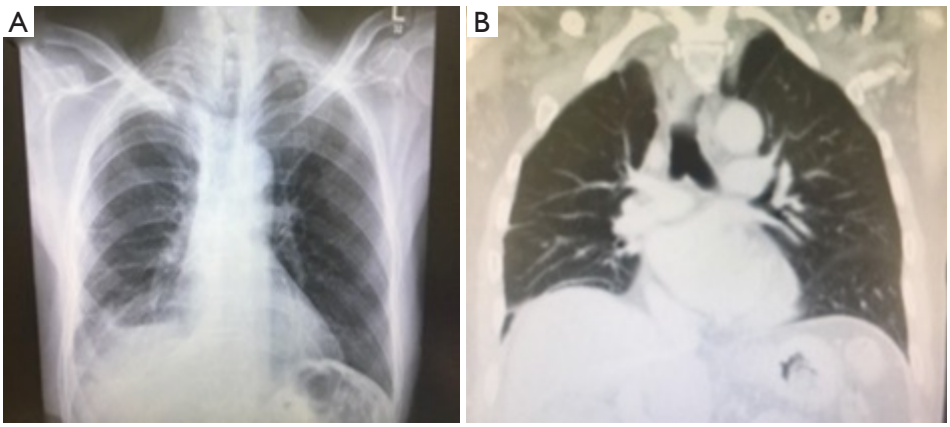


Figure 3 Early and late postoperative chest X-rays. (A) Postoperative chest X-ray of a patient with right pleural mesothelioma who underwent uniportal P/D plus HITHOC following neoadjuvant chemotherapy and was discharged on the third postoperative day. (B) CT chest image 12 months after surgery without signs of recurrence. HITHOC, hyperthermic intrathoracic chemotherapy; P/D, pleurectomy/decortication; CT, computed tomography.

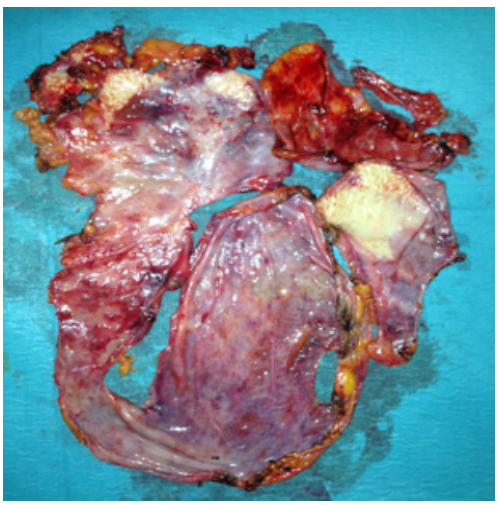
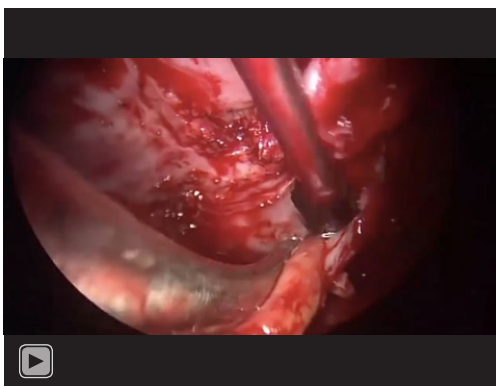


Figure 4 Specimen of pleurectomy invaded by an epithelioid MPM. MPM, malignant pleural mesothelioma.



Video 1 HITHOC following uniportal right VATS P/D in a 62-year-old male patient with stage III MPM. HITHOC, hyperthermic intrathoracic chemotherapy; VATS, video-assisted thoracoscopic surgery; P/D, pleurectomy/decortication; MPM, malignant pleural mesothelioma.

Different clinical trials are still ongoing to study the treatment options of MPM, focusing on EPD to analyze the best use in MPM, and whether it could be a viable option in the first place. Also, VATS P/D is considered to manage MPM symptomatically; however, several studies observed that its surgical complications risks weigh more than the possible benefits and that VATS pleurodesis is a more effective and less invasive method (3) (*Figure 3*).

The role of cytoreductive surgery is to remove the macroscopic pathology with an extra margin around the MPM (*Figure 4*). However, any residual microscopic disease can lead to MPM progression. To try and overcome this, HITHOC is administered (*Video 1*) and is associated with a higher disease-free interval and overall survival especially when administered at a high dose (15). Our preferred surgical approach is a VATS via a mini-thoracotomy of 8–12 cm instead of large thoracotomies with/without rib resection (38).

The study was reviewed and approved by the Institutional Review Board at King Faisal Specialist Hospital in Riyadh, Saudi Arabia. Written informed consent was obtained from the patient.

Discussion

Despite the innovations that have been incorporated into the management of the MPM over the years, the approach and the type of operative treatment is still controversial. The role of HITHOC with debulking surgery for the management of MPM has been heavily debated in the literature through different studies and trials.

In 1997, Shirakusa and Okabayashi reported for the first time the use of HITHOC via VATS for pleural disseminated lesions and malignant pleural effusions (6). In 2002, de Bree *et al.* (39) reported a series with 3 patients with pleural thymoma metastases and 11 patients with pleural mesothelioma showing acceptable morbidity rates and encouraging locoregional disease control.

In 2003, van Ruth *et al.* (7) reported on 20 patients who were operated on for stage I mesothelioma and HITHOC with a median follow-up of 14 months and a median survival of 11 months with a 1-year survival of 42%. The authors reported considerable morbidities such as bronchopleural fistula, diaphragm rupture, wound dehiscence, persistent air leakage, and chylous effusion.

In 2008, van Sandick reported a negative study (40). Fifteen MPM patients were treated with EPP plus radiotherapy (RT) versus 20 patients who underwent cytoreductive surgery—P/D or EPP—and HITHOC but operated on years before. The median overall survival was 29 months for EPP/RT patients and 11 months for HITHOC patients. The authors concluded the use of cytoreductive surgery in combination with HITHOC for MPM is not supported, and renal failure was common.

However, in the last 10 years, different surgical positive experiences have been reported in Europe, China and the United States, and the use of HITHOC for MPM has also been expanded. As a result of this increase, many systematic reviews have been recently published and all of them confirm a longer survival when HITHOC is added to P/D (35-37). In a recent systematic review and meta-analysis (8), 762 patients treated with HITHOC have been compared to the control group that did not receive HITHOC. The analysis showed an standardized mean difference (SMD) of 0.24, with a 95% CI of 0.06–0.41 in favour of the HITHOC group. The survival effect of HITHOC in epithelioid MPM *vs.* non-epithelioid MPM showed an SMD of 0.79 (95% CI: 0.48–1.10) in favour of epithelioid MPM.

Furthermore, we have recently demonstrated that HITHOC can offer a longer survival rate with fewer risks than before with good quality of life to patients affected by MPM. We have published as a pre-print a study comparing 12 patients with P/D and HITHOC to 13 patients with talc pleurodesis alone. The advantage for the HITHOC group is evident and the median survival for the epithelioid type is 45 months (41,42). In the HITHOC group, there was a patient who survived 8 years and received three operations including debulking surgery and HITHOC (43). Although all these studies are very encouraging, it is evident that more multi-center randomized control trials are necessary to give HITHOC its position in the decision-making process in the treatment of MPM (44).

Nevertheless, the future seems to integrate immunotherapy for the few patients for whom radical surgical therapy is intended. The recent publication of the Checkmate 743 trial (45) demonstrated a survival benefit of combination immunotherapy over standard chemotherapy in patients with MPM. Simultaneously, the CONFIRM trial (46) demonstrates a modest and significantly longer survival of second-line nivolumab versus placebo in patients who already received standard chemotherapy. We also are waiting for the results of the MARS2 trial which is a randomized multicentric trial comparing (extended) P/D versus standard P/D in patients with MPM (47).

Finally, the combination of the recent and future innovations in the treatment of MPM has a two-fold goals. The first is to realize the new paradigm of "precision (individualized) treatment" and the second is to achieve through the individualization of the treatment a better long-term survival (48,49).

In conclusion, the use of HITHOC as a perioperative adjuvant treatment for MPM will likely expand in specialized centers in the future. Nevertheless, as MPM is a rare tumour, a global effort is necessary to definitively prove its efficacy.

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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. The study was reviewed and approved by the Institutional Review Board at King Faisal Specialist Hospital in Riyadh, Saudi Arabia. Written informed consent was obtained from the patient.

References

1. van Kooten JP, Belderbos RA, von der Thüsen JH, et al. Incidence, treatment and survival of malignant pleural and peritoneal mesothelioma: a population-based study. Thorax 2022. [Epub ahead of print]. pii: thoraxjnl-2021-217709. doi: 10.1136/thoraxjnl-2021-217709.
2. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763-72.
3. Rintoul RC, Ritchie AJ, Edwards JG, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet 2014;384:1118-27.
4. Burt BM, Richards WG, Lee HS, et al. A Phase I Trial of Surgical Resection and Intraoperative Hyperthermic Cisplatin and Gemcitabine for Pleural Mesothelioma. J Thorac Oncol 2018;13:1400-9.
5. Opitz I, Lauk O, Meerang M, et al. Intracavitary cisplatin-fibrin chemotherapy after surgery for malignant pleural mesothelioma: A phase I trial. J Thorac Cardiovasc Surg 2019. [Epub ahead of print]. doi: 10.1016/j.jtcvs.2019.07.073.
6. Shirakusa T, Okabayashi K. Video-assisted thoracic surgery for lung cancer. Gan To Kagaku Ryoho 1997;24:520-4.
7. van Ruth S, Baas P, Haas RL, et al. Cytoreductive surgery combined with intraoperative hyperthermic intrathoracic chemotherapy for stage I malignant pleural mesothelioma. Ann Surg Oncol 2003;10:176-82.
8. Dawson AG, Kutywayo K, Mohammed SB, et al. Cytoreductive surgery with hyperthermic intrathoracic chemotherapy for malignant pleural mesothelioma: a systematic review. Thorax 2022. [Epub ahead of print]. pii: thoraxjnl-2021-218214. doi: 10.1136/thoraxjnl-2021-218214.
9. Giovanella BC, Stehlin JS Jr, Morgan AC. Selective lethal effect of supranormal temperatures on human neoplastic cells. Cancer Res 1976;36:3944-50.
10. Hahn GM, Braun J, Har-Kedar I. Thermochemotherapy: synergism between hyperthermia (42-43 degrees) and adriamycin (of bleomycin) in mammalian cell inactivation. Proc Natl Acad Sci U S A 1975;72:937-40.
11. Ried M, Lehle K, Neu R, et al. Assessment of cisplatin concentration and depth of penetration in human lung tissue after hyperthermic exposure. Eur J Cardiothorac Surg 2015;47:563-6.
12. Larisch C, Markowiak T, Loch E, et al. Assessment of concentration and penetration depth of cisplatin in human lung tissue after decortication and hyperthermic exposure. Ann Transl Med 2021;9:953.
13. Scherpereel A, Opitz I, Berghmans T, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. Eur Respir J 2020;55:1900953.
14. Migliore M, Ried M, Molins L, et al. Hyperthermic intrathoracic chemotherapy (HITHOC) should be included in the guidelines for malignant pleural mesothelioma. Ann Transl Med 2021;9:960.
15. Migliore M, Combellack T, Williams J, et al. Hyperthermic intrathoracic chemotherapy in thoracic surgical oncology: future challenges of an exciting procedure. Future Oncol 2021;17:3901-4.
16. Markowiak T, Koller M, Zeman F, et al. Protocol of a retrospective, multicentre observational study on

hyperthermic intrathoracic chemotherapy in Germany. BMJ Open 2020;10:e041511.
17. Ried M, Eichhorn M, Winter H, et al. Expert Recommendation for the Implementation of Hyperthermic Intrathoracic Chemotherapy (HITOC) in Germany. Zentralbl Chir 2020;145:89-98.
18. Migliore M, Nardini M. Does cytoreduction surgery and hyperthermic intrathoracic chemotherapy prolong survival in patients with N0-N1 nonsmall cell lung cancer and malignant pleural effusion? Eur Respir Rev 2019;28:190018.
19. Ried M, Potzger T, Braune N, et al. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience. Eur J Cardiothorac Surg 2013;43:801-7.
20. Işık AF, Sanlı M, Yılmaz M, et al. Intrapleural hyperthermic perfusion chemotherapy in subjects with metastatic pleural malignancies. Respir Med 2013;107:762-7.
21. Migliore M, Calvo D, Criscione A, et al. Cytoreductive surgery and hyperthermic intrapleural chemotherapy for malignant pleural diseases: preliminary experience. Future Oncol 2015;11:47-52.
22. Zhou H, Wu W, Tang X, et al. Effect of hyperthermic intrathoracic chemotherapy (HITHOC) on the malignant pleural effusion: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e5532.
23. Iyoda A, Yusa T, Hiroshima K, et al. Surgical resection combined with intrathoracic hyperthermic perfusion for thymic carcinoma with an intrathoracic disseminated lesion: a case report. Anticancer Res 1999;19:699-702.
24. Tilleman TR, Richards WG, Zellos L, et al. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg 2009;138:405-11.
25. Hod T, Freedberg KJ, Motwani SS, et al. Acute kidney injury after cytoreductive surgery and hyperthermic intraoperative cisplatin chemotherapy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2021;161:1510-8.
26. Markowiak T, Kerner N, Neu R, et al. Adequate nephroprotection reduces renal complications after hyperthermic intrathoracic chemotherapy. J Surg Oncol 2019;120:1220-6.
27. Ried M, Kovács J, Markowiak T, et al. Hyperthermic Intrathoracic Chemotherapy (HITOC) after Cytoreductive Surgery for Pleural Malignancies-A Retrospective, Multicentre Study. Cancers (Basel) 2021;13:4580.
28. Bilancia R, Nardini M, Waller DA. Extended pleurectomy decortication: the current role. Transl Lung Cancer Res 2018;7:556-61.
29. Migliore M, Calvo D, Criscione A, et al. Pleurectomy/decortication and hyperthermic intrapleural chemotherapy for malignant pleural mesothelioma: initial experience. Future Oncol 2015;11:19-22.
30. Klotz LV, Grünewald C, Bulut EL, et al. Cytoreductive surgery and hyperthermic intrathoracic chemoperfusion shows superior overall survival compared to extrapleural pneumonectomy for pleural mesothelioma. Zentralblatt für Chirurgie 2019;144:V137
31. Ambrogi MC, Bertoglio P, Aprile V, et al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. J Thorac Cardiovasc Surg 2018;155:1857-1866.e2.
32. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. Ann Thorac Surg 2015;99:472-80.
33. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955-63.
34. Zhao ZY, Zhao SS, Ren M, et al. Effect of hyperthermic intrathoracic chemotherapy on the malignant pleural mesothelioma: a systematic review and meta-analysis. Oncotarget 2017;8:100640-7.
35. Davis A, Ke H, Kao S, et al. An Update on Emerging Therapeutic Options for Malignant Pleural Mesothelioma. Lung Cancer (Auckl) 2022;13:1-12.
36. Järvinen T, Paajanen J, Ilonen I, et al. Hyperthermic Intrathoracic Chemoperfusion for Malignant Pleural Mesothelioma: Systematic Review and Meta-Analysis. Cancers (Basel) 2021;13:3637.
37. Cao C, Tian D, Park J, et al. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. Lung Cancer 2014;83:240-5.
38. Migliore M, Deodato G. Thoracoscopic surgery, video-thoracoscopic surgery, or VATS: a confusion in definition. Ann Thorac Surg 2000;69:1990-1.
39. de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic

chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. Chest 2002;121:480-7.
40. van Sandick JW, Kappers I, Baas P, et al. Surgical treatment in the management of malignant pleural mesothelioma: a single institution's experience. Ann Surg Oncol 2008;15:1757-64.
41. Migliore M, Nardini M, Meli A, et al. Comparison of VATS debulking surgery and HITHOC vs VATS talc pleurodesis alone in malignant pleural mesothelioma: a pilot study. Eur Respir J 2020;56:4489.
42. Migliore M, Fiore M, Tumino R, et al. Comparison of VATS Pleurectomy/Decortication Surgery plus Hyperthermic Intrathoracic Chemotherapy with VATS talc pleurodesis for the treatment of Malignant Pleural Mesothelioma: a randomized pilot study. medRxiv 2021. doi: 10.1101/2021.11.27.21265291.
43. Poon SS, Alberti C, Nardini M, et al. Salvage debulking surgery and hyperthermic intrathoracic chemotherapy for massive recurrent mesothelioma in the mediastinum. Interact Cardiovasc Thorac Surg 2022;35:ivac034.
44. Molnar TF, Drozgyik A. Narrative review of theoretical considerations regarding HITHOC between past and future. Ann Transl Med 2021;9:954.
45. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375-86.
46. Fennell DA, Ewings S, Ottensmeier C, et al. Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. Lancet Oncol 2021;22:1530-40.
47. Lim E, Darlison L, Edwards J, et al. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. BMJ Open 2020;10:e038892.
48. Migliore M, Halezeroglu S, Mueller MR. Making precision surgical strategies a reality: are we ready for a paradigm shift in thoracic surgical oncology? Future Oncol 2020;16:1-5.
49. Migliore M. Malignant pleural mesothelioma: between pragmatism and hope. Ann Transl Med 2020;8:896.

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