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REVIEW ARTICLE

Reassessing Surgical Strategy After MARS 2: A Focused Critical Review

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ABSTRACT

The MARS 2 trial is a landmark phase III randomized study comparing extended pleurectomy/decortication plus chemotherapy with chemotherapy alone in malignant pleural mesothelioma (MPM). In its final report, the surgical strategy was associated with shorter survival, a higher rate of serious adverse events, and worse outcomes in terms of quality of life and cost-effectiveness. These findings are directly relevant to contemporary thoracic oncology practice and should inform discussions of surgery with patients and multidisciplinary teams. This focused critical review examines MARS 2 through its final randomized report, the trial protocol, prior randomized studies of mesothelioma surgery, major international guidelines, and selected post-publication commentary identified through a targeted review of indexed literature and guidelines up to March 2026. Post-publication correspondence and thoracic surgical commentary are considered primarily to identify recurring concerns regarding applicability and external validity, rather than as evidentiary equivalents to randomized data. The available level I evidence does not support the routine use of extended pleurectomy/decortication within the treatment pathway evaluated in MARS 2. At the same time, the trial should not be reduced to an oversimplified “no surgery ever” message, as the remaining uncertainties relate to generalizability rather than to a reversal of the main randomized findings. The most appropriate interpretation is therefore both practice-changing and methodologically rigorous: strengthening evidence-based patient counseling in the present, while guiding the design of more precise future trials in carefully staged and highly selected populations.

Keywords: malignant pleural mesothelioma, MARS 2, pleurectomy decortication, surgery, multidisciplinary care.

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1. INTRODUCTION

Malignant pleural mesothelioma remains an aggressive thoracic malignancy with poor long-term outcomes and a persistent need for treatment strategies that balance survival, toxicity, and quality of life. The surgical debate in mesothelioma has been especially contentious because much of the historical evidence has come from retrospective series and institutional experience rather than randomized trials [1-4]. The MARS 2 program was developed specifically to address this evidence gap for pleurectomy/decortication in a contemporary multimodality setting [5,6].

The MARS 2 protocol framed the study as a pragmatic randomized comparison of surgery plus chemotherapy versus chemotherapy alone, with overall survival as the primary endpoint and secondary outcomes including safety, progression-free survival, health-related quality of life, and resource use [6]. It also incorporated features that are particularly important in surgical oncology trials, including site eligibility standards, surgeon accreditation and quality assurance, and the QuinteT Recruitment Intervention to support recruitment and informed consent [6,7].

The final MARS 2 publication has had a major impact because it reported a negative result for the surgical strategy. Yet interpretation of that result has generated substantial debate. Some clinicians have treated MARS 2 as closing the door on mesothelioma surgery, whereas others have argued that it mainly rules out routine surgery in a broad population and does not definitively settle the question in highly selected patients [5,8-14]. This distinction is not merely theoretical; it affects referral patterns, patient counseling, and future research design, and it must be interpreted alongside contemporary multidisciplinary mesothelioma care frameworks [15-19].

The aim of this review is not to relitigate the trial, but to clarify what MARS 2 establishes, what remains uncertain, and how its findings should be applied responsibly in clinical practice. Particular attention is given to the hierarchy of evidence: the final randomized report provides the foundation for efficacy and safety conclusions, while guidelines and post-publication commentary are used to contextualize implementation and generalizability rather than to counterbalance level 1 evidence [5,6,15-19].

2. METHODS

This manuscript is a focused critical review. A targeted, non-systematic literature review was undertaken up to March 2026 to identify sources directly relevant to interpretation of the MARS 2 trial. Priority was given to the MARS 2 final randomized report and trial protocol, prior randomized mesothelioma surgery studies, major international mesothelioma guidelines, consensus documents on surgical definitions, and direct post-publication editorials or correspondence specifically addressing the interpretation of MARS 2 [5,6,15-22].

Sources were included if they informed at least one of three predefined objectives: (1) characterization of the randomized evidence base for surgery in pleural mesothelioma, (2) contextualization of MARS 2 within contemporary multidisciplinary care, or (3) appraisal of external-validity concerns raised after publication of the trial. Duplicate publications and sources not directly relevant to these objectives were not retained. Post-publication commentary was analyzed to identify recurrent concerns about applicability, staging, operative extent, and treatment-pathway asymmetry, but these publications were not treated as evidentiary equivalents to randomized trials or guidelines [8-14].

Because the purpose of the review is interpretive rather than quantitative, no formal meta-analysis or risk-of-bias scoring was undertaken. The review therefore retains the strengths and limitations of a focused narrative synthesis while making the search logic and source-selection approach explicit.

3. WHAT MARS 2 WAS DESIGNED TO TEST

The MARS 2 protocol is explicit about the clinical uncertainty it sought to resolve. It notes that pleurectomy/decortication, including extended pleurectomy/decortication, was being offered despite the absence of randomized evidence demonstrating a survival or cost-effectiveness advantage over chemotherapy alone [6]. The trial therefore addressed a clear and clinically relevant question: does adding (extended) pleurectomy/decortication to chemotherapy improve outcomes compared with chemotherapy alone in suitable patients with pleural mesothelioma [6]?

The protocol's strengths are important because they shape the credibility of later interpretation. MARS 2 was multicentre, pragmatic, and designed around endpoints that reflect real-world decision-making: survival, serious adverse events, quality of life, and cost-effectiveness [6]. It also anticipated common problems in surgical randomization, particularly patient preconceptions and recruitment barriers, by integrating the QuinteT Recruitment Intervention [6,7]. The protocol also attempted to standardize surgical quality. Participating centers required mesothelioma multidisciplinary team infrastructure, and surgeons were subject to accreditation and observation requirements to support procedural fidelity [6]. This does not eliminate all variability, but it substantially strengthens the trial against the routine criticism that an unfavorable surgical result simply reflects poor technical performance.

At the same time, the study was intentionally pragmatic, and pragmatism comes with heterogeneity. The protocol allowed some flexibility in treatment pathways across sites and included a broad mesothelioma population, which later became central to external-validity critiques [6,12-14].

4. WHAT MARS 2 SHOWED

In the final report, Lim et al. randomized 335 patients after initial chemotherapy, with 169 assigned to surgery plus chemotherapy and 166 to chemotherapy alone [5]. At a median follow-up of 22.4 months, median overall survival was 19.3 months in the surgery arm versus 24.8 months in the chemotherapy-alone arm, with a statistically significant difference in restricted mean survival time at 2

years favoring chemotherapy alone [5]. This is the core result and should anchor all interpretation. The safety findings were equally important. The trial reported 318 serious adverse events in the surgery arm versus 169 in the chemotherapy-alone arm, corresponding to an incidence rate ratio of 3.6 [5]. The excess harms included more cardiac, respiratory, and infectious complications, as well as more additional procedures [5]. These are highly clinically relevant events in a population that often has limited physiologic reserve.

The broader interpretation also favored the non-surgical pathway when patient-centered and health-system outcomes were considered. MARS 2 reported worse patient-reported quality of life, fewer quality-adjusted life years, and higher costs with surgery, with surgery not considered cost-effective [5]. This consistency across survival, toxicity, quality of life, and economic outcomes is one reason MARS 2 is more than a narrowly negative trial; it shows a net disadvantage for the tested strategy.

The implication is straightforward: MARS 2 cannot reasonably be described as merely inconclusive. In the population and treatment pathway studied, adding (extended) pleurectomy/decortication did not improve outcomes and was associated with harm [5].

Table 1. Key findings of the MARS 2 trial.

Domain	Main finding	Interpretive significance
Design	Phase 3 multicentre randomized comparison of (extended) pleurectomy/decortication plus chemotherapy versus chemotherapy alone in pleural mesothelioma [5-6]	Provides level 1 evidence for the tested multimodality pathway.
Survival	Median overall survival was 19.3 months with surgery versus 24.8 months with chemotherapy alone; restricted mean survival time at 2 years favored chemotherapy alone [5]	The primary efficacy signal does not support routine addition of surgery.
Serious adverse events	318 serious adverse events in the surgery arm versus 169 in the chemotherapy-alone arm; incidence rate ratio 3.6 [5]	The surgical strategy imposed a substantial morbidity burden.
Quality of life	Patient-reported quality-of-life outcomes were worse in the surgical arm [5]	Harms extended beyond perioperative events to patient-centered outcomes.
Economic evaluation	Fewer quality-adjusted life years and higher costs with surgery; the strategy was not cost-effective in the trial setting [5]	The trial challenges routine use of surgery from both clinical and health-system perspectives.
Overall message	Within the tested pathway, extended pleurectomy/decortication did not improve outcomes and was associated with net disadvantage [5]	Interpretation should begin from the randomized result, not from retrospective precedent.

Note. Abbreviation: MARS 2, Mesothelioma and Radical Surgery 2.

5. WHY MARS 2 IS STRONG EVIDENCE

MARS 2 should be treated as high-level evidence because it addresses a question that had previously been dominated by retrospective series, surgical experience, and feasibility studies rather than definitive randomized comparisons [1-4,20-21]. By design, it directly addresses the longstanding evidence gap for extended pleurectomy/decortication in malignant pleural mesothelioma [5-6].

The trial also has notable methodological strengths beyond randomization. It was multicentre, used intention-to-treat analysis, employed objective survival endpoints, and included prespecified secondary outcomes that matter to patients and health systems [5-6]. In addition, the protocol documented formal surgical quality assurance and recruitment optimization processes, both of which strengthen interpretability in a difficult surgical oncology setting [6-7]. For these reasons, critique should refine the scope of application of MARS 2 rather than downgrade it to the same evidentiary level as non-randomized practice patterns.

6. INTERPRETATION CHALLENGES AND EXTERNAL VALIDITY

The main controversy after MARS 2 is not whether the trial result exists, but how broadly it should be generalized. The most frequently cited concerns in post-publication discussion relate to patient selection, staging intensity, operative burden, and treatment-pathway asymmetry [8-14]. These publications are useful because they identify recurring concerns about applicability; they should not, however, be interpreted as counter-evidence to the randomized trial itself.

The most recurrent issue is patient selection. Commentators have argued that eligibility criteria were broadened to support recruitment, potentially allowing inclusion of non-epithelioid and more advanced cases that many expert centers would not routinely select for surgery today [9-14]. This is best understood as an external-validity concern, not a refutation of the trial's internal validity.

Related critiques focus on staging. Contemporary specialist practice often relies on intensive staging, including PET-CT and invasive nodal assessment, to reduce understaging and refine selection [15-19]. A key concern raised after MARS 2 is that less intensive staging in some trial-era pathways may have increased the likelihood of operating on patients with unfavorable disease biology or nodal burden [12-14]. Whether or not this fully explains the observed survival difference, it is a legitimate generalizability issue.

Another point is operative burden. Consensus and specialist literature recognize that the extent of pleural mesothelioma surgery varies and that additional diaphragm or pericardial resection may substantially affect postoperative morbidity [22-23]. This concern is clinically plausible and is consistent with the adverse-event pattern reported in MARS 2, which showed major excesses in respiratory, cardiac, and infectious serious adverse events [5].

A further issue concerns asymmetry in postoperative systemic therapy and evolving access to immunotherapy. Some post-publication analyses have argued that patients in the surgical arm may have been less able to complete or resume systemic therapy, whereas the non-surgical pathway may have allowed more timely access to later-line treatments in an evolving immunotherapy era [12-14,24]. Even if this is interpreted as part of the real-world effect of choosing surgery, it means MARS 2 is best understood as a test of a multimodality strategy pathway rather than as a pure biological test of surgical cytoreduction alone.

Taken together, the most defensible synthesis is that MARS 2 provides strong evidence against routine use of (extended) pleurectomy/decortication in a broadly defined operable population treated through the tested pathway [5-6]. It does not establish that surgery benefits a narrower, rigorously staged subgroup; rather, it leaves that question unresolved and investigational [12,14-18].

Table 2. Main post-publication concerns about MARS 2 and their interpretive status.

Concern	Why it matters	Interpretive status in this review
Patient selection	Broader eligibility may have included patients whom some expert centers would not currently select for surgery [9-14]	Legitimate external-validity concern; does not negate the trial's internal randomized result.
Staging intensity	Less intensive staging may increase understaging and impair selection for aggressive surgery [12-19]	Supports caution in generalization; does not convert negative level 1 evidence into positive evidence.
Operative burden	Variation in extent of resection, including diaphragm/pericardial procedures, may influence morbidity [22-23]	Clinically plausible explanation for part of the observed excess harm; still consistent with the trial's reported outcomes.
Systemic therapy asymmetry	Surgery may delay or reduce completion of systemic therapy and later-line access [12-14,24]	Important for interpreting MARS 2 as a pathway trial rather than a pure cytoreduction experiment.
Guideline interpretation	Guidelines continue to emphasize multidisciplinary evaluation despite the negative trial [15-19]	Supports specialist triage and individualized discussion, not routine use of surgery.

Note. The concerns summarized above are treated as questions of applicability and implementation rather than as evidentiary equivalents to the randomized trial.

7. CLINICAL PRACTICE IMPLICATIONS

The immediate clinical implication is that extended pleurectomy/decortication should no longer be presented as a routine or default option for broadly resectable pleural mesothelioma. Patients should be informed that the best available randomized evidence showed shorter survival, greater serious morbidity, worse quality of life, and inferior cost-effectiveness for the surgical pathway tested in MARS 2 [5]. This should directly influence informed consent and multidisciplinary recommendation-making.

At the same time, a negative surgical trial does not eliminate the need for thoracic surgical expertise within mesothelioma multidisciplinary teams. Current guidelines continue to emphasize structured multidisciplinary assessment, careful staging, histologic characterization, and coordination of systemic therapy [15-19]. In practical terms, MARS 2 supports a more disciplined pathway: early referral to an experienced mesothelioma MDT, priority to evidence-based systemic treatment strategies, and discussion of surgery only in highly selected circumstances that remain investigational rather than standard-of-care.

Economic interpretation also requires contextual caution. MARS 2 found the surgical strategy not to be cost-effective within the trial setting [5], but the transferability of economic estimates across health systems is inherently limited. Access to specialized thoracic surgery platforms, perioperative critical care, postoperative rehabilitation, and subsequent systemic therapies varies widely across institutions and countries. In settings with constrained specialist infrastructure, the practical barriers to safely delivering complex mesothelioma surgery may be even greater, which reinforces caution rather than supporting routine expansion. Conversely, numeric cost-effectiveness estimates derived in one system should not be assumed to apply identically to all care environments.

8. FUTURE RESEARCH AFTER MARS 2

MARS 2 is a landmark trial, but it should not end mesothelioma surgery research altogether. The more constructive post-MARS 2 question is whether a substantially narrower subgroup, defined by favorable histology, earlier stage, rigorous nodal staging, and contemporary multimodality sequencing, might have a different risk-benefit profile [5-6,12,14]. At present, that question remains a research question rather than a routine-care conclusion.

Any future trial should therefore use stricter eligibility criteria and clearer pathway standardization. Candidate design elements include restriction to epithelioid histology or stratified randomization by histology, mandatory contemporary staging including PET-CT and invasive nodal assessment where indicated, and objective fitness criteria [15-19]. These refinements directly address the major external-validity concerns raised after MARS 2.

Future studies should also minimize asymmetry in systemic therapy delivery. One of the key interpretive controversies in MARS 2 is whether the surgical arm's reduced ability to complete or resume systemic therapy contributed materially to the survival disadvantage [5]. Next-generation trials should protocolize perioperative systemic therapy more tightly, incorporate immunotherapy-era standards, and prospectively capture treatment completion, treatment delays, and time to treatment resumption [15-16,24].

Surgical standardization should be strengthened as well. MARS 2 already incorporated surgeon quality safeguards [6], but future studies could further define operative extent, perioperative management, and pathology reporting standards to reduce heterogeneity across centers [22,23]. As in MARS 2, overall survival should remain central, but serious adverse events, quality of life, functional recovery, and cost-effectiveness must remain integral endpoints in this disease [5].

9. LIMITATIONS OF THIS REVIEW

This manuscript is a focused critical review, not a systematic review or meta-analysis, and it does not include individual patient-level reanalysis. Its purpose is interpretive: to synthesize the randomized evidence, place it in the context of current guidelines, and clarify how clinicians should apply MARS 2 in practice [5,6,15-18].

A second limitation is that some contextual arguments in the post-MARS 2 debate derive from editorials, correspondence, and expert commentary rather than comparative peer-reviewed studies [8-14]. For that reason, these sources are used here to identify recurring concerns about generalizability and implementation, but not to outweigh the trial's efficacy and safety findings. Those conclusions remain grounded primarily in the final MARS 2 report and the protocol that framed the tested strategy [5,6].

10.CONCLUSION

MARS 2 is practice-changing randomized evidence in malignant pleural mesothelioma. Within the population and pathway tested, adding (extended) pleurectomy/decortication to chemotherapy was associated with shorter survival, substantially more serious adverse events, worse patient-reported outcomes, and poorer cost-effectiveness than chemotherapy alone [5]. The available level 1 evidence therefore does not support routine use of extended pleurectomy/decortication as a default option for broadly operable disease. At the same time, the remaining uncertainties after MARS 2 concern generalizability rather than reversal of the main trial result. The appropriate response is not polarization, but precision: evidence-based counseling now, continued multidisciplinary evaluation, and any residual surgical role confined to carefully selected investigational settings that are better defined in future trials [12,14-18].

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