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COMMENTARY

# The Role of Surgery in Pleural Mesothelioma: A Journey through the Evidence, MARS 2 and Beyond

Avinash Aujayeb · Philippe Astoul · Francesco Londero · Andrea Zuin

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## ABSTRACT

Pleural mesothelioma (PM) is a rare incurable disease, predominantly linked to asbestos exposure. Not only is diagnosis difficult, but treatment choices are often limited to systemic anti-cancer treatment with chemotherapy or immunotherapy. Surgery has been employed for decades, but its application has been fiercely debated despite some randomized controlled trials such as the recent Mesothelioma and Radical Surgery 2 (MARS 2) study. We provide a commentary on this controversial topic.

**Keywords:** Pleural mesothelioma; Surgery; MARS 2; Pleurectomy; Pneumonectomy; Chemotherapy; Immunotherapy

A. Aujayeb (✉)
Respiratory Department, Northumbria Health Care NHS Foundation Trust, Care of Gail Hewitt, Newcastle NE23 6NZ, UK
e-mail: avinash.aujayeb@nhct.nhs.uk

P. Astoul
Department of Thoracic Oncology, Pleural Diseases and Interventional Pulmonology, North Hospital, Aix-Marseille University, Marseille, France

F. Londero · A. Zuin
Thoracic Surgery Unit, Cardiothoracic Department, University Hospital of Udine, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy

***Key Summary Points***

The Mesothelioma and Radical Surgery (MARS) trial has shown that extra-pleural pneumonectomy (EPP) for pleural mesothelioma (PM) is associated with higher morbidity and mortality when compared to extended pleurectomy/decortication (EP/D).

Observational data have shown that patients with PM might have better overall median survival with EP/D if epithelioid histology is present and patients are carefully selected with extensive preoperative staging.

The MARS 2 study has shown worse survival at 2 years with EP/D compared with chemotherapy alone, but the findings are contested.

Various guidelines still recommend surgery as part of a multimodal approach to PM.

## INTRODUCTION

Pleural mesothelioma (PM), previously known as malignant pleural mesothelioma, is an aggressive incurable cancer. Whilst any serosal surface can be affected, the pleural surfaces are involved in 80% of cases. The average patient is male, between 70 and 80 years of age, and usually has a history of occupational exposure to asbestos, which is the

main causative agent of PM [1]. There are a few distinct subtypes of PM, as defined by the World Health Organization—these are epithelioid, sarcomatoid and biphasic patterns, which are defined by their histological appearance (biphasic being a mixture of the other two patterns) [2].

There are several uses of surgery in the diagnosis and management of PM.

Initially, the diagnosis could be obtained via a video thoracoscopic biopsy with simultaneous management of any pleural fluid that might be present (over 90% of cases of PM are associated with fluid). Staging concerns might be addressed by performing mediastinoscopy (and biopsy) to assess whether nodal disease is present [3]. Surgery for treatment of PM has involved pneumonectomy, pleurectomy and decortication, with one of the first formal case series documented in the 1970s [4]. The rates of trapped lung (restriction of visceral expansion) in PM are approximately 33%, and surgery via partial pleurectomy for this problem was investigated in a previous randomized controlled trial (RCT), showing no survival advantage [5]. Cytoreductive surgery has also been described in the literature [6], but the development of immunotherapy has been a game changer overall [7].

In this paper, we will concentrate on the evidence of surgery for the treatment of PM; this will include extra-pleural pneumonectomy (EPP) and extended pleurectomy/decortication (EP/D), with a critical appraisal of selected literature around recent RCTs, specifically the MARS 2 trial [8]. This will be a narrative review and authors' expert opinion and practice. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## WHAT DO THE GUIDELINES AND CURRENT EVIDENCE SAY ABOUT SURGERY IN PM?

The evidence over the years has been mixed. Typically, as mentioned above, two types of surgery have been offered for PM—EPP and EP/D. EPP, the removal of the pleura, the lung, the pericardium and the hemidiaphragm 'en bloc', was assessed in a study investigating the effects of EPP versus no EPP for patients with PM—the Mesothelioma and Radical Surgery (MARS) trial [9]. A total of 24 patients were assigned to EPP and 26 to no EPP (83% and 77% of cases had epithelioid histology, respectively, in those groups), with results showing no overall survival (OS) advantage, an increased risk of death and poorer quality of life with EPP. A few years later, however, the 2018 American Society of Clinical Oncology (ASCO) mesothelioma guidance recommended curative-intent surgery with maximal cytoreduction for those with early-stage epithelioid disease [10]. That statement was borne out from analysis of the SEER (Surveillance, Epidemiology, and End Results) database, where the median survival, post-surgery, of patients with epithelioid disease was 19 months, while it was 12 months for patients with biphasic disease and 4 months for patients with sarcomatoid disease [11]. More recently, Bou-Samra et al. analysed 41,074 patients with PM between 2004 and 2017 [12]. They found that patients with PM (any histological subtype) who underwent surgery had a median survival of 19.8 months (95 CI 19.2–20.3) versus 7.9 months (95% CI 7.8–8.1) in the non-surgical group ($p < 0.001$). There was no reporting of outcomes for specific histological subtypes. More recently, Nakamura et al. retrospectively analysed 272 patients undergoing surgery [13]. Among them, 204 (75.0%), 43 (15.8%) and 25 (9.2%) patients underwent P/D, EPP and exploratory surgery, respectively. Over a median follow-up of 28.4 months, the median OS period was 40.7 months (95% CI 32.2–45.6 months), and over 95% of the patients had epithelioid histology.

Whilst the 2018 ASCO guidance recommends surgery, the joint European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) 2020 guidance on the management of PM suggests that only a very select group of patients should be chosen for radical surgery, and that surgery should only be performed in high-volume centres in clinical trials and as part of a multimodal approach [14]. The original MARS trial was reviewed, as well as a review by Bovolato where patients

with good performance status and epithelioid histology had better outcomes [15]. The 2018 British Thoracic Society guidance suggested not offering EPP in PM and not offering extended P/D outside of a clinical trial [3]. The latest guidance from the National Comprehensive Cancer Network is broader [16]. The concept of medically operable epithelioid PM is discussed in clinical stages of I–IIIA after induction chemotherapy (pemetrexed/cisplatin or carboplatin), evaluation of nodal disease with positron emission tomography (PET) scanning and surgical exploration to determine whether resection is possible.

### Surgery as a Palliative Treatment

Apart from its role in radical treatment, surgery may also be considered as a palliative treatment in patients with PM in several conditions as briefly mentioned above. Dyspnoea is the main symptom at presentation in patients with PM, usually due to pleural effusion [1]. With disease progression, the visceral pleura can be extensively infiltrated by tumour, and the underlying parenchyma loses its ability to properly expand—so-called trapped lung. Surgery has been appraised as a palliative treatment in the MesoVATS (video-assisted thoracoscopic (VATS) partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma) trial [5]. A total of 87 patients were randomized to partial pleurectomy by VATS and 88 to talc pleurodesis; surgery was associated with increased rates of respiratory complications and longer hospital stay. There was no survival advantage at 12 months, leading to the conclusion that surgical debulking does not offer any advantage in a palliative setting. When lung expansion is hampered by the presence of a thickened visceral pleura, talc pleurodesis is usually ineffective. There is currently no randomized trial evidence to inform practice, and the 2010 ERS and ESTS guidelines recommend surgical debulking, preferably through a VATS approach, to favour lung re-expansion [17]. This has not been modified in the latest reviewed guidelines [18], but it is worth considering that other less invasive measures, such as indwelling pleural catheters (IPC), might be contemplated in this context, as they are more readily available and can be placed by respiratory physicians [3]. IPCs can provide a patient-centred approach to managing malignant pleural effusions and improve quality of life. They can also induce pleurodesis, with or without talc application, thus allowing their ultimate removal [19]. The MesoTRAP is a feasibility study that is currently evaluating the effectiveness of IPC versus VATS pleurectomy/decortication in patients with PM, and results are pending.

## WHAT IS THE CONTROVERSY AROUND THE MARS 2 TRIAL?

The MARS 2 trial was thus designed to answer the question regarding the role of EP/D in providing a survival benefit in patients with PM [20]. EP/D adds the resection of the diaphragm and/or pericardium in the case of visible lesions, with an effort to trend to a complete resection, which can be a challenge due to the nature of the PM [21–23]. After two cycles of chemotherapy, eligible participants with PM were randomly assigned (1:1) to surgery and chemotherapy or chemotherapy alone. Patients with resectable PM and adequate preoperative exhaustive functional assessment were enrolled. Participants in the chemotherapy-only group received two to four further cycles of chemotherapy, and participants in the surgery and chemotherapy group received PD or E/PD, followed by two to four further cycles of chemotherapy. The results of this phase III trial enrolling 355 patients showed worse survival for those undergoing surgery up to 2 years, and more serious adverse events for those individuals with PM undergoing surgery compared with chemotherapy alone [8]. The results have been fiercely contested, and the debate has reignited the complex issues around the surgical treatment of PM.

At the core of the trial's controversy is its primary finding: EPD, a lung-sparing surgery aimed at cytoreductive treatment only, did not confer a survival benefit over chemotherapy alone. On the contrary, the median survival was shorter for the surgery group (19.3 months)

than for the chemotherapy-alone group (24.8 months). Furthermore, the surgery group experienced significantly more serious adverse events, including a threefold increase in complications such as cardiac and respiratory disorders [8]. This outcome challenges the traditional belief that surgical interventions improve survival in selected patients with PM, a cornerstone of treatment in many guidelines [24–26]. Critics of the MARS 2 trial's conclusions argue that the study design and execution may have influenced the results. One major point of contention is patient selection. The trial included patients with epithelioid and non-epithelioid subtypes of mesothelioma, despite the poorer prognosis associated with non-epithelioid disease. Some argue that this inclusion may have diluted the potential benefits of surgery, as non-epithelioid cases comprised a small but potentially impactful proportion of the cohort. Furthermore, staging protocols were criticized for relying predominantly on computed tomography (CT) scans without mandatory PET-CT or invasive mediastinal staging; however, the role of PET-CT for the diagnosis of pleural mesothelioma is controversial [27–29]. Such approaches might have led to the inclusion of patients with more advanced disease, reducing the likelihood of surgical success. It is important to note that when staging was only based on contrast-enhanced CT, 44% of patients considered with clinical T1 disease underwent EPD. This more aggressive surgery in comparison to PD can perhaps explain a higher perioperative mortality when taken with other factors such as the variability in surgeon experience and procedural protocol adherence, which could have affected outcomes. Indeed, it should be noted that in the MARS 2 trial, the high perioperative mortality rate of 9% at 3 months far exceeded the rates typically reported in other studies, raising concerns about procedural execution and postoperative care [25, 26]. This mortality rate, coupled with the significant morbidity observed, likely skewed the OS statistics, suggesting that the results might not apply to more controlled or experienced surgical environments. The type of surgery performed (with diaphragmatic resection) has also been deemed too invasive, and could have caused the increased mortality.

The timing and methodology of randomization can also be questioned. Randomization occurred after two cycles of chemotherapy, which might have introduced selection bias. Patients who tolerated chemotherapy poorly or exhibited disease progression were excluded, potentially creating an imbalance in baseline characteristics between groups. Additionally, while the intention-to-treat analysis accounted for such factors, the inclusion of patients with stable or responding disease at randomization might have inherently favoured chemotherapy over surgery. Another issue is that perhaps the study highlights the need for better patient selection rather than refuting the utility of surgery entirely [30, 31]. This evidence is illustrated by the selection of patients who had undergone surgery with T3 disease (35%: invasion of endothoracic fascia; 52%: extension into mediastinal fat; 31%: tumour extended into soft tissue of chest wall; 28%: involvement of pericardium), N2 disease (8%) and M1 disease (4%).

Figures 1 and 2 show the survival and quality of life scores from the MARS 2 trial.

## IMPLICATIONS FOR THE FUTURE

Despite the MARS 2 trial findings, we believe that the role of surgery should not be definitively ruled out for the management of PM. In light of the many controversies of the protocol, there are strong opinions being voiced that the MARS 2 trial does not offer convincing evidence that surgery harms patients but rather that patient selection is of paramount importance to surgically treat only those who may really benefit from such an aggressive treatment [30].

Vigorous debate exists around the selection of patients for surgery: some might argue that there is an inherent bias of retrospective studies which accounts for the favourable outcome figures in many surgical series and that the reported median survival does not differ significantly from that of patients treated with non-surgical modalities [31]. By contrast, some single-arm prospective protocol or single-institutional retrospective studies describe higher rates of long survivors after accurate selection

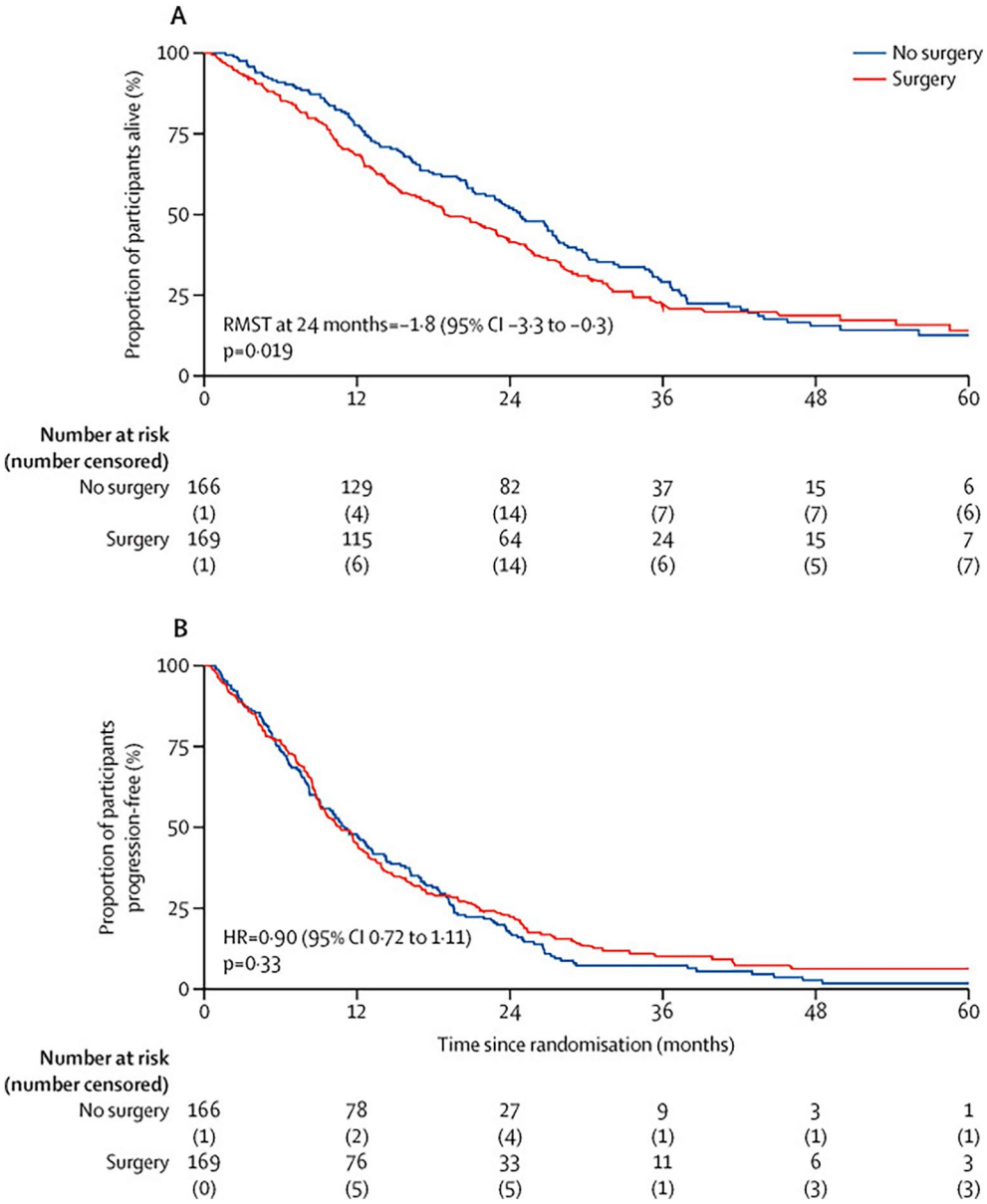


**Fig. 1** **A** Median survival: surgery 19.3 months (interquartile range [IQR] 10.0–33.7), no surgery 24.8 months (12.6–37.4). Survival probabilities at 24 months: surgery 0.41 (95% confidence interval [CI] 0.34–0.49), no surgery 0.52 (0.44–0.59). **B** Median progression-free survival: surgery 10.6 months (IQR 6.3–21.6), no surgery 11.0 months (5.9–19.6). Survival probabilities at 24 months: surgery 0.22 (95% CI 0.16–0.29), no surgery 0.17 (0.12–0.24). *HR* hazard ratio, *RMST* restricted mean survival time

and multimodal protocols employing chemo- and radiotherapy [32, 33]. Criticisms against patient selection in PM are indeed highly debatable: patients with lung cancer are strictly selected before considering a surgical indication, from both the staging and functional point of view. Even selecting surgical candidates based on the histology (and in PM it would be epithelioid versus sarcomatoid) is frequently done in other contexts, including lung cancer. As described above, the MARS 2 trial is criticized for including patients with sarcomatoid PM or

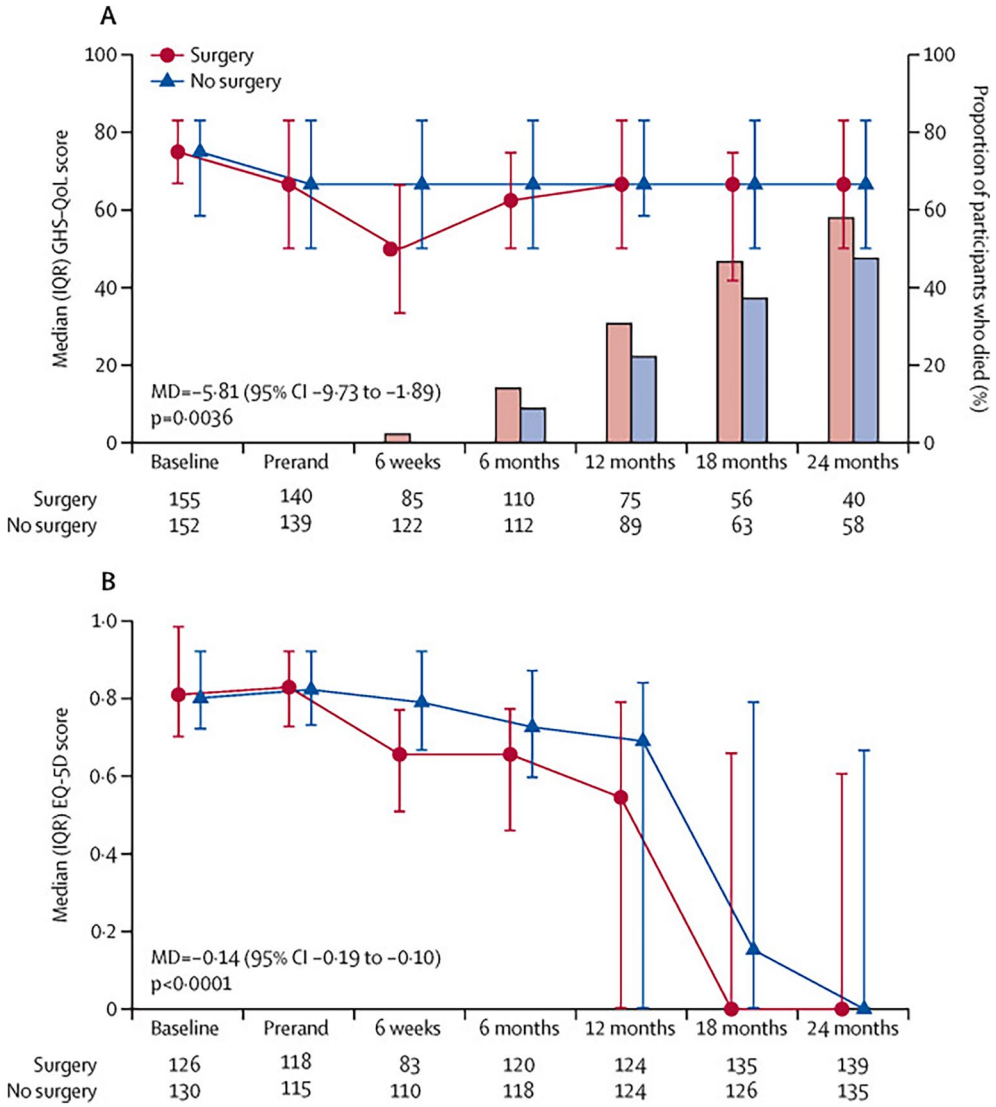


**Fig. 2** QLQ-C30 GHS–QoL scores range from 0 to 100; higher scores indicate better health. For EQ-5D, scores range from −0.594 to 1; higher scores indicate better quality of life, and death has a score of zero. *GHS–QoL* global health status–quality of life, *MD* mean difference, *Prerand* pre-randomization, *QLQ-C30* European Organisation for Research and Treatment of Cancer core health-related quality of life questionnaire

with advanced stages of disease. Moreover, one of the issues regarding PM is the frequent pathological upstaging after surgery, which accounts for the high rates of relapses and short survival rates, and as previously described, another point of concern against the MARS 2 results was that patients' restaging relied on CT scan only, a factor that might have contributed to operating on patients with more advanced disease.

Emerging tools in the field of imaging techniques could help to identify patients who stand to benefit from surgery in specialized, high-volume centres to minimize procedural risks and optimize outcomes. This careful and appropriate preoperative staging combined with newer systemic therapeutic modalities including immunotherapy [34, 35] or potential intrapleural therapy might alter patients' survival [36]. The assumption of a 'radical' resection is often

disproved by the incidence of local recurrence and development of distant metastasis [37]. This is probably due to microscopic residual disease or malignant cells seeding during the surgical procedure. It has been shown how malignant cells have this capability as a consequence of surgical manipulation, and this accounts for the development of recurrence even within the drainage tube tracts or in the peritoneal cavity following diaphragm excision [31, 37]. From this perspective, the employment of intraoperative adjuvant agents that act against microscopic residual disease might be a game changer for the pattern of local recurrence following cytoreductive surgery. Accordingly, several reports document improved OS in selected patients with intraoperative hyperthermic intrathoracic chemotherapy perfusion (HITHOC) following PD [38, 39]. The principle of this practice lies in the observation that heated chemotherapeutic drugs can increase their cytotoxic activity and penetration into residual malignant cells, while the systemic absorption is reduced. However, the pharmacokinetics of such drugs, for example cisplatin, warrant further study, although there is some evidence that drug-related adverse events might be reduced [40–42]. The potential benefits of HITHOC reside in increasing the cytoreductive effect of surgery while preserving a better quality of life compared with more radical resection, thus conceivably favouring the adherence to further postoperative treatments. However, to the best of our knowledge, these results are based on small retrospective series, and the efficacy of this procedure, as well as other intrapleural treatment, should be properly assessed in adequately powered randomized trials. Other therapeutic challenges have emerged in recent years, thanks to the evident progress in oncology offered by the introduction of novel biologic drugs, namely immunotherapy. In the setting of PM, several ongoing trials are assessing the potential benefits of a multimodal treatment including chemo-immunotherapy and surgery. The AtezoMeso study is currently evaluating the introduction of atezolizumab in patients with PM after PD and platinum/pemetrexed perioperative therapy in a double-arm phase III trial [43], and results are pending. In another Italian prospective phase II trial, researchers are testing the effect of pembrolizumab in combination with pemetrexed and cisplatin or carboplatin as neoadjuvant therapy followed by surgery and adjuvant pembrolizumab in patients affected by resectable stage I–IIIa epithelioid/biphasic PM [44]. Moreover, an interesting perspective would be to evaluate in humans the synergistic effect of RT and immunotherapy in the perioperative period as observed in animal models [45].

Eventually, the MARS 2 trial concluded that EP/D was associated with higher costs and fewer quality-adjusted life years than chemotherapy alone. These findings have implications for health systems and policymakers, particularly in resource-constrained settings, but perhaps more targeted patient selection might negate that effect.

Therefore, we argue that there will probably still be a role for surgery for PM in a multimodal setting, which will likely be enriched by the introduction of novel molecular therapies and tailored irradiation delivery protocols. The wide variability of treatments currently under appraisal will probably lead to a further personalization of therapies for PM, with a better selection of patients who may benefit the most from aggressive surgical resection.

At this point, it is worth noting what other treatments are available for patients with PM. It has been widely accepted that patients with PM with good performance status (PS) and no contraindications should be offered a combination of cisplatin and pemetrexed as first treatment [45]. The Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) demonstrated a 2-month OS benefit when the antiangiogenic drug bevacizumab was added to the systemic regime [46]. However, this drug still lacks approval from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). After the advent of immunotherapy, the most noteworthy innovation in the treatment of PM is represented by the association of the anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) ipilimumab and anti-programmed cell death protein 1 (PD-1) nivolumab. Two phase II trials—MAPS2 [47] and INITIATE [48]—have demonstrated promising results with this combination immunotherapy, which were later

confirmed by the Checkmate 743 trial [7]. As such, combination immunotherapy is often the first-line treatment for patients with PM with good PS.

Hemi-thoracic radiotherapy (RT) in the perioperative setting has been employed in several research protocols. The SAKK trial, which was prematurely concluded due to poor accrual, showed no significant survival advantage in patients who received high-dose radiotherapy rather than observation after induction chemotherapy and EPP [49]. Conversely, the Surgery for Mesothelioma After Radiation Therapy (SMART) trial, a phase I/II study, displayed encouraging results with a protocol of neoadjuvant intensity-modulated RT (IMRT) followed by EPP within 1 week [30]. While larger experiences are needed to confirm these results, neoadjuvant radiotherapy is currently an accepted treatment modality in patients undergoing non-lung-sparing resections [10]. In addition, the role of RT has also been appraised in the case of less extensive resections, such as PD/EPD. Minatel et al. demonstrated that PD followed by IMRT led to encouraging survival rates of 65% at 2 years, favouring a potential shift towards less impactful surgical protocols [50].

Attention is increasingly focused on the role of RT in the treatment of PM after the introduction of immunotherapy. Indeed, the most recent RT protocols rely on hypofractionated radiation delivery, which induces a large release of tumour-associated antigens and a significant immune response activation [51]. Some authors have argued that the immunogenic effect of hypofractionated RT might be responsible for the improved survival figures using the SMART protocol and that adding an immune checkpoint inhibitor-based treatment following RT may improve the therapeutic effect of surgical resection [46]. To date, this speculation is based on animal studies only, but they may represent an interesting perspective for phase II/III studies.

## CONCLUSION

The MARS 2 trial has undoubtedly advanced the discourse on treating PM by providing randomized data, but the debate about the methodological flaws will continue until further trials of surgery in patients with PM are performed with more refined criteria, such as only operating on patients with epithelioid histology with limited-stage disease and perhaps diaphragm-sparing operations. The MARS 2 findings have certainly ignited a critical re-evaluation of surgical practices, and whilst some interpret the results as a call to abandon surgery in favour of systemic therapies, others view them as a catalyst for refining surgical indications and methodologies, and this would be our view. Further research should also include adequately powered arms with patients receiving immunotherapy, which is fast becoming the mainstay of treatment, or maybe even intra-pleural therapies [52]. The controversy thus underscores the need for multidisciplinary collaboration, nuanced patient selection and continued research to optimize outcomes for patients with PM to design future therapeutic perspectives.

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***Ethical Approval.*** This article is based on previously conducted studies and does not

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