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Specimen weight and volume: important predictors of survival in malignant pleural mesothelioma[†]

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Abstract

OBJECTIVES: The tumour/node/metastasis (TNM) staging system for malignant pleural mesothelioma (MPM) is a worldwide standard, but has many limitations. Tumour volume has been suggested as a predictor of survival. Due to the complex anatomy, estimation of tumour volume via CT scan can be challenging. Surgical volume may be more accurate. Therefore, we prospectively determined resected specimen volumes and weights in consecutive patients undergoing extended pleurectomy and decortication (EPD) and correlated this with overall survival and T and N stage.

METHODS: We evaluated 116 patients undergoing EPD for MPM in a single university centre over a 6-year period. All resected specimens were weighed, and the volume was measured by a fluid displacement method. A Cox regression model was used to identify significant predictors of survival; hazard ratios were calculated. A Kaplan–Meier method was used to summarize overall and subgroup survival. Logistic regression models were used to identify predictors of T and N stage.

RESULTS: There were 95 males and 21 females with a median age of 68 range 43–88 years. Forty-one patients had an ECOG performance status (PS) 0, 70 had 1 and 4 had 2. The median time between initial diagnosis and surgery was 134 days. Histology was epithelioid in 59, biphasic in 55 and sarcomatoid in 2. The mean volume was 641 ml with an SD of 393.34 ml. The median volume was 567.5 ml. The mean weight was 620.8 g with an SD of 361.92 g. The median weight was 552.0 g. Two-year survival from initial diagnosis and from EPD was 44 and 28%, respectively. PS ($P = 0.002$), epithelioid histology ($P < 0.001$), specimen weight ($P < 0.001$), volume ($P < 0.001$), platelet count ($P = 0.015$), T1 stage ($P = 0.04$) and adjuvant therapy ($P = 0.01$) were predictive of survival. Tumour volume was a predictor of T stage ($P = 0.048$) and survival ($P = 0.03$). There was no relationship between N stage and tumour volume, weight or histology.

CONCLUSIONS: PS, specimen weight, volume, epithelioid histology platelet count and adjuvant chemotherapy are significant predictors of survival in patients undergoing EPD for MPM. There is a correlation between specimen volume and T stage. These data suggest that tumour weight and volume may be valuable components for staging MPM.

Keywords: Malignant pleural mesothelioma • Extended pleurectomy and decortication • Tumour volume • Outcomes • Staging

INTRODUCTION

Staging a malignancy is an important prognostic tool and plays a fundamental role in patient management. Various attempts have been made to establish a staging classification for malignant pleural mesothelioma (MPM), including the Butchart [1], Brigham [2] and tumour/node/metastasis (TNM) systems. Currently, the most widely used classification is TNM (7th Edition), by the American Joint Commission on Cancer (AJCC) [3], which was partly adapted from

lung cancer staging. Although there is an improvement on prior efforts, current TNM classification still remains imprecise for 'diffuse' tumours such as mesothelioma because of the inability to accurately measure the primary tumour (i.e. T stage).

The radiological imaging modalities that are used to determine TNM stage (e.g. CT scan and MRI) are more precise in measuring discrete tumours such as lung cancer. MPM, in contrast, is diffuse, varies in thickness in different areas and has a similar density to surrounding tissues. This makes it more difficult to calculate the tumour burden and the degree of invasion by standard radiological methods (Fig. 1). Consequently, MPM is often clinically understaged.

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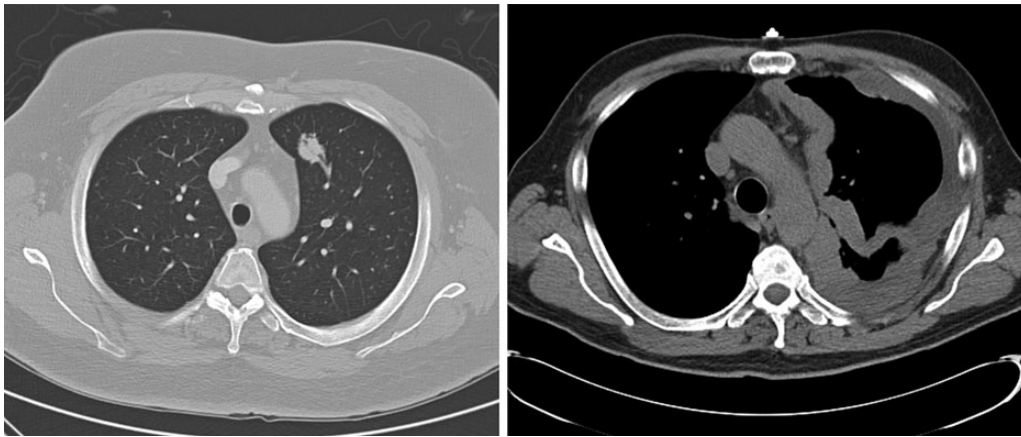


Figure 1: CT scan of a solid tumour/lung cancer (left); CT scan of a diffuse tumour/MPM (right). MPM: malignant pleural mesothelioma.

The two radical surgical procedures that are performed for maximal tumour resection are pleurectomy and decortication (PD) and extrapleural pneumonectomy (EPP). PD may include resection of the hemi-diaphragm and this is termed extended pleurectomy and decortication (EPD) [4]. Specimen volume can be measured more precisely in those patients who undergo either PD or EPD.

The current pathological designation of T stage depends primarily on tumour invasion into the visceral pleura and the surrounding tissues; it does not measure primary tumour burden. The importance of tumour volume in mesothelioma is poorly understood [5, 6]. We hypothesized that pathological volumetric measurements of resected specimens during EPD could provide valuable information regarding prognosis. Thus, in this study, we evaluated the pathological specimen/tumour volume of patients undergoing EPD, the impact on overall survival and its relationship to TNM classification.

MATERIALS AND METHODS

One hundred and sixteen consecutive patients undergoing EPD for biopsy-proven MPM were enrolled at a single centre between March 2008 and November 2014. The study was approved by the Institutional Review Board. Prospective clinical data were entered into an institutional database. The following variables were evaluated: age, gender, baseline ECOG performance status (PS), preoperative platelet count, white blood cell count, histology, specimen volume, specimen weight and pathological T and N stage. The time of diagnosis or initial intervention for symptoms and the date of EPD were used to calculate survival from these two time points to account for the bias of delayed surgery.

Patients underwent video-assisted thoracoscopic surgery (VATS) or open pleural biopsy to confirm the histological type. Any significant pleural effusion was drained either with a cuffed tunneled pleural catheter or with video-assisted thoracoscopic drainage and talc pleurodesis prior to EPD. The patients were divided into two groups, namely 'epithelioid histology' and 'non-epithelioid histology'. The non-epithelioid group consisted principally of patients with biphasic histology (epithelioid and sarcomatoid cell types). Two patients with pure sarcomatoid histology underwent surgical treatment, because of their small tumour volume. Preoperative imaging studies [CT and positron emission tomography (PET) scan] were performed to confirm unilateral disease without distant metastasis. The lymph nodes are evaluated on CT

and PET scans in all the patients, which are performed within 6 weeks of the surgery date. No invasive staging of the lymph nodes is performed for patients planned for PD, if this is confined to the ipsilateral side. If there were concerns regarding the contralateral side, they were investigated either with endo-bronchial ultrasound (EBUS) or with VATS. Pulmonary function testing and appropriate cardiac evaluation were conducted.

Thirty-seven patients (32%) underwent talc pleurodesis, and 31 (28%) had received a PleurX catheter prior to the surgery. Twenty-four (21%) patients received neoadjuvant therapy and 78 (67%) received adjuvant chemotherapy. The decision to perform adjuvant chemotherapy was based on histology as well as the patient's postoperative PS. In 6 patients, there was missing information regarding adjuvant therapy.

This study included only patients undergoing EPD as defined by Rice [4]. EPD, by this definition, is the removal of all gross tumour from the parietal and visceral pleura with resection of the diaphragm and/or pericardium (Fig. 2). In this cohort, seventy-four patients (63.8%) underwent pericardial resection. Partial or near complete resection of the ipsilateral hemi-diaphragm was accomplished in all patients, due to tumour invasion. Diaphragmatic and pericardial defects were reconstructed using GORE-TEX® material, when indicated. The surgeries were performed by a single surgeon (Wickii T. Vigneswaran). Operative resection was estimated to be >95% complete in all patients by the surgeon.

Pathological stage was based on the evaluation of the resected specimen by the pathologist. The volume of resected specimens was measured using the water displacement method (Fig. 3) by the pathologist before fixation. Detailed histological examination was performed to determine the cell type in multiple sections. The median specimen volume was determined and this was used to subdivide the patients into two groups, namely above and below the median tumour volume. Subsequently, four subgroups were created, to further analyse the predictive value of specimen volume. The new subgroups had the following volumes: ≤ 300 , 301–600, 601–900 and >901 ml. The purpose of this analysis was to determine the impact of tumour volume in overall survival and its significance as a prognostic factor for patients with MPM.

Statistical methods

Boxplots and mosaic plots were used to examine pairwise relationships among study variables. Statistical significance of these

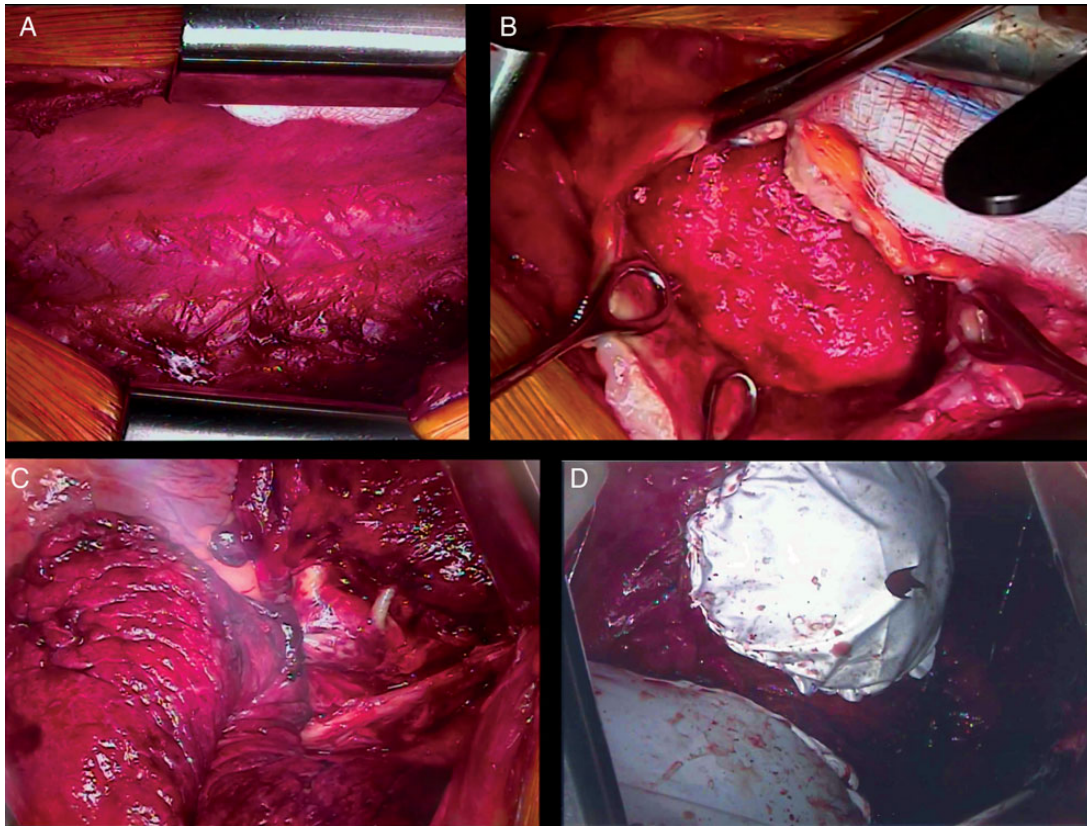


Figure 2: Intraoperative findings and diaphragmatic/pericardial reconstruction. (A) Intercoastal impressions on parietal pleura. (B) Dissection of parietal and visceral pleura away from the lung. (C) Surface of the lung after tumour removal. (D) Diaphragmatic and pericardial reconstruction with GORE-TEX® and window in the pericardial patch.

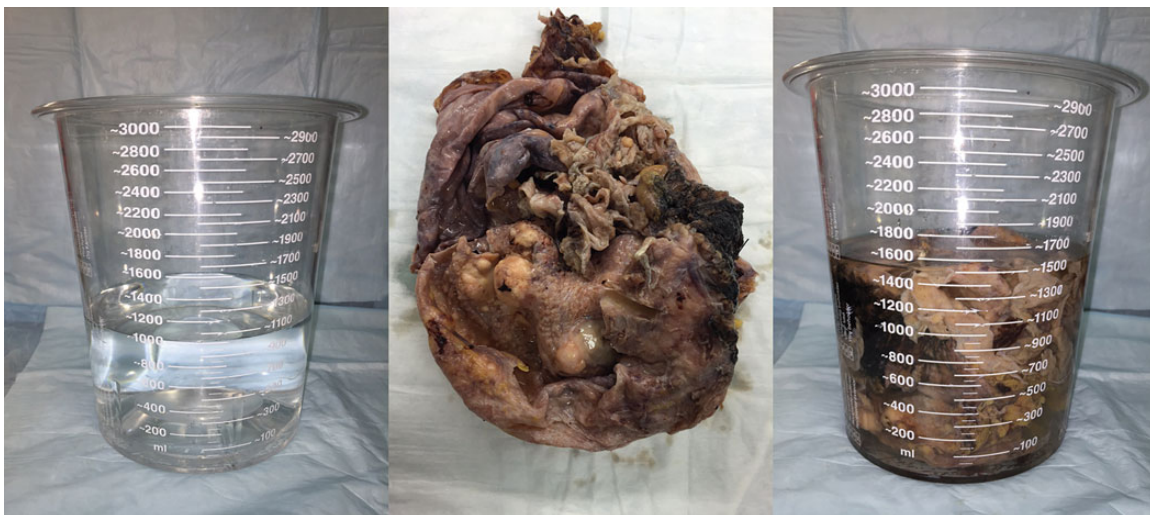


Figure 3: Volume measurement using the water displacement method.

relationships was assessed using the Wilcoxon rank sign test and Fisher's exact test. Logistic regression models of T (1–2 vs 3–4) and N (0 vs 1–3) stage were represented as binary variables, adjusted for continuous tumour volume/weight, histology and other factors. Overall survival rate was calculated from the date of diagnosis and date of surgery for all patients and in a subset of patients who survived longer than 30 days after surgery. A Kaplan–Meier method was used to summarize overall survival

rate for all subjects and separately for subgroups identified as significant predictors of survival in Cox regression models. Survival rate was also examined in multivariable Cox regression models that included candidate predictor variables that were not correlated with one another. The relationship between survival rate and tumour volume was examined in epithelioid and non-epithelioid tumours. To facilitate comparison in Kaplan–Meier curves, we created subgroups that corresponded to 'low'

or 'high' volume, respectively, associated with points below and above the median volume observed in the dataset. Further analysis for volume was performed using subsets characterized by four alternative cut-points. The new subgroups have the following volumes: ≤300, 301–600, 601–900 and >901 ml.

RESULTS

One hundred and sixteen consecutive patients underwent EPD for MPM. Most (81.9%) were male. The median age was 69, with a range of 43–88 years. The median interval between initial diagnosis and surgery was 4.4 months. About half of the patients (51%) had epithelioid histology; 47% were biphasic and only 2% had sarcomatoid disease. Sixty-one percent of patients were in ECOG PS of 1 preoperatively. Only 5% of the patients had T1 disease. The rest were equally distributed between T2 (22%), T3 (36%) and T4 (35%). Less than half (40%) were N0. The median specimen volume was 567.5 ml (range: 100–2200 ml; Table 1). In 26 patients (22.4%), the tumour volume was ≤300 ml, in 40 (34.5%) the tumour volume was 301–600 ml, in 21 (18.1%) patients the tumour volume was between 601 and 900 ml, and in 25 (21.6%) patients tumour volume was >901 ml.

Five patients (4.3%) died in the hospital or within 30 days of surgery. The median survival from diagnosis and after EPD was 22.9 and 15.5 months, respectively (Fig. 4). Overall, 2-year survival from diagnosis was 48.3% and from EPD was 31.5%. In 6 patients, not all the data were available for analysis and therefore excluded from subgroup survival analysis.

Univariable analysis and multivariable Cox regression model were used to demonstrate associations with survival following EPD (Table 2). Preoperative ECOG PS, preoperative platelet count, epithelioid histology, adjuvant therapy, early T stage, specimen volume and specimen weight were significant favourable predictors of survival, whereas neoadjuvant chemotherapy was unfavourable on univariable analysis. T stage was a marginal predictor. N stage did not show a statistical significance in this study. Preoperative ECOG PS, adjuvant chemotherapy, tumour volume and T1 stage

were the significant predictors of survival on multivariable regression analysis.

The median survival for patients with a specimen volume greater than 567.5 ml was 11.88 months compared with 22.56 months for patients with a specimen volume less than 567.5 ml ($P < 0.001$). Statistically significant survival differences were demonstrated in patients with epithelioid histology versus patients with non-epithelioid histology ($P < 0.001$). Patients with a good PS (PS 0) did significantly better than those with PS 1 and PS 2 ($P = 0.004$). The median survival for the subset of patients with tumour volume

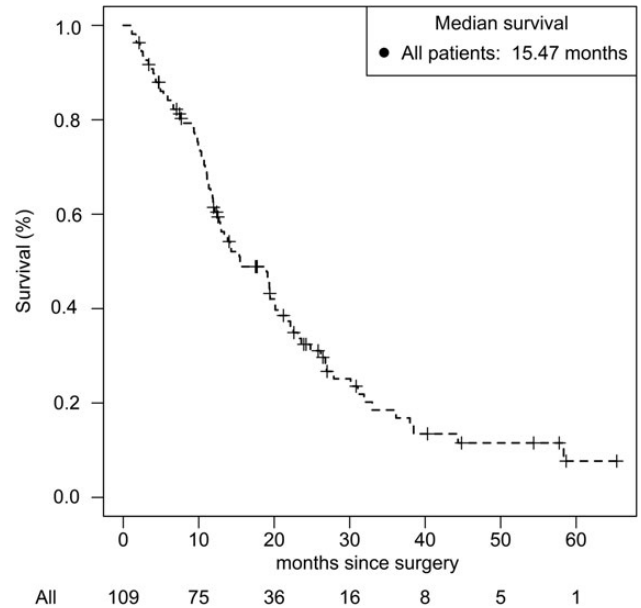


Figure 4: Kaplan-Meier survival curves for overall survival following extended pleurectomy and decortication.

Table 1: Distribution of clinical variables (n = 116)

Median specimen volume: 567.5 ml (range: 100–2200) ^a	
Median specimen weight: 552 mg (range: 90–2090)	
Histology	Epithelioid–59 (51%) Biphasic–55 (47%) Sarcomatoid–2 (2%)
ECOG performance status (PS)	PS 0–41 (36%) PS 1–71 (61%) PS 2–4 (3%)
T stage	T1–6 (5%) T2–26 (22%) T3–42 (36%) T4–41 (35%)
N stage	Tx–1 (1%) N0–46 (40%) N1–8 (7%) N2–42 (36%) N3–3 (3%) Nx–17 (15%)

^aIn 6 patients, specimen volume was not measured (n = 110).

Table 2: Individual associations with >30-day survival following EPD (n = 111)

Variables (n)	Univariable analysis	Multivariable regression
ECOG PS 1 and 2 (71) vs 0 (40)	HR = 2.138, P = 0.002	
Male (92)	HR = 1.383, P = 0.272	
Adjuvant (78)	HR = 0.602, P = 0.06	HR = 0.459, P = 0.012
Neoadjuvant (24)	HR = 1.93, P = 0.014	HR = 1.764, P = 0.082
% Epithelioid (59)	HR = 0.986, P = <0.001	
Volume (ml)	HR = 1.001, P = 0.001	HR = 1.001, P = 0.021
Weight (g)	HR = 1.001, P = <0.001	
Preoperative platelets	HR = 1.003, P = 0.008	
Preoperative white blood count	HR = 1.002, P = 0.935	
T stage = 2 (26) vs 1 (6)	HR = 4.279, P = 0.052	HR = 5.622, P = 0.028
T stage = 3 (42) vs 1(6)	HR = 3.923, P = 0.062	HR = 4.55, P = 0.047
T stage = 4 (41) vs 1(6)	HR = 4.672, P = 0.036	HR = 5.156, P = 0.033
N stage = 1 (8) vs 0 (46)	HR = 1.423, P = 0.433	
N stage = 2 (42) or 3 (3) vs 0 (46)	HR = 1.068, P = 0.803	
Nodal 1–3 (53) vs 0 (46)	HR = 1.119, P = 0.655	

EPD: extended pleurectomy and decortication; PS: performance status.

less than 300 ml was 26.94 months, between 301 and 600 ml was 19.45 months, between 601 and 900 ml was 12.68 months, and over 900 ml was 11.07 months ($P < 0.001$, Fig. 5). A pairwise comparison was performed for these subsets to investigate significant separation points, with findings presented in Table 3. The correlation between tumour volume and tumour weight was 0.97 and, therefore, tumour weight was not included in the multivariable model.

Neoadjuvant therapy did not have an effect on either tumour volume or tumour weight measurements ($P = 0.37$ and 0.90 , respectively). Talc pleurodesis prior to EPD also did not influence volume and weight calculations ($P = 0.10$ and 0.19 , respectively). Similarly, no significant relationship was observed between positive nodal status and tumour weight or volume ($P = 0.90$ and 0.18 , respectively).

DISCUSSION

Although significant improvements have recently been made in the diagnosis and treatment of patients with MPM, more study needs to be done to improve mesothelioma staging [7]. Imaging is widely used to clinically stage mesothelioma preoperatively using the TNM classification, but this remains largely inaccurate, and

most patients are upstaged at surgery [3, 8]. CT may identify the tumour grossly, but it is unable to provide precise information about tumour volume and invasion.

Recent improvements in the imaging study software allow for computation of the tumour volume by manual or automated delineation of structures surrounding the tumour. This type of volumetric assessment of mesothelioma has limitations because of the variable technical experience and different ability of the individual radiologist, as well as the need for manual correction of the computer output [9–12]. For example, both pleural effusion and tumour can have similar Hounsfield Unit values on CT scan, and thus, one can artificially increase image-based tumour volume unless special attention is given to such details [9]. The role of PET scans remains controversial in MPM. Its prognostic importance and the correlation between total glycolytic volume and pathological tumour volume are still to be determined. Additionally, PET scan does not reliably identify malignant lymph node involvement [13, 14].

The measurement of pathological specimen volume resected at surgery also has its limitations, as visible tumour might include extraneous tissue, such as fat or muscle resected along with the tumour. Another factor that could explain the difference between pathological and radiological measurements is the resolution, as pathological volume is measured in increments of 25 ml, whereas a typical voxel of a CT scan is 0.0015 ml (thus, there are ~17 000 pixels in 25 ml) [9].

The ultimate value of measuring tumour volume (both surgically and radiologically) is to establish more accurate staging for prognosis. TNM system is the best available staging classification to date for cancer staging of solid tumours. In MPM, however, current T staging does not measure the tumour burden, which is the purpose of the 'T' in TNM. Although the thickness of the tumour is proposed as an indirect measure of tumour burden, tumour volume is a more accurate measure of the tumour burden. In the analysis of large databases of MPM patients, there is an association between current T stage and overall survival. Our findings suggest that tumour volume is a better predictor of survival and likely provides more accurate staging for MPM. N stage is less predictive, except for the presence or absence of nodal disease [15]. We observed a correlation between resected volume and the currently used T stage. Remarkably, however, tumour volume represents tumour burden than current T and N stage.

As previously reported, we found that PS is a significant predictor of survival [16]. We similarly observed the well-known impact of histology on overall survival. Epithelioid patients survived on average 8 months longer than the non-epithelioid group. Notably, tumour volume appears equally important as a histological type or PS in predicting outcome.

We examined the impact of lymph node involvement on survival and found no difference between nodal and non-nodal disease. In this study, early T stage, but not N stage, was a predictor of survival. This finding is in disagreement with the initial analysis of the IASLC database [15] and contrary to other reports in the literature, possibly because the sample size in our study is comparatively small and therefore, we cannot arrive at definitive conclusions as made in larger databases [2, 15, 17]. We also did not observe a relationship between positive nodal stage and increased tumour volume, which is in disagreement with limited information available in the literature from other studies [5].

Neoadjuvant therapy adversely affected survival in univariable analysis but not in multivariable analysis. It did not demonstrate any correlation with the pathological tumour volume either; however,

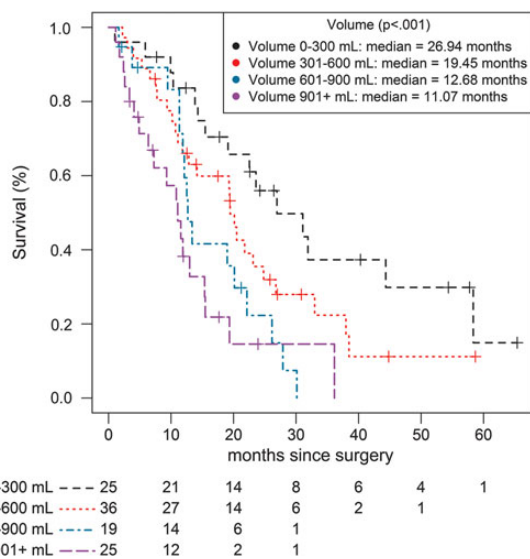


Figure 5: Kaplan-Meier survival curves for different tumour volume subsets.

Table 3: Pairwise comparison of tumour volume subsets for survival following EPD ($n = 105$)

Tumour volume	Hazard ratio	P-value
301–600 vs <300 ml	1.74	0.33
601–900 vs <300 ml	1.94	0.02
>900 vs <300 ml	1.69	<0.001
601–900 vs 301–600 ml	1.69	0.37
>900 vs 301–600 ml	2.37	0.03
>900 vs 601–900 ml	1.40	0.75

EPD: extended pleurectomy and decortication.

only 21% of our patient received neoadjuvant therapy. Adjuvant therapy was a predictor of better outcome in our study as noted in larger databases [15]. Adjuvant therapy is invariably reserved for patients who show good performance following surgery and therefore, a selection bias towards better patient population and patients' outcome exists. This selection bias can lead to better outcomes in patients receiving adjuvant therapy compared with the patients who did not receive it. We observed favourable outcome in patients receiving adjuvant therapy. This finding persisted in the analysis using a multivariate regression model, suggesting that adjuvant therapy is an independent predictor of survival following EPD. This will require further validation.

In summary, in this cohort of 116 patients undergoing EPD for MPM, we found that both specimen volume and weight are significant predictors of survival, and equally important as the histological type or PS. The correlation is stronger than the T or N stage. Using these two parameters in staging and clinical decision-making in MPM needs further validation in larger multicentre studies.

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Conflict of interest: none declared.

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