Going to MARS may shorten our patient's survival

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Over the past decade, extended pleurectomy decortication (ePD) has replaced extrapleural pneumonectomy (EPP) as the procedure of choice to achieve as complete a surgical resection as possible—macroscopic complete resection (MCR)—for pleural mesothelioma (PM).[1,2] The best surgical results are widely accepted to be an R1 resection with microscopic residual disease.[3] Alternatively, an R1 resection can be achieved by the lung-sacrificing operation, an EPP.[4] ePD has become the preferred operation because of lower perioperative mortality and similar or better long-term survival.[5] For patients with disease localized to the ipsilateral hemithorax, MCR in combination with chemotherapy is associated with prolonged survival in selected patients.[6-9] The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) task force have published guidelines that recommend surgery as a component of both diagnosis and treatment with curative and palliative intents.[10-12] Given the lack of level 1 evidence supporting ePD as part of a multimodal treatment plan over systemic therapy alone,[10-14] Lim and colleagues[15] performed a phase 3, national multicenter superiority trial in the United Kingdom, the Extended Pleurectomy Decortication and Chemotherapy versus Chemotherapy Alone for Pleural Mesothelioma (MARS 2) randomized controlled trial.

Data	MARS 2 Limitations
• 1030 Evaluated / 335 enrolled.	• No Intent-to-Treat Analysis.
• Surgery: 19.3 months	• Inadequate Pre-Operative Evaluation.
• Chemotherapy: 24.8 months.	• Operative Mortality: 9%.

Data and limitations of MARS 2.

CENTRAL MESSAGE

Although MARS 2 reported decreased survival with extended pleurectomy decortication and chemotherapy compared to chemotherapy alone, the trial does not warrant eliminating surgery in pleural mesothelioma.

See Commentary on page XXX.

MARS 2 TRIAL DESIGN AND OUTCOME SUMMARY

The investigators tested the hypothesis that ePD with chemotherapy is superior to chemotherapy alone. Assuming a median overall survival (OS) of 16.8 months in the chemotherapy alone group, they calculated a sample size of 328 patients to provide 80% power to detect a hazard ratio (HR) of 0.70 and a 5% type I error rate. Patients were deemed candidates for ePD based on surgeon assessment of computed tomography (CT) scans alone. Positron emission tomography (PET) scans in most cases and mediastinal staging were not performed. Patients deemed candidates were randomized after 2 cycles of chemotherapy to surgery and chemotherapy or chemotherapy alone irrespective of their response to chemotherapy. In the surgical group, patients received 2-4 additional adjuvant cycles of chemotherapy. In the chemotherapy group, patients received an

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TABLE 1. Benchmark trials for systemic therapy

Author	Year	Trial name	Study design	Total patients	Control arm	Median OS, mo	Experimental arm	Median OS, mo
Vogelzang et al[16]	2003	NA	Phase III RCT	456	Cisplatin	9.3	Cisplatin/pemetrexed	12.1
Baas et al[17]	2021	CheckMate 743	Phase III RCT	713	Cisplatin/ pemetrexed	14.1	Nivolumab/lpilimumab	18.1
Zalcman et al[18]	2016	MAPS	Phase III RCT	448	Cisplatin/ pemetrexed	16.1	Cisplatin/pemetrexed/ bevicizumab	18.8
Rimner et al[8]	2016	IMPRINT	Phase II single arm	45	None	NA	Neoadjuvant therapy/ surgery/adjuvant IMRT	23.7

OS, Overall survival; *NA*, not applicable; *RCT*, randomized controlled trial; *IMRT*, intensity-modulated radiotherapy.

additional 2-4 cycles of chemotherapy without surgery. The primary outcome was OS from the time of randomization. Secondary outcomes included progression-free survival, safety, and health-related quality of life.

Over the study period (June 2015 to January 2021), 1030 patients were evaluated and 335 were randomized. Most patients (87%) were men and had epithelioid mesothelioma (86%). The investigators reported a shorter median OS in the surgery and chemotherapy group compared with the chemotherapy alone group (19.3 months vs 24.8 months; $P = .019$), as well as a difference in restricted median survival time at 2 years of −1.9 months. They also noted more cardiac, respiratory, and infectious adverse events in the surgery group. Based on these results, they concluded that ePD was associated with worse survival at 2 years and with more serious adverse events compared with chemotherapy alone.

BENCHMARK DATA FOR CHEMOTHERAPY ALONE

In their introduction, the authors note that the OS of patients with PM is 9 to 12 months despite using 16.8 months to generate the power calculations (Table 1). In 2003, Vogelzang and colleagues[16] reported a median OS of 12.1 months with cisplatin and pemetrexed versus 9.3 months with cisplatin alone. Although PM remains a fatal disease with poor survival, the outcome of patients who receive systemic therapy without surgery has improved over the past decades. In CheckMate 743, a landmark clinical trial published in 2021, cisplatin and pemetrexed were the control arm and had median OS of 14.1 months for all patients.[17,19] The median OS was 16.5 months for the 75% of patients in this trial who had epithelioid histology. Similarly, Zalcman and colleagues[18] reported the MAPS trial in 2016, in which they randomized patients to cisplatin and pemetrexed with or without bevacizumab and found a median OS of 16.1 months in the cisplatin and pemetrexed arm, which included 19% of patients with biphasic and sarcomatoid histology. The recent trials suggest that patient OS has improved by approximately 4 months with standard (platinum/pemetrexed) chemotherapy over the last 2 decades. These outcomes should be the new historical standard against which we compare recent data.

BENCHMARK DATA WITH CHEMOTHERAPY AND SURGERY

In the surgery and chemotherapy arm in MARS 2, the median OS of 19.3 months was comparable to older series rather to than more contemporary trials (Table 2). In the 1990s, Rusch and colleagues[20] reported a median OS of 17 months for patient who underwent ePD with hyperthermic intrathoracic chemotherapy (HITOC). Sugarbaker and

TABLE 2. Benchmark series for surgical outcomes

Author	Year	Total patients	Intervention	Median OS, mo
Rusch et al[20]	1992	28	ePD and HITOC	17
Sugarbaker et al[21]	1999	176	EPP, chemotherapy, and radiotherapy	19
Lang-Lazdunski et al[22]	2015	102	ePD with povidone-iodine	32
Zhou et al[23]	2022	95	ePD with chemotherapy ± radiotherapy	22
		187	EPP with chemotherapy ± radiotherapy	15
Breda et al[24]	2021	155	ePD and chemotherapy	34
Klotz et al[25]	2022	71	ePD and HITOC with chemotherapy for epithelioid disease	28.2
Lapidot et al[26]	2022	184	ePD and HITOC with chemotherapy for epithelioid disease	31.5
		355	ePD and HITOC with chemotherapy all patients	20.7

OS, Overall survival; *ePD*, extended pleurectomy decortication; *HITOC*, hyperthermic intrathoracic chemotherapy; *EPP*, extrapleural pneumonectomy.

colleagues[21] studied the outcomes of 176 patients and found a median OS of 19 months in those who underwent EPP, chemotherapy and adjuvant radiotherapy.

The outcomes in these early series reflect a time of patient care that predated our knowledge of prognostic factors to optimize patient selection, PET/CT scans to improve the accuracy of clinical staging, and contemporary perioperative care practices. More contemporary series have demonstrated improved OS compared with those original reports. In 2015, Lang-Lazdunski and colleagues[22,27] reported a median OS of 32 months for patients undergoing ePD. In 2022, Zhou and colleagues[23] reported their series of ePD and EPP recipients from 2000 to 2019 and noted a median OS of 22 months for their ePD cohort, and that epithelial histology, MCR, adjuvant radiotherapy, and operation in recent years were associated with improved survival. In a recent study of 155 consecutive patients with epithelioid mesothelioma were treated with ePD and chemotherapy, the reported median OS was 34 months.[24] Klotz and colleagues[25] reported their experience in 57 consecutive patients with epithelioid mesothelioma undergoing ePD and HITOC between 2014 and 2018. Their protocol involved 4 cycles of adjuvant chemotherapy with platinum and pemetrexed, and they noted a median OS of 28.2 months. In the largest series of ePD reported to date, Lapidot and colleagues[26] achieved MCR in 85.6% of 355 patients over a 9-year period at Brigham and Women's Hospital, despite 48% having a nonepithelioid histology. The median OS was 20.7 months overall, but 31.5 months for 184 patients with epithelioid histology.

The International Association for the Study of Lung Cancer (IASLC) Pleural Mesothelioma Staging Project has published a series of articles to inform revisions for the forthcoming ninth edition of the staging classification.[28] These articles report the OS of surgically resected patients based on aggregated data from multiple institutions. In the T-descriptor article, Nowak and colleagues[29] reported median OS (T1, 48.9 months; T2, 27.5 months; T3, 21.1 months) and 3-year OS rates (T1, 62%; T2, 37%; T3, 33%). In the N-descriptor article for patients with surgically resected and pathology-staged disease, Bille and colleagues[30] noted that patients with pN0 had a longer median OS compared to those with pN1 disease (33.8 months vs 25 months), as well as a higher 3-year survival OS rate (48% vs 41%). Patients in MARS 2 did worse than those patients in the IASLC dataset with either T3 or N1 disease.

METHODOLOGIC LIMITATIONS

MARS 2 has several trial design limitations. First, surgery included patients with biphasic and sarcomatoid histology. Since CheckMate 743, the NCCN now recommends that patients with biphasic and sarcomatoid histologies receive dual agent checkpoint inhibitors as first-line therapy.[17] Although CheckMate 743 was not published until the end of the enrollment period for MARS 2, biphasic and sarcomatoid histologies are well-known poor prognostic factors for surgical resection.[21,23,26,31-33] The authors reported 8 patients with sarcomatoid disease in the surgical arm and 3 in the chemotherapy arm, even though they did adjust for histology.

Second, the presurgical evaluation was inadequate. The authors reported 6 patients with M1 disease in the surgical arm and 4 in the chemotherapy arm. Operating on patients with M1 disease reflects a lack of adequate presurgical staging. Patients were assessed for resectability based on a tumor board review of CT scans alone. Not all patients underwent PET-CT scans, which have been used almost universally for evaluating patients with diagnosed or suspected PM for the last 20 years. PET scans are even encouraged for malignant pleural effusions. This lack of clinical staging is a major flaw. Not only did patients not undergo PET scans, but they also did not undergo invasive mediastinal staging (endobronchial ultrasound or cervical mediastinoscopy) despite recommendations from the NCCN, ESMO, and ESTS/ERS to perform this as a component of surgical staging.[11-14] Although invasive mediastinal staging is strongly recommended, some centers perform additional staging, such diagnostic laparoscopy if suspicion of abdominal disease is present, contralateral video-assisted thoracoscopic surgery (VATS) if a contralateral effusion is present, or VATS biopsy to confirm histology and subtype.

Third, although the T stage was balanced, the subgroups based on involvement of the diaphragm or extension into the underlying pulmonary parenchyma differed. Interestingly, the findings for the T subgroups are not possible to ascertain from CT scans, but they were reported in both the surgical and nonsurgical groups. Similarly, nodal upstaging between clinical and pathologic analyses occurs in most series. Nodal disease is notoriously difficult to evaluate with a CT scan without mediastinal staging, and even then, additional nodes in other stations are often present. The authors did report pathological N stage, but a comparison to the chemotherapy group was not possible.

Fourth, neoadjuvant chemotherapy was given without strong data. In fact, Sugarbaker and colleagues[34] showed that patients treated with EPP and postoperative radiation with several, mostly ineffective, chemotherapy regimens had a median survival of 18 to 19 months. A subsequent trial reported by Krug and colleagues[35] evaluated 4 cycles of neoadjuvant cisplatin and pemetrexed prior to surgery and radiation showed an overall survival of only 16.8 months. These trials suggest that a neoadjuvant approach might not be optimal. Moreover, the inclusion of a split-course chemotherapy regimen (2 cycles preoperatively and 2-4 cycles postoperatively) in the surgical arm compared to continuous 4 to 6 cycles of chemotherapy in the control

arm ignores the biological principles that treatment should be given in regular cycles for maximal effect based on the log-kill, Golde-Coldman, and Skipper-Schabel-Wilcox model hypotheses.[36] This issue was magnified further by the decreased number of total cycles received by surgical patients (ie, decreased dose intensity) compared to the chemotherapy alone group, making comparisons inappropriate. Only 39% of patients received adjuvant chemotherapy after surgery, while 56% received the planned 6 cycles of chemotherapy in the other group. Furthermore, the use of a dated chemotherapy regimen without the current standard of either bevacizumab or pembrolizumab magnifies this problem.

Another major bias is that twice as many patients in the chemotherapy alone group received further systemic therapies (immune checkpoint inhibitors, further chemotherapy, or other systemic therapy) which certainly improved the survival in that group. This finding, if adjusted for, might have enhanced the survival of patients in the surgery arm.

Fifth, the trial design should have had intention-to-treat analysis with enrollment prior to neoadjuvant therapy. The original MARS trial predicted that induction chemotherapy (3 cycles of platinum-based therapy) would produce serious consequences in terms of patient viability for surgery. In this study, a total of 301 patients were identified for possible inclusion, with a total of 251 patients (83%) subsequently unable to proceed to randomization because of such factors as clinical decision, patient decision, patient withdrawal, disease progression, or death, which were often directly the result of neoadjuvant chemotherapy.[37] Similarly, in MARS 2, only 264 patients (13%) proceeded to randomization, including 136 randomized patients (31%) who dropped out after 2 cycles of neoadjuvant chemotherapy. Progression of more than one-third of patients after neoadjuvant therapy is well known and clearly reported. Rimner and colleagues[8] reported progression on neoadjuvant therapy in the IMPRINT trial, in which patients received neoadjuvant chemotherapy, ePD, followed by intensity-modulated radiotherapy. They enrolled 45 patients in whom survival was calculated prior to neoadjuvant therapy. Twenty of these 45 patients did not proceed to surgery, owing to disease progression, unresectability, or complications from chemotherapy. Overall, 33% (n = 15/45) experienced progressive disease during neoadjuvant chemotherapy, which was expected given the low response to chemotherapy.[16-18] For comparison, among patients treated with chemotherapy only in CheckMate 743, >50% at 6 months and 74% at 12 months experienced progression in the chemotherapy-only arm with cisplatin and pemetrexed.[16-18] These results highlight the fact that early progression on chemotherapy is common; thus, the lack of an intention-to-treat analysis in MARS 2 specifically selected for patients who tolerated chemotherapy.

The lack of an intention-to-treat analysis is a critical error that prevents evaluation of patients who progress or do not complete neoadjuvant therapy. OS was assessed from randomization, which was performed after 2 cycles of chemotherapy. After these 2 cycles, 695 patients were excluded and listed as "ineligible," which suggests that this trial design applies to an extremely narrow subset of patients. In the "baseline characteristics and systemic treatments" table, the authors report that 100% in both arms completed the 2 neoadjuvant cycles. Because patients were included only if they tolerated these 2 cycles, the 100% ability to receive chemotherapy is a tautology and does not reflect grouping differences based on the ability to tolerate neoadjuvant therapy. Progression during chemotherapy was noted in 176 patients, but the number who remained resectable but did not proceed to surgery is unclear. If designed appropriately with randomization prior to the start of therapy, many patients would have progressed after 2 cycles of chemotherapy and switched to another treatment or to palliative measures. Instead, this design specifically selected for patients based on their response to chemotherapy, which likely explains the longer OS with chemotherapy compared to other reports.

Sixth, surgeons were required to have performed 5 ePDs to participate, yet 45% of patients underwent surgery in low-volume centers that performed ≤3 ePDs annually. Additionally, there was a wide variation in surgical procedures performed. ePDs are not truly standardized; therefore, the details of the procedure, such as extent of diaphragm and pericardium resection, preservation of the peritoneum, and extent of visceral pleurectomy, should be carefully described and, ideally, standardized.[1] Also, the authors did not explain why patients with M1 disease received anatomic lung resections, pleurodesis and exploration, or resection. This lack of standardization is even more concerning with the description of 5 patients (3%) who were classified as "R0 resections" as well as 37 patients (22%) who underwent an R2 resection. The authors did not mention how an R0 was achieved or why the rate of R2 resection was so high; furthermore, how these patients were handled postoperatively or in the analysis was not reported. An R2 resection is well known to provide no surgical benefit.[38] The lack of description of patterns of recurrence also prevents the ability to evaluate the adequacy of surgical pleurectomy and decortication. Compounding the risk for poor surgical outcomes are the low cutoff values for the pulmonary capacity (forced vital capacity and lung CO diffusion capacity), which likely are responsible for the increased number of early pulmonary deaths.

The MARS 2 study reported a 30-day mortality of 4% and a 90-day mortality of 9%, higher than most recent reports for ePD. Zhou and colleagues[23] reported a 90-day mortality of 4.2% in their ePD cohort, and Lang-Lazdunski and colleagues[22] reported no 90-day mortality

among 102 patients. Breda and colleagues[24] reported a 30-day mortality of 0.6% and 90-day mortality of 3.2%. Klotz and colleagues[25] reported no 90-day mortality despite the added toxicity of HITOC. Lapidot and colleagues[26] reported 30-day mortality of 3% and 90-day mortality of 4.6%. Taoli and colleagues[5] presented a meta-analysis in which the 30-day mortality was 1.7% but did not report 90-day mortality. Bueno and Opitz[3] summarized mortality rates for most series and reported rates of 0 to 4.1% with ePD and 0 to 1.1% with PD. The lack of mention of surgical functional criteria, as well as low cutoffs for critical pulmonary tests, are reflected in the increased number of early pulmonary deaths.

Seventh, the comparison of adverse events uses the US Department of Health and Human Services CTCAE classification system, which is appropriate for medical treatments and perhaps minor procedures but is not designed for the evaluation of complications from major surgery. Standard surgical complications should be reported with the Clavien-Dindo classification system or the Comprehensive Complication Index.[39-41] Granted, different grading systems make comparisons more complicated, but oversimplification and use of inappropriate systems do not adequately assess the outcomes.

Finally, the statistical analysis of survival was performed for the first 42 months based on the point at which the Kaplan-Meier curves intersected. Based on this analysis, the authors report a hazard ratio of 1.28 (95% CI, 1.02-1.60; $P = .032$). Lim and colleagues[42] published the trial design in 2020 and did not include this in their statistical analysis section. Similarly, they reported a difference in restricted median survival time at 2 years of −1.9 months, which implies that the overall curve did not reach significance. Beyond about 24 months, survival appears similar in the 2 groups. The difference in early survival and lack of difference in later survival may be related to poor surgical quality, which decreased the initial survival in the surgical arm with a trial design enriched for patients who did well with chemotherapy. Additionally, the investigators did not report a justification for the superiority margin of 30% in this trial.

An overperforming chemotherapy group and an underperforming surgical group in MARS 2 amplified the observed effect on OS. Taken together, these results show that the surgical outcomes in the MARS 2 trial are outliers. Recent trials and international datasets show that surgical outcomes have improved over the past 20 years. Additionally, MARS 2 is an outlier for postoperative mortality, which is higher than all reports of ePD performed at expert centers.

CONCLUSIONS

Lim and colleagues should be commended for executing this difficult trial that randomized patients with PM to a surgical arm and a nonsurgical arm. However, the trial design with randomization of patients after neoadjuvant therapy prevents accurate assessment of response to therapy and selects candidates who responded well to chemotherapy. This design is likely responsible for the unusually long survival after chemotherapy. Furthermore, the lack of complete staging prevents accurate assessment of whether patients were truly surgical candidates. Given that survival after surgery was lower than in modern series and the postoperative mortality was higher than in all other modern series, their results are outliers, suggesting that patients were not appropriately evaluated for surgery.

Patients with PM have limited therapeutic options, but some selected patients achieve very long survival with multimodal therapy including cytoreductive surgery as well as other modalities, such as radiotherapy, which was not evaluated in MARS 2. Eliminating surgery from treatment options in favor of chemotherapy may decrease patient survival. Although MARS 2 provides interesting data that require evaluation, surgery should not be eliminated from treatment options based on these results. However, centers offering cytoreductive surgery for PM should consider a median OS of 24 months and a 90-day mortality of <5% as the benchmark for evaluating surgical outcomes. While selection criteria are debatable, the optimal surgical candidates have epithelioid histology, low tumor volume, good performance status, and reasonable lung function.

In summary, the investigators conclude that "in this multicenter randomized trial, (extended) pleurectomy decortication and chemotherapy was associated with worse survival, a higher rate of serious adverse events, poorer quality of life, and higher costs among individuals with resectable pleural mesothelioma compared with chemotherapy alone." However, their conclusion neglects to consider that "chemotherapy alone" refers to an extremely narrow subset of patients with resectable PM. Therefore, we recommend exercising caution when interpreting the results of the MARS 2 trial, as patients appropriate for surgery may be overlooked with nonselective application of the results to all PM patients. Most surgeons with a genuine interest in PM agree that surgery continues to have a role in well-selected PM patients. Going forward, recognition of the flaws in this study by our medical oncology colleagues will help better identify appropriately-selected surgical patients.

Conflict of Interest Statement

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