The MARS2 Trial — Is Surgical Treatment of Pleural Mesothelioma a Relic of the Past?

Ann. Ital. Chir., 2026: 1–4
https://doi.org/10.62713/aic.4384

Michael T. Ou[1,2,†], Kenny Nguyen[1,†], Jeffrey B. Velotta[1,3,4]

[1]Division of Research, Kaiser Permanente Northern California, Pleasanton, CA 94588, USA
[2]Department of Surgery, University of California, San Francisco, CA 94143, USA
[3]Division of Thoracic Surgery, Kaiser Permanente Oakland Medical Center, Oakland, CA 94611, USA
[4]Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA 91101, USA

Introduction

Extrapleural pneumonectomy (EPP) was once a cornerstone of treatment for pleural mesothelioma until the Mesothelioma and Radical Surgery (MARS) trial reported a higher risk of death and poorer quality of life in patients who received EPP [1]. Subsequently, a shift in practice occurred in which extended pleurectomy decortication (EPD), a procedure that spares the lung, became the surgery of choice and was advocated by major societies [2–5]. Now, with the recent publication of the MARS2 trial, practice patterns are again susceptible to change. Our aim is to guide readers on the applicability of the MARS2 trial to current practice.

MARS2 evaluated outcomes of chemotherapy plus EPD versus chemotherapy alone in patients with pleural mesothelioma. It is the largest randomized controlled trial of EPD to date. The authors of the trial conducted an open-label, multicenter study with an intention-to-treat analysis over a period of 6 years. A total of 335 patients were randomly assigned, with surgery performed at 5 different surgical centers within the UK. The major finding of MARS2 was that chemotherapy plus EPD cohort was associated with worse survival at 2 years, more serious adverse events, worse quality-of-life, and all at double the cost [6].

The trial should be applauded for its novelty, large sample size, and comprehensiveness. It weathered the Coronavirus Disease-2019 (COVID-19) pandemic, included two quality-of-life measurements, and even included cost of care comparisons. MARS2 was a massive undertaking that required significant strategic planning, execution, and assessments. The authors' efforts and commitment to the highest levels of research should be commended.

Submitted: 30 September 2025 Revised: 31 October 2025 Accepted: 7 November 2025 Published: 30 January 2026
Correspondence to: Jeffrey B. Velotta, Division of Research, Kaiser Permanente Northern California, Pleasanton, CA 94588, USA; Division of Thoracic Surgery, Kaiser Permanente Oakland Medical Center, Oakland, CA 94611, USA; Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA 91101, USA (e-mail: jeffrey.b.velotta@kp.org).
[†]*These authors contributed equally.*
Editor: Roberto Cirocchi

However, after the publication of this trial, issues regarding the generalizability of this study were raised. We will review the most pertinent ones.

Areas of Attention

Patient Inclusion

MARS2 included 12% of non-epithelioid disease, with subgroup analyses demonstrating a restricted mean survival time difference of –3 months compared to epithelioid disease. These results are in line with prior literature showing no surgery benefit in non-epithelioid disease [7]. In fact, most major guidelines label non-epithelioid disease as a contraindication to surgery. However, despite including this group, non-epithelioid disease between the surgery and the chemotherapy groups were equally distributed. Overall survival may be skewed upon inclusion of this cohort, but comparative analysis between groups should be relatively unmarred.

More than half-way after patient recruitment, the American Society of Clinical Oncology (ASCO) 2018 staging guidelines were released that emphasized mediastinal staging and positron emission tomography-computed tomography (PET-CT), which was then incorporated into subsequent enrollment. This meant that only 40% of patients had PET-CT, and nodal disease was included; over 20% of patients had N1 disease and 7% had N2 disease. However, post-hoc analyses demonstrated no differences in survival despite the use of PET-CT, possibly owing to well randomization with balanced groups. Although these issues may affect the absolute values of their results, we believe these issues do not significantly affect the comparisons between their two arms — these are the inherent strengths of a randomized controlled trial. Perhaps what is more interesting and should be highlighted is the subgroup analysis of overall survival for T1-2, N0 epithelioid only disease. Despite this stratification, a survival benefit for surgery was not appreciated. The exact number of patients included was not disclosed but based on patient characteristics of the entire group (68% T1-2, 72% N0), it is possible that this calculation was underpowered. If these results were valid, the finding of no survival benefit even in this subset of patients with

early disease would be convincing. However, the questions remain whether patients received adequate systemic therapy, and whether staging criteria without PET-CT and nodal sampling in a large subset of patients were accurate. We will touch more upon this later.

Perhaps the most confounding factor in patient selection for MARS2 is that patients who had progression after 2 cycles of chemotherapy were still randomized as long as they were within surgically resectable limits. In practice, these patients would not have been offered surgery. Progression of disease after neoadjuvant treatment is a negative prognostic indicator and reduces the potential benefits of surgery. These patients are typically offered alternative systemic therapies or entry into clinical trials rather than surgery. The inclusion of this cohort is a significant limitation that favors the chemotherapy group and may explain why surgery was found to be detrimental. Performing surgery on patients who are known to have little to no benefit is counterintuitive.

Disease Burden and Therapy

Although the overall cT distributions appear similar (T1: 75/169 vs 81/166; T2: 36/169 vs 36/166; T3: 58/169 vs 49/166), the surgical arm had more aggressive T2 disease with 83% of T2 tumors (30/36) having pulmonary parenchymal invasion compared to only 50% (18/36) in the chemotherapy alone arm. An imbalance also exists in access to salvage therapy: 39% of chemotherapy-only patients received immunotherapy compared to 21% in the surgical arm. This is not surprising as most patients in surgery also did not complete the recommended chemotherapy cycles.

The MARS2 trial did aim to preserve fidelity amongst its surgeons by requiring the first operation and an addition randomly selected operation be peer reviewed. However, details on what standardization occurred were not specified and the option to convert from a EPP to EPD if necessary was not possible. Given that a quarter of patients had nodal disease and 3% had metastatic disease, achieving adequate macroscopic resection may not have been possible due purely to trial constraints. Furthermore, there was aggressive tissue removal including diaphragm resection in 83% of the surgery cohort, even in those with no pathological involvement of the diaphragm. This raises the question of whether patients who did not need extensive resection received unnecessary surgery, and whether there was not enough resection for those who did.

Chemotherapy

Guidelines recommend 4–6 cycles of platinum-pemetrexed chemotherapy. In the MARS2 surgical arm, only 57% in the surgical arm completed the four cycles compared with 89% in the chemotherapy arm. These results should be interpreted in two ways. Surgery itself may be a limiting factor to finishing adjuvant therapy. The ASCO 2025 guidelines do not place emphasis on the sequence of chemotherapy and surgical resection, citing the European Organization for Research and Treatment of Cancer (EORTC) 1205 trial that included patients with T1-3, N0-1, M0 disease [8]. Given that MARS2 was designed as an intention-to-treat trial, the drop off in patients able to finish adjuvant therapy provides us real-world, practical data. However, this brings us to an important question: was chemotherapy essentially compared to surgery alone? Without the full impact of systemic treatment, the benefits of only 2 cycles of chemotherapy are difficult to interpret. Optimists may say that chemotherapy patients may be naturally advantaged but not enough to alter survival outcomes to where benefits of EPD would not be detected. On the other hand, conservatists will claim that this trial is essentially a head-on comparison that was bound to favor chemotherapy as prior literature has already demonstrated that cytoreductive surgery by itself should not be thought of as curative therapy.

Since the Publication of MARS2

Almost a year after publication, a few authors of the MARS2 trial presented another manuscript challenging the results of the original paper, titled "*Why the MARS2 Trial Does not Mean the End of All Mesothelioma Surgery*" [9]. They conducted a post-hoc analysis on a sample of surgery patients (79 patients, 50% of MARS2 surgical cohort) based on contemporary staging criteria and pathological requirements. Justification for this subgroup analysis was stated plainly: "We have found that only 1 in 3 [patients] of [the MARS2 trial] would be offered surgery in current practice" [9]. Their results were remarkable. Patients with clinical stage 1 or 2, epithelioid disease (27 patients, 34%) had a median survival of 32 months, compared to 8.5 months in patients that would have been excluded from surgery with contemporary staging criteria (52 patients, 66%). It seems that with appropriate inclusion criteria, EPD positively affects overall survival.

After MARS2, guidelines from the National Comprehensive Cancer Network remain fairly unchanged, starting that EPD should be performed in carefully evaluated patients and that EPP may still play a role in certain cases [10]. In contrast, ASCO 2025 guidelines have updated their recommendation to state that surgical cytoreduction should not be routinely offered to all patients based solely on anatomic resectability, but rather highly selected patients with appropriate staging. In fact, a 2025 survey conducted by the Mesothelioma Center reported that over 70% of thoracic surgeons would be more selective in offering surgical treatment in light of the MARS2 trial, with 69% of physicians (both surgical and non-surgical) believing EPD still has benefits for some mesothelioma patients [11]. It seems that while a portion of physicians are convinced that surgery no longer plays a role in mesothelioma [12], most continue to be skeptical that surgery is a relic of the past.

The role of video-assisted thoracoscopic surgery (VATS) for the treatment of pleural mesothelioma remains unclear. VATS has been used in pleural mesothelioma as a treatment

for pleural effusion and in certain cases of palliation. However, literature regarding VATS pleurectomy/decortication in offering a survival benefit is sparse. There are currently no high-quality clinical trials comparing minimally invasive surgery to open surgery for the treatment of pleural mesothelioma. The most recent clinical trial, MesoVATS, examined VATS pleurectomy and decortication for patients with mesothelioma with pleural effusion, and did not find any survival benefit but rather more complications for VATS compared to talc pleurodesis [13]. Despite its utility in other cancers, using VATS to complete a thorough pleurectomy and decortication is generally challenging. An argument can be made that patients offered surgery tend to be healthier and with earlier stage cancer, in which minimally invasive surgery surgery may offset many of the complications of open thoracotomy, improving survival despite a less complete surgery. However, robust data to support this argument does not yet exist.

Hyperthermic, intrathoracic chemotherapy (HITHOC) remains a promising treatment. Systematic reviews have demonstrated this technique to be safe and feasible [14,15], while also providing increased overall survival [16,17]. A pilot study comparing VATS talc pleurodesis to VATS pleurectomy/decortication plus HITHOC in patients with early stage malignant pleuromesothelioma found a median overall survival of 15 months and 45 months, respectively. However, these results were conducted in small sample of $<$15 patients in each group [18]. Current guidelines do not prescribe HITHOC as standard of care, but rather an adjunct that can be considered in specialized centers as strong evidence remains lacking. Despite a growing body of literature reporting on the mortality benefits of HITHOC, randomized clinical trials need to be conducted to futher assess its efficacy. We remain optimistic and urge further exploration of this promising therapy.

Final Thoughts

The MARS2 trial is the first ever randomized trial to evaluate EPD in pleural mesothelioma. Their overall findings argue against EPD due to overall worse survival and more adverse events compared to chemotherapy alone. Despite this, these results should be viewed within the limitations of the trial design and patient imbalances; MARS2 cannot be used to justify the complete retirement of cytoreduction in the treatment pleural mesothelioma. Surgical cytoreduction may still benefit a well-staged, carefully selected cohort of patients, such as patients with early stage (T1–T2), epithelioid disease without nodal involvement, especially if followed by additional adjuvant chemotherapy or immunotherapy. Perhaps what the MARS2 trial has more importantly done is to call to our attention the importance of pre-operative staging and careful selection of patients within expert centers, among a multidisciplinary team. With careful selection, cytoreduction likely still plays an important role in the treatment of pleural mesothelioma.

Abbreviations

EPP, extrapleural pneumonectomy; EPD, extended pleurectomy decortication; ASCO, American Society of Clinical Oncology; VATS, video-assisted thoracoscopic surgery, HITHOC, hyperthermic, intrathoracic chemotherapy.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: MTO, JBV, KN. Literature review: MTO, KN, JBV. Synthesis of information: MTO, KN, JBV. Manuscript drafting: MTO, KN, JBV. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, *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. The Lancet. Oncology. 2011; 12: 763–772. https://doi.org/10.1016/S1470-2045(11)70149-8.

[2] Kindler HL, Ismaila N, Armato SG 3rd, Bueno R, Hesdorffer M, Jahan T, *et al*. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology. 2018; 36: 1343–1373. https://doi.org/10.1200/JCO.2017.76.6394.

[3] Woolhouse I, Bishop L, Darlison L, De Fonseka D, Edey A, Edwards J, *et al*. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. Thorax. 2018; 73: i1–i30. https://doi.org/10.1136/thoraxjnl-2017-211321.

[4] Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, *et al*. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2022; 33: 129–142. https://doi.org/10.1016/j.annonc.2021.11.005.

[5] Mangiameli G, Bottoni E, Voulaz E, Cariboni U, Testori A, Crepaldi A, *et al*. Extended Pleurectomy/Decortication for Malignant Pleu-

ral Mesothelioma: Humanitas's Experience. Journal of Clinical Medicine. 2021; 10: 4968. https://doi.org/10.3390/jcm10214968.

[6] Lim E, Waller D, Lau K, Steele J, Pope A, Ali C, *et al*. Extended pleurectomy decortication and chemotherapy versus chemotherapy alone for pleural mesothelioma (MARS 2): a phase 3 randomised controlled trial. The Lancet. Respiratory Medicine. 2024; 12: 457–466. https://doi.org/10.1016/S2213-2600(24)00119-X.

[7] Meyerhoff RR, Yang CFJ, Speicher PJ, Gulack BC, Hartwig MG, D'Amico TA, *et al*. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. The Journal of Surgical Research. 2015; 196: 23–32. https://doi.org/10.1016/j.jss.2015.01.043.

[8] Kindler HL, Ismaila N, Bazhenova L, Chu Q, Churpek JE, Dagogo-Jack I, *et al*. Treatment of Pleural Mesothelioma: ASCO Guideline Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2025; 43: 1006–1038. https://doi.org/10.1200/JCO-24-02425.

[9] Waller D, Bilancia R, Ventura L, Tenconi S, Socci L, Bille A. Why the MARS2 Trial Does Not Mean the End of All Mesothelioma Surgery. Cancers. 2025; 17: 724. https://doi.org/10.3390/cancers17050724.

[10] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Malignant Pleural Mesothelioma (Version 2.2026). 2025. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1512 (Accessed: 12 December 2025).

[11] Selby K, Rodgers T. Mesothelioma Surgery Post MARS 2 Trial: Survivor & Specialist Voices. 2025. Available at: https://www.asbestos.com/featured-stories/mars-2-mesothelioma-surgery-perspectives/ (Accessed: 26 September 2025).

[12] Lim E, Opitz I, Woodard G, Bueno R, de Perrot M, Flores R, *et al*. A Perspective on the MARS2 Trial. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2025; 20: 262–272. https://doi.org/10.1016/j.jtho.2024.12.014.

[13] Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, *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 (London, England). 2014; 384: 1118–1127. https://doi.org/10.1016/S0140-6736(14)60418-9.

[14] Ambrogi MC, Bertoglio P, Aprile V, Chella A, Korasidis S, Fontanini G, *et al*. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. The Journal of Thoracic and Cardiovascular Surgery. 2018; 155: 1857–1866.e2. https://doi.org/10.1016/j.jtcvs.2017.10.070.

[15] Burt BM, Richards WG, Lee HS, Bartel S, Dasilva MC, Gill RR, *et al*. A Phase I Trial of Surgical Resection and Intraoperative Hyperthermic Cisplatin and Gemcitabine for Pleural Mesothelioma. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2018; 13: 1400–1409. https://doi.org/10.1016/j.jtho.2018.04.032.

[16] Dawson AG, Kutywayo K, Mohammed SB, Fennell DA, Nakas A. Cytoreductive surgery with hyperthermic intrathoracic chemotherapy for malignant pleural mesothelioma: a systematic review. Thorax. 2023; 78: 409–417. https://doi.org/10.1136/thoraxjnl-2021-218214.

[17] Elsayed HH, Sharkawy HY, Ahmed MA, Abdel-Gayed M, Eldewer M. Effect of intraoperative hyperthermic intrathoracic chemotherapy after pleurectomy decortication for treatment of malignant pleural mesothelioma: a comparative study. Updates in Surgery. 2024; 76: 2893–2901. https://doi.org/10.1007/s13304-024-01986-1.

[18] Migliore M, Fiore M, Filippini T, Tumino R, Sabbioni M, Spatola C, *et al*. Comparison of video-assisted pleurectomy/decortication surgery plus hyperthermic intrathoracic chemotherapy with VATS talc pleurodesis for the treatment of malignant pleural mesothelioma: A pilot study. Heliyon. 2023; 9: e16685. https://doi.org/10.1016/j.heliyon.2023.e16685.