

# Cutting Out Surgery? Why Extended Pleurectomy Decortication Likely Falls Short in Pleural Mesothelioma

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## The clinical question

Does extended pleurectomy decortication (EPD) combined with chemotherapy improve outcomes compared to chemotherapy alone in patients with resectable pleural mesothelioma?

## Take Home Message

Patients who underwent extended pleurectomy decortication plus chemotherapy had worse survival, more serious complications, poorer quality of life, and higher healthcare costs compared to those who received chemotherapy alone. Overall, extended pleurectomy decortication likely does not improve survival in resectable pleural mesothelioma and may even be harmful.

## Background

Malignant pleural mesothelioma (MPM) is an aggressive cancer primarily caused by asbestos, with a median survival rate of 9-12 months. First line treatment is chemotherapy which offers modest survival benefit. However, in the absence of major systemic therapy, surgery has been widely used as an additional treatment to remove visible tumors. EPD compared to extrapleural pneumonectomy (EPP) is less invasive and the most performed surgery for mesothelioma worldwide. Despite being routinely recommended by international guidelines, there are no prior trials that evaluate whether EPD improves survival or quality of life. EPD has been assumed to be safer than EPP given prior evidence that has showed higher mortality and poorer quality of life with EPP. Effectiveness of EPD has only been evaluated by retrospective studies that are subject to selection bias. Given the lack of high-quality evidence, MARS2 was designed to compare EPD plus chemotherapy vs chemotherapy alone for overall survival, progression free survival, quality of life, and cost effectiveness. If EPD prolongs survival, it may provide an acceptable risk-benefit ratio and remain an important tool for mesothelioma treatment; however, failure to improve survival or evidence of excessive harm may challenge decades of surgical practice and shift towards systemic therapies.

# Study Design



- **Study design:** Multicenter, open-label, pragmatic, parallel two-group, and superiority randomized controlled trial.
- **Primary Outcome:** Overall survival defined as time from randomization to death from any cause.

## Secondary Outcome(s):

- Progression free survival
- Serious adverse events
- Health-related quality of life
- Cost effectiveness and healthcare resource use

**Intervention:** Experimental group received chemotherapy (2 initial rounds pre-surgery and 2-4 additional rounds post-surgery) plus extended pleurectomy decortication. Comparator group received chemotherapy alone (2 initial rounds followed 2-4 additional rounds after randomization).

# Population

## Inclusion Criteria:

- Patients with age  $\geq 16$  years with confirmed mesothelioma diagnosis (based on cytology or histopathology).
- Eligible subtypes: Epithelioid, Sarcomatoid, Biphasic.
- Disease confined to one hemi-thorax, based on CT scan assessment.
- Disease deemed surgically resectable and fit for surgery, as determined by a MARS 2 surgical site surgeon.

## Exclusion Criteria:

- Severe respiratory impairment defined by: ECOG status  $\geq 2$ , or if PFT is performed then pre-operative FEV1  $< 20\%$  predicted, TLco  $< 20\%$  predicted.
- Serious concomitant disorder that would compromise safety of participant during surgery.
- Severe heart failure (defined as NYHA class III or IV, or ejection fraction  $< 30\%$ ).
- End stage kidney disease requiring dialysis
- Liver failure (e.g. encephalopathy and/or coagulation abnormalities)
- Existing co-enrolment in another interventional clinical trial that aims to improve survival.



## Baseline Characteristics:

Patients were enrolled from June 19th, 2015, to January 21st, 2021. 1030 participants from 26 sites were screened of which 335 participants were randomly assigned. 169 patients were assigned to surgery + chemotherapy group, and 166 patients were assigned to chemotherapy alone group. There were no differences between the two groups in terms of age, sex, histology, staging, and performance status. 86% of patients had epithelioid subtype of mesothelioma. Only 39% of patients in the surgery + chemotherapy group completed all 6 cycles of chemotherapy, compared to 56% in the chemotherapy alone group. 39% of chemotherapy alone patients received immunotherapy, compared to 22% in the surgery + chemotherapy group. Two patients from chemotherapy alone group crossed over to surgery + chemotherapy group, and 13 patients from surgery + chemotherapy group crossed over to chemotherapy alone.

## Outcomes

### Primary Outcomes:

- Median Overall Survival (OS):
  - Surgery + Chemotherapy Group: 19.3 months (IQR: 10.0-33.7)
  - Chemotherapy Alone Group: 24.8 months (IQR: 12.6-37.4)
- Restricted Mean Survival Time (RMST) at 2 Years: -1.9 months shorter in the surgery group (95% CI: -3.4 to -0.3,  $p = 0.019$ ).
- Hazard Ratio (HR) for death (First 42 Months): 1.28 (95% CI: 1.02-1.60,  $p = 0.032$ ), indicating a 28% increased risk of death in the surgery + chemotherapy group.
- Survival at 5 years:
  - Surgery + Chemotherapy Group: 14% (95% CI: 8-22%)
  - Chemotherapy Alone Group: 13% (95% CI: 7-20%)
- Cause of death: Most deaths in both groups were due to disease progression.



### Secondary Outcomes:

- Median Progression Free Survival (PFS)
  - Surgery + Chemotherapy Group: 10.6 months (IQR: 6.3-21.6)
  - Chemotherapy Alone Group: 11.0 months (IQR: 5.9-19.6)
- HR for progression or death: 0.90 (95% CI: 0.72-1.11,  $p = 0.33$ )
- Overall, no significant difference in disease progression between the two groups.
- For global health and social functioning, no change in mean difference between groups with follow-up time.

- For physical and role functioning (ability to perform daily activities), the mean difference between groups reduced over time.
- Positive symptom scores for pain, fatigue, dyspnea, insomnia, loss of appetite, and financial difficulties were worse for the participants in surgery + chemotherapy group.
- EQ-5D scores were collected to prevent against a healthy cohort effect, with a trend of reduction in surgery + chemotherapy group.
- Total healthcare cost per patient:
  - Surgery + Chemotherapy: £30,436 (\$41,871)
  - Chemotherapy Alone: £15,805 (\$21,743)
  - Mean Difference in Costs: £14,631 (\$20,128) (95%CI: £11,279 to £17,983 (\$15,517 to \$24,740))
- Quality-Adjusted Life Years (QALYs):
  - Surgery + Chemotherapy Group: 1.02 (95% CI: 0.94 to 1.10)
  - Chemotherapy Alone Group: 1.21 (95% CI: 1.13 to 1.29)
  - Mean Difference: -0.19 (95% CI: -0.30 to -0.08)
- Surgery was NOT cost-effective at any willingness-to-pay threshold.
- Impact of Histological Subtype:
  - Epithelioid Mesothelioma: HR = 1.12 (95% CI: 0.86-1.47)
  - Non-Epithelioid Mesothelioma (Biphasic/Sarcomatoid): HR = 2.66 (95% CI: 1.22-5.81), p = 0.049, suggesting that surgery was particularly harmful for non-epithelioid subtypes.

### **Adverse Events:**

- Total Number of Serious Adverse Events (SAEs):
  - Surgery + Chemotherapy Group: 318 serious adverse events
  - Chemotherapy Alone Group: 169 serious adverse events
- Incidence Rate Ratio (IRR) for SAEs: 3.6 (95% CI: 2.3–5.5, p < 0.0001) → 3.6x higher risk of serious complications in the surgery + chemotherapy group
- For surgery + chemotherapy group: 30-day mortality (4%) and 90-day mortality (9%)
- Most common SAEs in surgery + chemotherapy group:
  - Cardiac complications (30 vs. 12 events; IRR = 3.01 [CI: 1.13-8.02])
  - Respiratory disorders (84 vs. 34 events; IRR = 2.62, [CI: 1.58-4.33])
  - Infections (124 vs. 53 events; IRR = 2.13, [CI: 1.36-3.33])
- Additional surgical or medical procedures required (15 vs. 8 events; IRR= 2.41, [CI: 1.04-5.57])

# Commentary

## **Study strengths:**

The study is the first ever multicenter, randomized, pragmatic trial evaluating the outcomes between surgery + chemotherapy vs. chemotherapy (including immunotherapy) alone in patients with malignant pleural mesothelioma. In doing so, it is minimizing bias and providing strong evidence for clinical decision making. It further includes sensitivity analyses including adjustments for chemotherapy cycles and additional treatments that help account for confounding variables. It measures overall survival, progression-free survival, serious adverse events, quality of life, and cost-effectiveness, giving a well-rounded evaluation of treatment impact.

The study demonstrates that extended pleurectomy decortication (EPD) with chemotherapy does not improve survival compared to chemotherapy alone. Worse survival outcomes (median survival: 19.3 vs. 24.8 months) and a higher incidence of serious adverse events (3.6-fold increase) in the surgery + chemotherapy group challenge previous assumptions about the benefits of surgery.

## **Study Limitations:**

Despite the extensive analyses and accounting for confounders, the study does have some limitations, some of which are evident by its design. While overall survival (OS) is an objective endpoint, other factors like treatment adherence and supportive care might have been influenced by unblinded treatment assignment. The study primarily included epithelioid mesothelioma (86%), with fewer patients with biphasic (9%) or sarcomatoid (3%) subtypes. The findings may not be generalizable to non-epithelioid mesothelioma, which has a worse prognosis and different treatment responses. The Kaplan-Meier curves cross at 42 months, suggesting possible long-term effects of surgery, however, only 30 patients remained in follow up beyond 42 months, limiting the conclusions about very long-term outcomes. A longer follow-up period with more participants might clarify whether surgery has late survival benefits in a subset of patients. Lastly, surgery was significantly more expensive (£30,436 vs. £15,805), with worse cost-effectiveness than chemotherapy alone. However, the cost analysis does not consider long-term healthcare expenses, such as palliative care costs for non-surgical patients.

Overall, this is an important paper for the interventional pulmonologist who diagnose and manage symptomatic malignant pleural effusions secondary to mesothelioma as it carries implications for which therapies maybe offered and discussed with the patients.



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## Suggested Reading

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## Article Citation

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