Main text: 3196 words

Abstract: 244 words

The association between pleural fluid exposure and survival in pleural mesothelioma

Running title: A retrospective cohort study in 761 patients

Rachelle Asciak*[1,2,3] MD
Nikolaos I Kanellakis*[1,2,4] PhD
Anna Bibby[5] PhD
Andrew Kidd[6,7] MBChB
Stephen Gerry[8] DPhil
Rachel Mercer[2] MBChB
Nick Maskell[5] MD
Kevin G Blyth[6,7] MD
Peter Fsadni[3] PhD
Stephen Montefort[3] PhD
Ioannis Psallidas**[1,2] PhD
Najib M Rahman**[1,2,4] DPhil

*Joint first author
**Joint senior author

1. Laboratory of Pleural and Lung Cancer Translational Research, Nuffield Department of Medicine, University of Oxford, Old Rd, Headington, Oxford OX3 7LE. UK
2. Pleural Unit, Churchill Hospital. Oxford University Hospitals Foundation Trust, Old Rd, Headington, Oxford OX3 7LE. UK
3. Mater Dei Hospital, Triq Dun Karm, L-Imsida, MSD2090. Malta
4. National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford, Oxford, OX3 7LE. UK
5. North Bristol NHS Trust, Southmead Rd, Bristol BS10 5NB. UK
6. Institute of Cancer Sciences, University of Glasgow, University Avenue, G12 8QQ, Glasgow. Scotland
7. Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow, G51 4TF. Scotland
8. Centre for Statistics in Medicine, University of Oxford, Old Rd, Headington, Oxford OX3 7LE. UK

Corresponding Author:
Rachelle Asciak
Email: rachasciak@gmail.com Telephone: 0044 7922211674
Address:
Oxford University Hospitals Foundation Trust
Churchill Hospital
Old Road
Headington
Oxford, United Kingdom
OX3 7LE

Take home message:
Pleurodesis success is associated with improved survival in patients with mesothelioma and malignant pleural effusion, however it is unclear whether the duration of exposure to pleural fluid is associated with survival.

Summary conflicts of interest:

There are no conflicts of interest relevant to this work to declare for any of the authors.

Funding info:

NI Kanellakis and NM Rahman are supported by a National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) grant.

Prior abstract presentation:

Abstract entitled 'The association between pleural fluid exposure and survival in malignant pleural mesothelioma: a retrospective cohort study in 761 patients' was presented at the European Respiratory Society congress in 2020 as a spoken presentation.

Abstract

Background

Most patients with malignant pleural mesothelioma (MPM) present with malignant pleural effusion (MPE). There is *in vitro* evidence that MPE may not be a simple bystander of malignancy, but potentially has biological properties improving cancer cell survival and promoting cancer progression. If this is the case, MPE management may need to shift from current symptomatic strategies to aggressive fluid removal to impact on survival.

Research question

Is there an association between pleural fluid exposure and survival in MPM?

Study design and Methods

Data on 761 patients diagnosed with MPM between 2008-2018 were collected from patient medical records in 3 UK pleural units. Data included factors previously identified as influencing prognosis in MPM. Medical imaging was reviewed for presence, size and duration of pleural effusion. Time-dependent covariate analysis of pleural fluid exposure and survival (model included weight loss, serum albumin, Hb, MPM subtype, performance status, chemotherapy, age), and multivariable cox regression analysis of pleurodesis and survival were conducted.

Results

Median overall survival was 278 days (IQR 127-505, 95% CI 253-301). Pleural fluid exposure duration showed no association with survival (HR 1.0, 95% CI 1.0-1.0). Median survival was 473, 378 and 258 days with complete, partial, and no pleurodesis (p 0.008).

Interpretation

Pleurodesis success appears to be associated with improved survival, however it is unclear whether duration of MPM exposure to pleural fluid is associated with survival within the limitations of this retrospective study. Future prospective studies are required to assess this potentially important mechanism.

Malignant pleural mesothelioma (MPM) is an aggressive and incurable malignancy, associated with previous asbestos exposure. The median age at diagnosis is 75 years, with overall survival being about 38% at 1 year and 7% at 3 years.[1]

Malignant pleural effusion (MPE) is often present at diagnosis in MPM.[2] Clinical management guidelines recommend symptom-guided management of MPE, with asymptomatic small effusions often managed conservatively.[3] However, there is some evidence that MPE may have additional effect beyond simply causing symptoms and may have biological properties that promote tumour growth and resistance to chemotherapy.[4] MPE fluid is often exudative, with high levels of proteins including growth factors and cytokines.[5,6] It is possible, in theory, that MPE fluid provides a conducive microenvironment for tumour cell proliferation, with abundant pro-mitotic nutrients and growth factors.[4] However, this hypothesis has never been studied in humans to date.

If MPE fluid does have biological properties that enhance cancer cell survival and promote progression, current MPE management strategies may be flawed. This theory would support a shift away from symptomatic management towards complete early drainage of fluid with aggressive fluid prevention (e.g. pleurodesis or surgery) to reduce the contribution of pleural fluid to cancer progression. However, studies in this area are mostly pre-clinical and do not necessarily reflect the *in vivo* MPE environment.

This study aimed to further the understanding of the biological role of pleural fluid, through a database of MPM patients, enabling a real-life analysis by retrospectively studying the association of pleural fluid exposure and survival in a large cohort.

Methods

Participants and data extraction

Eligible patients were those diagnosed with MPM between 2008 and 2018 (08/01/2008 to 28/02/2018) in one of three UK, tertiary-referral, pleural units. Patients were followed up until they died or were censored on data collection date (25th July, 19th July, 5th November 2018 for Glasgow, Bristol and Oxford data respectively). Date of death was collected from the medical records.

Ethics

This research was approved by the Health Research Authority (HRA): IRAS project ID 244245.

Outcomes

The primary objectives were to explore associations between pleural fluid duration and overall survival, and independent association of pleurodesis success and overall survival in MPM. The secondary objectives were to explore associations between pleural fluid presence (at start of chemotherapy) and chemotherapy response, and associations between pleural fluid presence (at MPM diagnosis) and size (at MPM diagnosis) with survival in MPM.

The primary outcome was overall survival, with independent variables of pleural fluid duration and pleurodesis success. The secondary outcomes were chemotherapy response with the independent variable of pleural fluid presence at start of chemotherapy, and

overall survival with independent variables of pleural fluid presence and size at MPM diagnosis.

Baseline demographics, known factors already associated with prognosis in MPM (e.g. weight loss, MPM subtype, performance status, haemoglobin (Hb) and serum albumin),[7] chemotherapy,[8,9] age,[10–16] the presence of malignant comorbidities, and details of any treatment received for MPM were recorded.

Presence and size of pleural effusion at MPM diagnosis and at the start of chemotherapy

Available posteroanterior chest x-rays at the point of diagnosis, and at the start of chemotherapy, were reviewed for the presence and size of MPE. MPE size was categorised using a previously published scoring system:[17–20]

- 1 - Blunting of costophrenic angle
- 2 – Fluid occupying ≤25% of hemithorax
- 3 - Fluid occupying 25-50% of hemithorax
- 4 - Fluid occupying 50-75% of hemithorax
- 5 - Fluid occupying >75% of hemithorax.

Duration of pleural effusion at MPM diagnosis

Pleural effusion duration was calculated from the date of MPM diagnosis, defined as multidisciplinary team meeting or histocytological confirmation of MPM. Available serial posteroanterior chest x-rays and thoracic ultrasound scan reports were reviewed (the investigators looked at both chest x-ray and ultrasound reports written by the reporting radiologist/sonographer, and also at the chest x-ray image itself to confirm presence/lack of pleural effusion) for each subsequent clinic appointment to assess for presence of MPE.

Where pleural fluid was reported on chest x-ray but thoracic ultrasound during the same period was reported to detect no pleural effusion, then this was documented as 'no pleural effusion' for purposes of this study. This is in recognition of the fact that pleural thickening and small pleural effusion appear similar on chest x-ray. The duration of MPE was calculated as the total number of days MPE was present (Supplementary material: Method of calculation of total duration of effusion). Due to the inherent bias that patients who die soon after MPM diagnosis would have shorter duration of exposure to MPE recorded, percentage of post-MPM diagnosis life exposed to MPE fluid was calculated, similar to Thomas R et al,[21] where the total number of days spent in hospital after a procedure was calculated as a percentage of total days in the trial (from procedure to death or to end of follow up period).

Pleurodesis success

Data were collected on whether pleurodesis was achieved at any point after MPM diagnosis or not, regardless of whether pleurodesis was spontaneous, indwelling pleural catheter (IPC)-related, or secondary to chemical or surgical pleurodesis. Data were also collected on the number of pleural interventions required to control fluid accumulation. Pleurodesis success was defined and categorised according to a combination of radiological and clinical parameters:

- Complete pleurodesis - no further MPE documented on radiology (available CT, chest x-ray or ultrasound) at any point after the MPM diagnosis and no further pleural intervention required (until death/time of data collection);
- Partial pleurodesis - persistent small to moderate (size 1-2, i.e. ≤25% of hemithorax) MPE but not requiring further pleural intervention for symptom-

relief (patients who achieved pleurodesis temporarily but eventually had small-moderate asymptomatic MPE develop again were categorised as 'partial pleurodesis' too);

- No pleurodesis - persistent recurrent MPE requiring further intervention to relieve symptoms (patients who achieved pleurodesis temporarily but then had relapse requiring intervention to drain symptomatic MPE were categorised as 'No pleurodesis' too).

Patients with non-expandable lung would often fall under the latter two categories however this was not specifically looked into.

Chemotherapy response

To determine chemotherapy response, data was collected on all patients undergoing chemotherapy from computed tomography (CT) scan taken after the end of chemotherapy. Stable disease, partial or complete response (as determined by reporting radiologist) were considered to be chemotherapy-responsive, while progression of disease was considered to be chemotherapy-unresponsive.

Time / treatment bias

Given that the management and diagnosis of MPM may have changed over time, in terms of earlier diagnosis or better availability of treatment, the data were divided into 2 year epochs, according to the year in which the MPM diagnosis was made, to assess for epoch time bias (potential improved survival due to improvements in healthcare over time). There were only 3 patients diagnosed in 2018 (when data collection ceased) therefore these were included in the epoch 2016-2018, while all other epochs were 2 year periods: 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2016-2018.

Statistics

To assess for independent association of pleurodesis success with survival, multivariable regression analysis (Cox) was conducted including pre-determined variables which were potentially associated with survival in MPM according to the literature: weight loss, MPM histological subtype, ECOG PS, serum albumin, serum Hb, age, and chemotherapy, as well as pleurodesis success. A backward selection model was used, including known predictors of outcome in MPM (which were retained) and then associations of clinical interest and those that demonstrated significance in univariable modelling (at the 0.1 threshold), In addition, Kaplan Meier curves were used to estimate survival according to pleurodesis success.

Pleural effusion duration was also assessed using a Cox model with a time-dependent covariate,[22] with the dependent variable as survival in number of days from MPM diagnosis. The significance levels satisfied the proportional hazards assumption (>0.05).

Chi square and Fisher's exact test were used to compare patients who received chemotherapy and had MPE at the start of chemotherapy to those who received chemotherapy but did not have an effusion at the start of chemotherapy, and to analyse chemotherapy response according to size of MPE at the start of chemotherapy.

In addition, cox univariable regression was used to compare survival in patients who received MPM treatment (chemotherapy, radiotherapy, immunotherapy, surgery), achieved complete, partial or no pleurodesis, according to the MPM histological subtype, whether talc was received, and according to MPE presence at MPM diagnosis, presence of

weight loss, MPE size at MPM diagnosis, age, ECOG PS, serum Hb, and serum albumin at MPM diagnosis.

GraphPad PRISM version 8.3.0 for macOS (GraphPad Software, San Diego, California USA, www.graphpad.com) and IBM SPSS Statistics for Macintosh version 25.0.0.1 (Armonk, NY: IBM Corp) were used for data analysis, statistics and graphs. A p value of <0.05 was considered to be statistically significant.

Results

Baseline demographics and data completeness

A total of 761 patients diagnosed with MPM were included (median age 73, IQR 67-80, 95% CI 72-74) years; 72% epithelioid, 10% biphasic, 18% sarcomatoid histological subtypes). Table 1 shows the baseline characteristics. There were 9/761 (1.18%) patients with inadequate data on survival.

Primary analysis

Survival according to duration of MPE *after the MPM diagnosis*

Higher percentage of post-MPM diagnosis life exposed to MPE was associated with longer survival (*p* 0.001, HR 1.004, 95% CI for HR 1.002-1.007), when unadjusted for other factors.

A time dependent covariate analysis of MPE exposure and survival was performed, including weight loss, serum albumin at diagnosis, Hb at MPM diagnosis, MPM subtype, ECOG PS, age and whether chemotherapy was received or not. When duration of MPE (in number of days since MPM diagnosis) was analysed as a time-dependent covariate, there was no significant relationship between MPE exposure time and survival (HR 1.000, 95% CI for HR 1.000-1.000).

Survival according to pleurodesis success

Successful pleurodesis was strongly associated with survival in univariable analysis. The median survival was 473, 378 and 258 days in patients with complete pleurodesis (*n*=128), partial pleurodesis (*n*=107), and no pleurodesis (*n*=99) respectively (*n*=143 had

no effusion throughout their MPM disease, *n*=284 had inadequate data): *p* <0.0001, HR 0.750, 95% CI for HR 0.652-0.864, unadjusted for other factors (Figure 1). Patients who received intrapleural talc (*n*=194), be it talc slurry through a chest drain or talc poudrage at thoracoscopy, had longer median survival than patients who did not receive any talc intrapleurally (*n*=187) (481 *vs* 369 days, *p* 0.002, HR 0.705, 95% CI for HR 0.567-0.877).

Multivariable regression analysis (Cox) was conducted including weight loss at diagnosis, MPM subtype, ECOG PS, Hb at diagnosis, serum albumin at diagnosis, age, and chemotherapy received, together with pleurodesis success and pleurodesis success remained significantly associated with longer survival (*p* 0.008) (Table 2).

Survival association with baseline features

Weight loss, MPM subtype, ECOG PS, serum albumin and Hb at MPM diagnosis, age, and chemotherapy were all significantly associated with survival in MPM by univariable analysis, remaining significantly associated with survival (except for Hb and age) by multivariable analysis. Radiotherapy and immunotherapy were not associated with survival; a small number of patients who underwent surgery survived longer (Supplementary data).

Survival was not associated with presence of other malignant comorbidities, or with time epoch for years 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2016-2018 respectively (data not available *n*=10). Survival varied according to different Pleural units: Glasgow, Bristol and Oxford (median survival was 264, 369, 421 days respectively; data not available on date of death or alive/dead status in *n*=10; Bristol *vs* Oxford: HR 1.022, 95% CI 0.814 – 1.284; Glasgow *vs* Bristol: HR 1.393, 95% CI 1.163 – 1.667; Glasgow *vs* Oxford:

HR 1.414, 95% CI 1.184 – 1.690; p <0.0003) (Supplementary data and Supplementary Table 1).

Secondary analyses

Survival according to the presence and size of MPE at MPM diagnosis

Median survival was 321 *vs* 286 days for patients with and without MPE at MPM diagnosis respectively: p 0.237, HR 0.611, 95% CI of HR 0.270-1.384 (inadequate data in n=10).

Twenty-one patients had inadequate data on size of effusion or survival, and 740 patients were analysed. Of these, 143 (19.3%) had no effusion (size 0), 257 (34.7%) had size 1-2, 287 (38.8%) had size 3-4, and 53 (7.2%) had size 5 MPE at MPM diagnosis. There was no association between effusion size and median survival (276, 297, 351, and 297 days respectively; sizes 0 *vs* 1-2: HR 1.117, 95% CI for HR 0.900 – 1.386; 0 *vs* 3-4: HR 1.189, 95% CI for HR 0.959 – 1.474; 0 *vs* 5: HR 1.038, 95% CI for HR 0.7485 – 1.441; 1-2 *vs* 3-4: HR 1.081, 95% CI for HR 0.9038 – 1.292; 1-2 *vs* 5: HR 0.9363, 95% CI for HR 0.6807 – 1.288; 3-4 *vs* 5: HR 0.843, 95% CI for HR 0.608 – 1.170; p 0.456).

Chemotherapy response and presence of MPE

There were 272 patients documented to have received first line chemotherapy. Forty-five patients did not have adequate data on MPE presence and chemotherapy response, 227 patients were analysed further. When comparing patients who received chemotherapy and had a MPE at the start of chemotherapy (n=167, 73.6%) with those who received chemotherapy but did not have a MPE at the start of chemotherapy (n=60, 26.4%): 104

(62.3%) and 37 (61.7%) respectively responded to chemotherapy, while 63 and 23 respectively did not (p 1.0, two-sided, Fisher's exact test).

There was no significant difference in chemotherapy response when comparing the effect of the size of the MPE in patients who had a MPE at the start of chemotherapy (n=167): 117 (70.1%) patients had size 1-2 MPE (77 (65.8%) patients responded to chemotherapy), 46 (27.5%) patients had size 3-4 MPE (23 (50%) responded to chemotherapy), and 4 (2.4%) patients had size 5 MPE (4 (100%) responded to chemotherapy); χ^2 6.0, df 2, p 0.05 [Chi square].

Discussion

This is the largest study in the literature to specifically address the association of MPE presence and survival in mesothelioma based on clinical data. Pleurodesis success appears to be associated with improved survival in MPM, however longer MPE duration was not associated with worsened survival in MPM albeit within the limits of this retrospective data.

The previously known factors associated with survival in MPM were also found to be associated with survival in our data, and therefore our cohort is likely to represent real-life data. Furthermore, our analysis demonstrated that both MPM with and without MPE at diagnosis carry a similar poor prognosis, as also noted by Bibby A, et al,[23] in contrast to other primary tumours such as lung cancer, where the presence of MPE indicates advanced stage of malignancy.

The size of effusion on chest x-ray at MPM diagnosis was not associated with survival. There are conflicting results of the association between MPE size and survival in the literature. In a study of 120 patients with MPE (not specifically MPM-related MPE), massive MPEs were associated with worse survival than in patients with moderate MPE (8 *vs* 11 months respectively, p <0.001),[24] however another study of 102 patients with MPE found that size of MPE did not influence the 30 day survival rate.[25] Our data included a larger cohort of patients, and accounted for other confounders too, including the factors that are known to be associated with survival in MPM.[7] Thus, the relationship between MPE volume and "stage" or aggression of mesothelioma remains unclear.

An association between time exposed to MPE and survival was not demonstrated with Cox regression and time-dependent analyses. Although *in vitro* data suggest that MPE presence is associated with increased malignant cell growth,[4] this has to date never been assessed using human data. Does this data therefore mean that MPE presence is irrelevant to cancer progression in humans? There are a number of reasons for which this conclusion may not be safe, even within this large dataset.

Pleurodesis success has been associated with improved survival.[26,27] There are several possible explanations for this finding. Firstly, more advanced bulky MPM tumour may prevent full apposition and adhesion of visceral and parietal pleura, hence preventing pleurodesis. Secondly, there is *in vitro* evidence of the apoptotic effect of talc on MPM cells and lung cancer cells, while having no effect on normal pleural mesothelial cells' apoptosis.[28,29] This effect may in part be due to higher levels of endostatin within pleural fluid after talc instillation, converting the pleural space from a highly angiogenic to an angiostatic environment.[30] Pleurodesis success was a predictor of survival in this dataset, even when all known predictors were accounted for, and thus it is possible that pleurodesis has an effect on survival, the mechanisms for which require exploration. In relation to the main study findings presented here, separation of MPE presence and pleurodesis success is also challenging. However, it should be noted that talc pleurodesis is also more likely to be considered in patients with higher ECOG PS, thus confounding by indication. In addition, the mode of talc delivery (slurry via chest drain, or poudrage at thoracoscopy, which may well code for different ECOG PS) was unknown, and this poses a further limitation.

Similarly, chemotherapy is only considered in patients who are fit enough to receive it, and in MPM is usually only considered in patients with ECOG PS 0-2, thus patients having lower ECOG PS were more likely to receive first line chemotherapy in this study.

There are several limitations to this study. This is a retrospective analysis with the associated biases, and it was not possible from this data to determine exposure time of MPM to MPE prior to the date when MPM was diagnosed, therefore it should be acknowledged that there would be variability in exposure before presentation which might affect the results. Data was collected from existing medical records, and so chest x-rays will be opportunistic and some patients may have pleurodesed earlier than detected. Small to moderate MPE not requiring therapeutic pleural procedures were included in exposure time to MPE fluid, even if the volume was small and may not have been enough to bathe the pleural tumour adequately. In addition, it is not always possible to differentiate pleural fluid from thickening on chest x-ray (which was used as the main method of calculating exposure), and what was documented to be persistent MPE may have been pleural thickening, which is a hallmark of MPM. With regards to determining chemotherapy response, MPM can be very indolent, so what was reported as 'stable' disease after chemotherapy may not necessarily mean chemotherapy responsive since the MPM may have been chemotherapy resistant but slow to progress. Finally, due to the retrospective nature of the data, the final Cox regression model dropped 85.9% of cases because of missing values (analysing 14.1% of the initial dataset), highlighting the issue of missing data. Although data on presence and size of pleural effusion at the start of chemotherapy was available, data on the duration of pleural effusion throughout the course of chemotherapy was not, and it was not possible to analyse the effect of pleural effusion throughout the course of treatment on treatment-response.

Interpretation

In this large dataset, pleurodesis success appears to be associated with improved survival in MPM, but it is unclear whether prolonged exposure to MPE worsened survival or chemotherapy response in MPM, given the potential biases in this retrospective analysis. Clinically, a key unanswered question is whether MPE should be drained as early and completely as possible in order to improve morbidity and mortality in MPM, and this data suggests that a prospective study with robust radiological detection of fluid and objective outcome criteria is now required.

Acknowledgements

Guarantor: RA.

Author contributions: RA, NIK, IP, NMR designed the study; RA, AB, AK, RM collected data; RA, AB, SG, IP, NMR analysed data; all authors contributed to the writing of the manuscript and proof reading.

Funding: NI Kanellakis and NM Rahman are supported by a National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) grant.

Take home Point

Study question: Is there an association between pleural fluid exposure and survival in MPM?

Results: Pleurodesis success was associated with improved overall survival, however longer duration of malignant pleural effusion was not associated with overall survival in this cohort.

Interpretation: Clinically, a key unanswered question is whether MPE should be drained as early and completely as possible in order to improve morbidity and mortality in MPM, and this data suggests that a prospective study with robust radiological detection of fluid and objective outcome criteria is now required.

References

1. National Mesothelioma Audit report 2018 (audit period 2014–16). RCP London. Published June 21, 2018. Accessed June 30, 2018. https://www.rcplondon.ac.uk/projects/outputs/national-mesothelioma-audit-report-2018-audit-period-2014-16

2. Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax*. 2018;73(Suppl 1):i1-i30. doi:10.1136/thoraxjnl-2017-211321

3. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(7):839-849. doi:10.1164/rccm.201807-1415ST

4. Cheah HM, Lansley SM, Varano Della Vergiliana JF, et al. Malignant pleural fluid from mesothelioma has potent biological activities. *Respirology*. 2017;22(1):192-199. doi:10.1111/resp.12874

5. Stathopoulos GT, Kollintza A, Moschos C, et al. Tumor Necrosis Factor-α Promotes Malignant Pleural Effusion. *Cancer Res*. 2007;67(20):9825-9834. doi:10.1158/0008-5472.CAN-07-1064

6. Zebrowski BK, Yano S, Liu W, et al. Vascular Endothelial Growth Factor Levels and Induction of Permeability in Malignant Pleural Effusions. *Clin Cancer Res*. 1999;5(11):3364-3368.

7. Brims FJH, Meniawy TM, Duffus I, et al. A Novel Clinical Prediction Model for Prognosis in Malignant Pleural Mesothelioma Using Decision Tree Analysis. *J Thorac Oncol*. 2016;11(4):573-582. doi:10.1016/j.jtho.2015.12.108

8. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol*. 2005;23(28):6881-6889. doi:10.1200/JCO.20005.14.589

9. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21(14):2636-2644. doi:10.1200/JCO.2003.11.136

10. Marinaccio A, Nesti M, Regional Operational Centers. Analysis of survival of mesothelioma cases in the Italian register (ReNaM). *Eur J Cancer*. 2003;39(9):1290-1295.

11. Milano MT, Zhang H. Malignant pleural mesothelioma: a population-based study of survival. *J Thorac Oncol*. 2010;5(11):1841-1848. doi:10.1097/JTO.0b013e3181f1cf2b

12. Montanaro F, Rosato R, Gangemi M, et al. Survival of pleural malignant mesothelioma in Italy: a population-based study. *Int J Cancer*. 2009;124(1):201-207. doi:10.1002/ijc.23874

13. Musk AW, Olsen N, Alfonso H, et al. Predicting survival in malignant mesothelioma. *European Respiratory Journal*. 2011;38(6):1420-1424. doi:10.1183/09031936.00000811

14. Neumann V, Rütten A, Scharmach M, Müller K-M, Fischer M. Factors influencing long-term survival in mesothelioma patients—results of the German mesothelioma register. *Int Arch Occup Environ Health*. 2004;77(3):191-199. doi:10.1007/s00420-003-0498-6

15. Nojiri S, Gemba K, Aoe K, et al. Survival and prognostic factors in malignant pleural mesothelioma: a retrospective study of 314 patients in the west part of Japan. *Jpn J Clin Oncol*. 2011;41(1):32-39. doi:10.1093/jjco/hyq159

16. van der Bij S, Koffijberg H, Burgers JA, et al. Prognosis and prognostic factors of patients with mesothelioma: a population-based study. *British Journal of Cancer*. 2012;107(1):161-164. doi:10.1038/bjc.2012.245

17. Light RW, Rogers JT, Cheng D, Rodriguez RM. Large pleural effusions occurring after coronary artery bypass grafting. Cardiovascular Surgery Associates, PC. *Ann Intern Med*. 1999;130(11):891-896.

18. Cartaxo AM, Vargas FS, Salge JM, et al. Improvements in the 6-Min Walk Test and Spirometry Following Thoracentesis for Symptomatic Pleural Effusions. *Chest*. 2011;139(6):1424-1429. doi:10.1378/chest.10-1679

19. Livingston MH, Mahant S, Ratjen F, et al. Intrapleural Dornase and Tissue Plasminogen Activator in pediatric empyema (DTPA): a study protocol for a randomized controlled trial. *Trials*. 2017;18. doi:10.1186/s13063-017-2026-0

20. Misra H, Dikensoy O, Rodriguez RM, et al. Prevalence of pleural effusions post orthotopic heart transplantation. *Respirology*. 2007;12(6):887-890. doi:10.1111/j.1440-1843.2007.01174.x

21. Thomas R, Fysh ETH, Smith NA, et al. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. *JAMA*. 2017;318(19):1903-1912. doi:10.1001/jama.2017.17426

22. Fisher LD, Lin DY. Time-Dependent Covariates in the Cox Proportional-Hazards Regression Model. *Annual Review of Public Health*. 1999;20(1):145-157. doi:10.1146/annurev.publhealth.20.1.145

23. Bibby AC, Halford P, De Fonseka D, Morley AJ, Smith S, Maskell NA. The Prevalence and Clinical Relevance of Nonexpandable Lung in Malignant Pleural Mesothelioma. A Prospective, Single-Center Cohort Study of 229 Patients. *Annals ATS*. 2019;16(10):1273-1279. doi:10.1513/AnnalsATS.201811-786OC

24. Martínez-Moragón E, Aparicio J, Sanchis J, Menéndez R, Cruz Rogado M, Sanchis F. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. *Respiration*. 1998;65(2):108-113. doi:10.1159/000029240

25. Amin Z, Iskandar SD, Sibli. Prognostic Factors of 30-day Survival of Patients with Malignant Pleural Effusion. *Indian J Palliat Care*. 2017;23(3):321-324. doi:10.4103/IJPC.IJPC_2_17

26. Hassan M, Mercer RM, Maskell NA, et al. Survival in patients with malignant pleural effusion undergoing talc pleurodesis. *Lung Cancer*. 2019;137:14-18. doi:10.1016/j.lungcan.2019.09.003

27. Korsic M, Badovinac S, Cucevic B, Janevski Z. Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study. *Wien Klin Wochenschr*. 2015;127(23-24):963-969. doi:10.1007/s00508-015-0716-8

28. Nasreen N, Mohammed KA, Dowling PA, Ward MJ, Galffy G, Antony VB. Talc Induces Apoptosis in Human Malignant Mesothelioma Cells In Vitro. *Am J Respir Crit Care Med*. 2000;161(2):595-600. doi:10.1164/ajrccm.161.2.9904123

29. Lee P, Sun L, Lim CK, Aw SE, Colt HG. Selective apoptosis of lung cancer cells with talc. *European Respiratory Journal*. 2010;35(2):450-452. doi:10.1183/09031936.00113109

30. Nasreen N, Najmunnisa N, Mohammed KA, et al. Talc mediates angiostasis in malignant pleural effusions via endostatin induction. *Eur Respir J*. 2007;29(4):761-769. doi:10.1183/09031936.00061606

Tables

Table 1: Summary statistics for baseline characteristics of cohort

Parameter	Summary statistics	Data not available for analysis (*n*, %)
Age at diagnosis in years (median (IQR, 95% CI))	73 (67-80, 72-74)	0
Status at time of data collection Alive Dead	 69 683	9 (1.2)
Overall survival (days) in patients who died (*n*=683) (median (IQR, 95% CI))	278 (127-505, 253-301)	9 (1.2)
Follow up time (days)* (median (IQR, 95% CI))	301 (139-544, 281-337)	2 (0.3)
Weight loss at diagnosis (*n*, %)	233 (33.9)	74 (9.7)
Haemoglobin at diagnosis (g/l) (median (IQR, 95% CI))	133 (120-147, 132-135)	44 (5.8)
Serum albumin at diagnosis (g/l) (median (IQR, 95% CI))	34 (29-38, 33-34)	54 (7.1)
ECOG PS at diagnosis (*n*, %) 0 1 2 3 4	 174 (27.4) 323 (50.8) 87 (13.7) 45 (7.1) 7 (1.1)	125 (16.4)
Mesothelioma histological subtype (*n*, %) Epithelioid Biphasic Sarcomatoid	 511 (72.1) 70 (9.9) 128 (18.1)	52 (6.8)
Chemotherapy received (*n*, %) Yes No	 272 (36.3)** 477 (63.7)	12 (1.6)
Surgery for mesothelioma (*n*, %)	11 (1.4)***	0
Malignant co-morbidities No Yes	 655 (86.2) 105 (13.8)	1 (0.1)

Table 1 showing the summary statistics for the baseline characteristics of the MPM population studied. *ECOG PS = Eastern Cooperative Oncology Group performance status. *Follow up time = calculated from diagnosis of MPM to date of death or censoring. **Chemotherapy response: responded n=151 (151/248, 60.9%), did not respond n=97, not available n=24. ***Surgery: partial pleurectomy n=1, extrapleural pneumonectomy n=4, pleurectomy decortication n=4, single pleural /lung mass resected n=2.*

Table 2: results of multivariable Cox regression analysis with pleurodesis success

Variable	Degrees of freedom	*p* value; Hazard Ratio, 95% CI for Hazard Ratio
Weight loss at MPM diagnosis	1	0.09; 0.77, 0.57-1.04
Hb (g/l) at MPM diagnosis	1	0.21; 0.99, 0.99-1.0
Serum albumin (g/l) at MPM diagnosis	1	0.004; 0.96, 0.93-0.99
MPM histological subtype coded as follows in SPSS: **1=epithelioid** **2=biphasic** **3=sarcomatoid**	2	<0.0001
ECOG PS at diagnosis	3	0.02
Chemotherapy received	1	0.08; 1.35, 0.97-1.9
Age at MPM diagnosis	1	0.67; 1.0, 0.99-1.02
Pleurodesis success **0=none** **1=partial pleurodesis** **2=complete pleurodesis**	2	0.008

Table 2 shows the results of multivariable Cox regression analysis of factors found to be associated with survival in MPM according to the literature, with the addition of pleurodesis success to the model. Cases dropped during this analysis: 1258 (83.6%) highlighting the issue of missing data. *CI = confidence interval; ECOG PS = Eastern cooperative oncology group performance status; MPM=malignant pleural mesothelioma.*

Figure legend

Figure 1 shows Kaplan Meier survival curves according to whether patients achieved complete, partial or no pleurodesis.