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Survival in patients with malignant pleural effusion undergoing talc pleurodesis

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ABSTRACT

Objectives: Recent observations indicate a potential survival benefit in patients with malignant pleural effusion (MPE) who achieve successful pleurodesis in comparison to patients who experience effusion recurrence post pleurodesis. This study aimed to explore this observation using two datasets of patients with MPE undergoing talc pleurodesis.

Materials and Methods: Dataset 1 comprised patients who underwent talc pleurodesis at Oxford Pleural Unit for MPE. Dataset 2 comprised patients enrolled in the TIME1 clinical trial. Pleurodesis success was defined as absence of need for further therapeutic procedures for MPE in the three months following pleurodesis. Data on various clinical, laboratory and radiological parameters were collected and survival was compared according to pleurodesis outcome (success vs. failure) after adjusting for the aforementioned parameters.

Results: Dataset 1 comprised 60 patients with mean age 74.1 ± 10.3 years. The most common primary malignancies were mesothelioma, breast and lung cancer. 29 patients (48.3%) achieved pleurodesis. The adjusted odds ratio (aOR) for poor survival with pleurodesis failure was 2.85 (95% CI 1.08–7.50, =p 0.034).

Dataset 2 comprised 259 patients from the TIME1 trial. The mean age was 70.8 ± 10.3 and the most common primary malignancies were mesothelioma, lung and breast cancer. Pleurodesis was successful in 205 patients (79%). aOR for poor survival was 1.62 (95% CI 1.09–2.39, p = 0.015).

Conclusion: Achieving pleurodesis seems to impart a survival benefit in patients with MPE. Further studies are required to explore factors that may contribute to this phenomenon and to address the difference in survival between pleurodesis and indwelling pleural catheter interventions.

1. Introduction

Patients with malignant pleural effusion (MPE) are often symptomatic with breathlessness and their management is typically centred on palliation of their symptoms. [1] Therapeutic aspiration of the pleural fluid brings short-term benefit as the effusion tends to recur quickly and longer term palliative methods are frequently required [2]. The standard management in the UK for patients with MPE who do not have unexpandable lung is performing pleurodesis by applying talc to the pleural space [3].

The life expectancy of patients with MPE is usually expressed in months with median survival times ranging between 3–12 months. [1] It is common practice to reserve pleurodesis for patients with a good level of fitness commensurate with better performance status and to offer therapeutic thoracentesis to frailer patients with a more limited prognosis. A useful tool to predict survival in patients with MPE is the LENT score which is a robust method that provides important prognostic information, but it is yet to be prospectively validated [4]. The score utilises four readily available parameters namely; the pleural fluid LDH level, the Eastern Cooperative Oncology Group (ECOG) performance status, the serum neutrophil to lymphocyte ratio and the histology of the primary tumour to predict the survival of a given patient. More recently, a new tool has been devised to predict the mortality risk

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at three months in patients with MPE based on clinical and biochemical parameters and is called the PROMISE score [5].

It has been previously noted that in patients with mesothelioma, the survival of patients who undergo pleurodesis (regardless of the method used) is longer in comparison to patients who do not receive this treatment [6] and similar findings were noted in MPE secondary to non-pleural malignancies [7]. It could be argued that this survival difference is inherently related to the selection bias of better performance status patients who are offered pleurodesis; however, this difference was still observed when survival only in patients with higher performance status was studied [7]. Recent data suggest that a survival benefit is seen in MPE patients who have successful pleurodesis in comparison to those who fail pleurodesis and this has been reported in cohorts of patients with mesothelioma [8,9] and other malignancies [10] and where talc [9,11] or other substances such as bleomycin [10] were used to induce pleurodesis.

This study aimed to explore whether there was a difference in survival according to pleurodesis outcome in patients with MPE undergoing pleurodesis using large databases of prospectively collected data on patients with MPE undergoing talc pleurodesis.

2. Methods

The study utilised two independent and non-overlapping datasets of patients who underwent talc pleurodesis for MPE.

2.1. Dataset 1

The first dataset (Dataset 1) comprised all patients who underwent thoracoscopic talc poudrage or chest drain insertion and talc slurry for management of MPE on the procedure list of the Oxford Pleural Unit between 2016 and 2017. From sixty nine patients included in this dataset, only patients whose outcome of pleurodesis was known and who survived for one month or longer were included. Pleurodesis failure was defined as the need for additional therapeutic procedures on the same side within three months of pleurodesis regardless of whether the additional procedures were conducted together with X-ray evidence of fluid recurrence. Data on baseline demographic, clinical, pleural fluid characteristics and time to death were collected.

2.2. Dataset 2

The second dataset (Dataset 2) comprised patients enrolled in the TIME1 randomised controlled trial (RCT) [12]. This trial prospectively studied the effect of analgesia type (non-steroidal vs. opioids) and chest drain calibre (12 F vs. 24 F) on the rate of pain and procedure outcome in patients with MPE undergoing talc pleurodesis. It recruited 320 patients from three countries (UK, US and Canada) between 2007 and 2013 and used a 2 × 2 factorial design. All-cause mortality data for trial patients were collected for 12 months post randomisation. The co-primary endpoints were the rate of pleurodesis success at three months and pain scores.

In TIME1, pleurodesis failure was defined as the need for further ipsilateral therapeutic pleural intervention to relieve dyspnoea within three months after randomisation or the presence of symptoms and $\geq$50% opacification on chest X-ray on the same side of pleurodesis even if an intervention was not performed. Of the TIME1 trial patients, 285 were included in the final analysis of primary endpoints.

In this study for the purpose of post-hoc analysis, we included trial patients who survived for at least one month following randomisation and who had data on whether pleurodesis was successful or not.

Baseline characteristics of patients from both datasets were presented as frequencies and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables according to normality of distribution of data. Comparisons according to pleurodesis outcome were done. Chi^2 or Fisher exact tests were used for comparisons of categorical variables and student -T or Mann-Whitney tests were used for comparisons of continuous variables as appropriate.

Survival analysis

For both Datasets, survival according to pleurodesis outcome was assessed using the Kaplan Meier method and compared using the log rank test.

Median survival and 95% confidence intervals are presented according to the following factors and comparisons made using the log rank test:

- Primary malignancy: for patients with known primary tumour, cases were classified as either lower risk (LENT score [4] class one and two, comprising mesothelioma, breast cancer, gynaecologic and, haematologic malignancy and renal cell carcinoma) or higher risk (LENT class three comprising lung cancer and “other” primary)
- Pleural fluid LDH: patients classified as lower risk; LDH < 1500 U/L or higher risk; LHD ≥ 1500 U/L.
- Unexpandable lung (as a surrogate for extent of pleural disease)
- Serum total white cell count as a surrogate for the neutrophil to lymphocyte ratio
- Whether patients received systemic cancer therapy (data only available for Dataset 1)

To adjust for the potential effects of other co-variates on survival, together with pleurodesis outcome all factors were entered into a Cox proportional hazards model. Odds ratio (OR) with 95% confidence intervals (CI) are presented.

3. Results

3.1. Dataset 1

In this study, 60 patients were included: nine patients were excluded due to uncertainty regarding pleurodesis outcome in two, non-availability of survival data in two, and survival less than a month in five patients. Baseline characteristics are shown in Table 1.

At the end of the follow up period (median 23 months, range 6–34 months), 20 patients (33.3%) were alive. Of these patients, 13 (45.8%) belonged to the group who had successful pleurodesis and seven (23.5%) had pleurodesis failure. Table S1 shows the median survival in Dataset 1 patients, as well as survival differences according to clinical, radiological and laboratory parameters.

The median survival for all patients in Dataset 1 was 11 months (95% CI 6.62–15.37 months). Median survival for patients who had successful pleurodesis was 16 months (95% CI 8.06–23.93), while for those who failed pleurodesis median survival was 5 months (95% CI 2.57–7.48), p = 0.007 (log rank test). The Kaplan-Meier survival plot according to pleurodesis outcome for patients in Dataset 1 is shown in Fig. 1.

The unadjusted OR for poor outcome using a Cox regression model using the variables presented in Table S1 is shown in Table S2. These variables were entered into Cox regression model to obtain the adjusted odds ratios (aOR) for poor survival and these are presented in Table 2. The aOR for poor survival with pleurodesis failure was 2.85 (95% CI 1.08–7.50, =p 0.034).

3.2. Dataset 2

Of the 285 patients included in the final analysis of the TIME1 trial, 26 patients had poor survival (less than 4 weeks) and were excluded and hence this post-hoc analysis was done on 259 patients. Table 3 shows the baseline characteristics of this cohort.

By the end of the 12-month follow up period, 79 patients were alive. Of those, 70 had successful pleurodesis (34%) and nine had failed pleurodesis (17%). The median survival for all patients in Dataset 2 was 11 months (95% CI 10.42–11.57). According to pleurodesis outcome,

Table 1
Baseline characteristics for patients in Dataset 1. Data for continuous variables is presented as mean ± SD or median (IQR) and for discrete variables as frequency (per cent).

Variable	Patients (n = 60)	Pleurodesis Success (n = 29)	Pleurodesis Failure (n = 31)	Significance
Age, years	74.1 ± 10.3	71.9 ± 8.4	76.2 ± 11.6	Mean difference 4.3 y (95%CI −1 – 9.6) p = 0.111
Sex, male	31 (51.6%)	17 (58.6%)	14 (45.1%)	Chi^2 3.20, df1, p = 0.082
Primary				
Mesothelioma	22 (36.6%)	10 (34.4%)	12 (38.7%)	Chi^2 1.19, df6, p 0.977
Breast	14 (23.3%)	6 (20.6)	8 (25.8%)	
Lung	13 (21.6%)	7 (24.1)	6 (19.3%)	
Gynecologic	3 (05%)	2 (6.8%)	1 (3.2%)	
GI	3 (5%)	2 (6.8%)	1 (3.2%)	
Hematologic	2 (3.3%)	1 (3.4%)	1 (3.2%)	
Other	3 (5%)	1 (3.4%)	2 (6.4%)	
Systemic therapy	35 (58.3%)	24 (82.7%)	11 (35.4%)	Chi^2 13.77,df1, p < 0.001
Pleural Fluid LDH, IU/L	270 (164-625) (n = 45)	268.5 (196.7 – 386.3) (n = 22)	310 (144 – 1194) (n = 23)	P = 0.570
Pleural Fluid protein. g/L	41.52 ± 7.44 (n = 42)	44.05 ± 6.24(n = 21)	39.0 ± 7.82 (n = 21)	Mean difference 2.18 g/L(95%CI 0.63 – 9.46), p = 0.026
Pleural Fluid glucose, mmol/L	4.40 (3.55 – 5.85) (n = 41)	4.05 (3.53 – 5.30) (n = 20)	5.20 (3.20 – 6.35) (n = 21)	P = 0.251
Method of talc administration, poudrage	34 (56.6%)	20 (68.9%)	14 (45.2%)	Chi^2 3.458, df1, p = 0.063
Unexpandable lung	6 (10%)	0 (0%)	6 (19.3%)	Fisher Exact test, p = 0.024

IQR: interquartile range; SD: standard deviation.
CI: confidence interval.

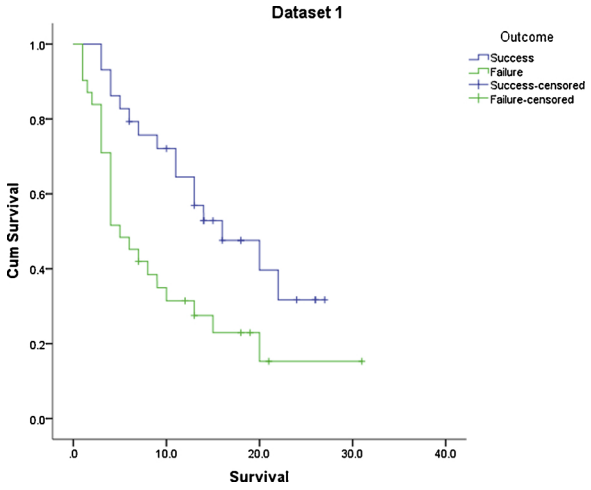

Fig. 1. Kaplan-Meier survival curve by pleurodesis outcome for Dataset 1. Survival is presented in months.

Table 2
Adjusted odds ratio for poor survival in patients of Dataset 1 using Cox proportional hazards model (45 patients included).

	Beta	Standard error	Sig.	aOR	95.0% CI for aOR	
					Lower	Upper
High-risk primary malignancy*	1.302	.477	0.006	3.677	1.443	9.367
Unexpandable lung	0.260	0.843	0.758	1.296	0.248	6.771
High Pleural Fluid LDH*	0.476	0.735	0.517	1.610	0.381	6.801
Pleurodesis failure	1.048	0.493	0.034	2.852	1.084	7.500
Systemic Therapy	0.189	0.561	0.735	1.209	0.403	3.626

Key: * as per LENT score.
aOR: adjusted odds ratio.
CI: confidence interval.

median survival for patients who had successful pleurodesis was 11 months (95% CI 10.81–11.18), while for those who failed pleurodesis the median survival was 6.4 months (95% CI 4.87–7.93); p = 0.001 (log rank test). Fig. 2 shows the Kaplan-Meier survival plot for patients in Dataset 2 according to pleurodesis outcome. Table S3 shows the median survival of Dataset 2 patients. Table S4 shows the unadjusted OR for poor survival according to different clinical and laboratory variables.

Table 4 shows the aOR for poor survival using the Cox proportional hazards model and based on pleurodesis outcomes and controlled for the type of the tumour, the presence of unexpandable lung and the serum white cell count (222 patients included in the model). Another model is presented in Table S5 where pleural fluid LDH level is adjusted for, however this model was based on data from only 157 patients. The two models showed aOR of 1.62 and 1.86, respectively for poor survival and pleurodesis failure.

4. Discussion

This post-hoc analysis from two datasets confirms previously observed survival differences between patients with MPE who achieve successful pleurodesis when compared with those refractory to pleurodesis. After adjusting for important factors that affect survival in patients with MPE; particularly the type of the primary cancer [13] and pleural fluid LDH levels, this survival benefit was still observed.

We attempted to control for other variables that comprise the LENT score [4], and so included as a co-variable the total serum white cell count. This is not a component of the LENT score but is included in the PROMISE score and higher white cell counts are associated with higher rates of three-month mortality [5]. In this study, the white cell count was found to correlate with survival, but only in univariate analysis.

In multivariate analysis other variables that potentially adversely affect survival in patients with MPE included (from both datasets) the presence of unexpandable lung as a surrogate marker for the extent of pleural malignancy, and whether patients received systemic treatment for cancer (Dataset 1). When all these co-variables were analysed in the same model, with pleurodesis outcome, pleurodesis failure remained a significant predictor of survival.

The longer survival associated with attempting pleurodesis for managing MPE has been reported by several groups [6–9,11]. Although it could be argued that this reported difference is simply due to publication bias, as negative results are not published by authors or publishers, the same difference was observed in our study. We used information available from two different datasets; one with real-life data

Table 3
Baseline characteristics for TIME1 (Dataset 2) patients. Data for continuous variables is presented as mean ± SD or median (IQR) and for discrete variables as frequency (per cent).

	Total (n = 259)	Pleurodesis success (n = 205)	Pleurodesis failure (n = 54)	Significance
Age, years	70.8 ± 10.3	70.6 ± 10.3	71.9 ± 19.9	P = 0.444
Sex, male	159 (65%)	131 (64%)	38 (70%)	Chi^2 0.789, df1, p = 0.235
Primary malignancy				
Mesothelioma	104 (40%)	75 (36.6%)	29 (53.5%)	Chi2 06.686 df6, p = 0.011
Lung	50 (19.4%)	36 (17.5%)	14 (25.9%)	
Breast	28 (10.8)	23 (11.3%)	5 (9.4%)	
Gynaecologic	8 (3.1%)	6 (2.9%)	2 (3.7%)	
Gastrointestinal	6 (2.4%)	6 (2.9%)	0	
Haematologic	4 (1.6%)	4 (1.9%)	0	
Other/unconfirmed	59 (22.7)	55 (26.9%)	4 (7.5%)	
Pleural Fluid LDH, IU/L	577 (328 – 1112) (n = 177)	585 (342 – 999) (n = 141)	531 (260 -1730) (n = 37)	P = 0.921
Pleural Fluid Protein, g/L	45.39 ± 8.7 (n = 185)	45.42 + 8.9 (n = 147)	45.29 + 7.9 (n = 38)	P = 0.934
Pleural Fluid PH	7.48 ± 0.30 (n = 136)	7.53 ± 0.32 (n = 108)	7.35 ± 0.18 (n = 28)	Mean difference 0.173 (95% CI 0.05 – 0.29) p = 0.007
Method of talc administration, poudrage	172 (66.4%)	144 (70.2%)	28 (46.2)	Chi^2 6.48, df1, p = 0.011
Unexpandable lung	40 (17%) (n = 234)	26 (14%) (n = 187)	14 (29.8%) (n = 47)	Chi2 6.686, df1, p = 0.011

IQR: interquartile range; SD: standard deviation.
CI: confidence interval.

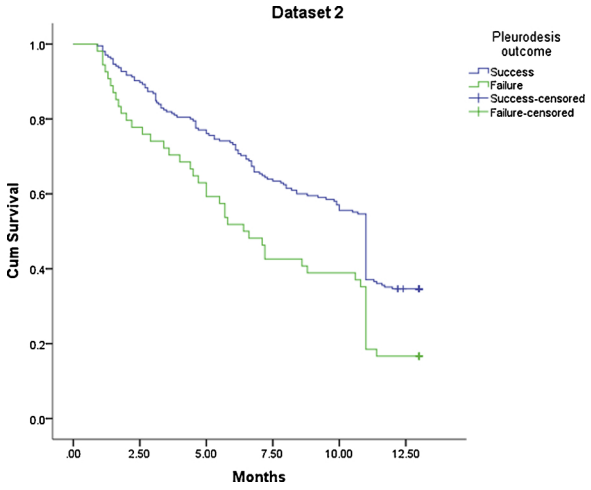

Fig. 2. Kaplan-Meier survival curve by pleurodesis outcome for Dataset 2. Survival is presented in months.

Table 4
Adjusted odds ratio for poor survival using Cox proportional hazards model (222 patients from TIME1 included).

	Beta	Standard error	Sig.	aOR	95.0% CI for aOR	
					Lower	Upper
Unexpandable lung	0.208	0.208	.318	1.231	0.819	1.850
High risk primary*	0.313	0.169	.064	1.368	0.982	1.905
Serum White cell count	0.055	0.030	.068	1.056	0.996	1.120
Pleurodesis failure	0.483	0.199	.015	1.621	1.097	2.396

Key: * as per LENT score.
aOR: adjusted odds ratio.
CI: confidence interval.

prospectively collected as part of clinical care and another with data accrued from an RCT, and applied a similar definition of pleurodesis failure. Our results concur with previously reported observations of longer survival in those who achieve successful pleurodesis.

The higher prevalence of mesothelioma in this study can be attributed to a majority of patients being from UK, which globally, has one of the highest rates of mesothelioma [14,15]. An additional observation of interest is the difference in pleurodesis success rates between the two datasets. There is no clear explanation, but criteria for offering talc pleurodesis in an RCT may differ from those used in a clinical setting, where both clinician and patient preferences, rather than the rigid trial inclusion criteria are determinants of treatment choice, and thus may affect pleurodesis outcomes.

An important limitation of this study is the unavailability of data on performance status of patients from either dataset. Other confounders that could not be accounted for due to lack of data included the extent of metastatic disease, the time between initial cancer diagnosis and pleurodesis, and the degree of response to anti-cancer treatment.

Several factors may explain the apparent survival benefit of achieving a successful pleurodesis. Pleurodesis induces an intra-pleural inflammatory reaction [16] and it has been previously reported that patients who mount a higher and more sustained neutrophilic response post-pleurodesis were more likely to achieve successful pleurodesis [17]. This inflammatory response may contribute to an enhanced immune response to malignant cells. It has also been suggested that the presence of bacteria in the pleural space whether intentionally (in the setting of pleurodesis) [18] or inadvertently as an intrapleural infection [19], is associated with a survival benefit, although the quality of evidence is low. In addition, higher pleural tumour burden has been previously linked to lower rates of pleurodesis success [20] and this could be a consequence of lack of appropriate inflammatory response in advanced malignancy.

Another factor that may link pleurodesis failure with lower life expectancy is a deleterious biological effect of a persistent MPE which theoretically facilitates propagation of malignancy. However, in a trial comparing the efficacy of indwelling pleural cather (IPC) versus pleurodesis for symptom control for patients with MPE, no difference in survival was noted between the two study groups [21]. Further therapeutic procedures are usually required for patients who fail pleurodesis and it could be that such interventions and the inevitable risk of adverse events are - at least in part - responsible for the lower survival.

As the popularity of IPC treatment increases, the clinician's interest in pleurodesis as the primary intervention for MPE is declining in some parts of the world. Results from this post-hoc analysis study should give pause for thought on the potential benefits of pleurodesis, although the results are by no means definitive. Additionally, data suggest that prior

attempts at talc pleurodesis does not adversely affect the prospect of drainage should an IPC be required in the future [22]. Furthermore, the suggestion that IPC use in MPE is associated with initial shorter hospital stay and fewer subsequent hospital visits has been challenged by a recent observational study from our unit, that found that almost one in five patients treated with an IPC for MPE had to return to hospital, either for IPC-related infection, or other catheter-associated issues [23]. A recently published trial showed that combining both therapeutic options by instilling talc slurry via an IPC in patients with an expandable lung leads to significantly higher likelihood of achieving pleurodesis at 35 days [24].

In conclusion, this study supports the observation that there is an association between achieving successful pleurodesis and survival in patients with MPE. Further studies are required to explore factors that may contribute to this phenomenon such as alterations in the intrapleural immune response following chemical pleurodesis and whether the persistence of pleural fluid has a biological effect on tumour behaviour. To address the key issues of survival, as well as palliation of symptoms and hospital stay talc pleurodesis and IPC interventions need to be compared in prospective studies in patients with MPE.

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Contribution

MH conceived the study. MH, RA, RMM, DJM and EOB collected the data in Dataset 1. NAM, RFM, IP and NMR are the main authors of the TIME1 trial and are responsible for Dataset 2. MH performed the statistics and wrote the first draft of the manuscript. NMR critically revised the first draft. All authors reviewed and approved the final manuscript. MH and NMR are responsible for the overall content as guarantors.

Declaration of Competing Interest

None to be declared by the authors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.09.003.

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