



AUDIT, RESEARCH AND GUIDELINE UPDATE

## Pleurodesis outcome in malignant pleural mesothelioma

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### ABSTRACT

Few data exist on the pleurodesis outcome in patients with malignant pleural mesothelioma (MPM). A retrospective review of the Western Australian Mesothelioma Registry over 5 years revealed 390 evaluable patients. Only a subset of patients (42.3%) underwent pleurodesis, surgically (n=78) or by bedside instillation of sclerosants (n=87). Surgical pleurodesis showed no advantages over bedside pleurodesis in efficacy (32% vs 31% failures requiring further drainage, p=0.98), patient survival (p=0.52) or total time spent in hospital from procedure till death (p=0.36). No clinical, biochemical or radiographic parameters tested adequately predict pleurodesis outcome.

### INTRODUCTION

Malignant pleural mesothelioma (MPM) kills one patient every 4 h in the UK. Pleural effusion affects 95% of patients with MPM and often causes significant dyspnoea.<sup>1</sup>

Current clinical practices for MPM effusions are derived from 'generic' studies of malignant pleural effusions based predominantly on patients with metastatic (lung, breast, gynaecological and gastrointestinal) carcinomas. Pleurodesis is the conventional recommended treatment. MPMs differ from metastatic carcinomas in their pathobiology, and the usefulness of pleurodesis in MPM requires clarification.<sup>1</sup>

Studies on pleurodesis in MPM have been retrospective, underpowered and employed differing pleurodesis methods and definitions of success. Reports of surgical pleurodesis for MPM were small (n=4–12) and with limited follow-up (≤30 days). Two audits of pleuroscopic talc pleurodesis for malignant effusions included subgroups of 88 and 66 patients with MPM, and both showed a lower pleurodesis success rate for MPM compared with other metastatic effusions (74.1% vs 85.4%, p<0.001 and 61% vs 74%, p=0.012).<sup>2,3</sup>

We present the largest study on the outcome of MPM effusions to determine (1) the percentage and characteristics of patients with MPM who required pleurodesis for effusion control; (2) the success rate of surgical and bedside pleurodesis; and (3) the need for pleural interventions in patients who failed pleurodesis.

### METHODS

The Western Australia Mesothelioma Registry, which includes all patients with mesothelioma in Western

Australia (population ~2.0 million), was interrogated over a 5-year period from 1 August 2004.

The medical records of patients who attended the major teaching hospitals in Western Australia were reviewed. The primary outcome was success or failure of pleurodesis. Pleurodeses were defined as a complete success (no further fluid accumulation detected), a partial success (fluid returned but no further intervention required) or a failure (further fluid drainage needed) following the American Thoracic Society/European Respiratory Society consensus. Survival was calculated from the date of diagnosis until death or the end of the study (1 May 2012).

Analyses were performed on SigmaPlot v.12. p Values <0.05 were considered significant.

### RESULTS

Of the 494 cases of mesothelioma recorded, 478 patients had proven MPM. Of these, 390 (86% men, mean (SD) age 70 (10.4) years) had accessible medical records from a teaching hospital (see online supplement) and were analysed. Patients with epithelioid MPM had better survival (406 days, IQR 201–778) than those with biphasic (285 days, IQR 151–492) or sarcomatoid disease (149 days, IQR 73–293) (p<0.05).

### Incidence of pleurodesis

Pleurodesis was attempted in 165 patients (42.3%), either by surgery (n=78) or bedside instillation of talc (n=86) or bleomycin (n=1). Surgical pleurodesis was performed during video-assisted thoracoscopy (VATS) (n=64), pleuroscopy (n=3) or thoracotomy (n=11); all surgical pleurodesis procedures included talc poudrage and, in addition, 12 had pleurectomy. No differences in age, gender or mesothelioma histological subtypes were found between the groups in whom pleurodesis was and was not performed (see online supplement).

Median survival was significantly longer in the group that underwent pleurodesis: 443 (IQR 197–746) vs 318 (128–574) days (p=0.002). Thirty-three patients (23 in the pleurodesis group) were alive at the end of follow-up. Patients who underwent pleurodesis spent more time in hospital than those in the non-pleurodesis group (median 20 days (IQR 12–31) vs 14 days (IQR 5–25), p<0.001; 5.1% (IQR 2.1–11.1%) vs 4.4% (IQR 1.3–10.0%) of individual patients' remaining lifespan, respectively, p=0.15).

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### Pleurodesis outcome

Complete success was achieved in 29.7% and partial success in 38.8% of patients treated with pleurodesis. Pleurodesis failed in 31.5% of patients, necessitating further drainages (table 1).

Patients undergoing surgical pleurodesis were significantly younger than those treated with bedside pleurodesis: mean (SD) age 67.1 (10.4) years vs 72.3 (10.5) years ( $p<0.01$ ). The surgical group underwent pleurodesis early, often at the same time as diagnostic surgery (median 0.0 days (IQR 0.0–29.5) after diagnosis vs 54.0 days (IQR 18.0–110.0) in the bedside pleurodesis group,  $p<0.01$ ).

Success rates did not differ between surgical and bedside pleurodesis (table 1). No differences were found in the survival and episodes or days of hospitalisation between the surgical and bedside pleurodesis groups (table 1). The size of the effusion on x-rays, pleural fluid biochemistry (protein, lactate dehydrogenase, pH and glucose levels) and mesothelioma histological subtypes did not predict the outcome of pleurodesis.

The total days of hospitalisation (from any cause) was shortest in the complete success group, followed by the partial success and the failure groups (median 16, 19 and 25 days, respectively,  $p=0.07$ ). Patients in whom pleurodesis failed and who required further pleural interventions spent more days in hospital than those who had complete or partial success (median 25.0 vs 18.0 days,  $p=0.03$ ; 6.1% vs 4.8% of individual patients' remaining lifespan, respectively,  $p=0.08$ ).

The median survival times from diagnosis to death were 323, 461 and 409 days in the complete success, partial success and failure groups, respectively ( $p=0.11$ ). The median survival times from the time of pleurodesis among the three groups were 275, 428 and 230 days, respectively ( $p=0.19$ ).

Four patients died within 14 days of attempted pleurodesis (range 5–13), none related to the procedure. Empyema complicated pleurodesis in five (3.0%) patients (four surgical and one bedside) and one patient developed a chest wall abscess.

Ninety-two further pleural procedures (including 38 thoracotomies, 26 thoracenteses and 21 surgical interventions) were performed on the 52 patients in whom pleurodesis failed

(median 1.0 procedure per patient (IQR 1.0–2.0); see online supplement). The median time from pleurodesis to failure (needing further drainage) was 30 days in the surgical pleurodesis group and 71 days in the bedside pleurodesis group ( $p=0.34$ ).

### DISCUSSION

In this largest study of pleurodesis outcomes in patients with MPM, 42% of patients underwent pleurodesis. Pleurodesis success rates were suboptimal: <30% of patients achieved complete lifelong control of their effusion and 32% required further pleural drainages. Surgical pleurodesis provided no advantages over bedside pleurodesis in success rate, survival or duration of hospitalisation. None of the clinical, biochemical or radiological parameters studied adequately predicted pleurodesis failure. These results provide, for the first time, MPM-specific data to inform clinicians/patients on the efficacy of pleurodesis and may influence clinical care.

MPM remains incurable and symptom palliation for breathlessness is paramount. Conventional teaching suggests that malignant effusions should be drained and pleurodesis considered in symptomatic patients. However, MPM differs from metastatic pleural carcinomas in their pathobiology, which may explain the lower success rate of pleurodesis.<sup>1</sup> First, pleurodesis failure increases progressively the longer the patient survives. In the Cancer and Leukemia Group B study of malignant effusions ( $n=454$ ), adequate fluid control was achieved in approximately 75% of patients at 1 month but in only 50% at 6 months. Since the median survival for MPM is significantly longer than metastatic pleural carcinomas (12 vs 3 months), pleurodesis is less likely to provide lifelong fluid control in MPM. Second, MPMs usually involve large areas of the pleural surfaces. Blockade of the parietal stomata and lymphatic drainage system can contribute to rapid fluid accumulation, thus hindering pleurodesis. Visceral pleural disease often causes trapped lung, impairing pleurodesis. Third, some researchers believe that pleurodesis is less successful in the presence of a larger pleural tumour load, as is often found in MPM.

**Table 1** Characteristics of patients and outcomes of pleurodesis

	Overall (n=165)	Surgical pleurodesis (n=78)	Bedside pleurodesis (n=87)	p Value
<b>Pleurodesis outcome</b>				
Complete success	29.7%	28.2%	31.0%	$p=0.82$
Partial success	38.8%	39.7%	37.9%	$p=0.94$
Failure	31.5%	32.1%	31.0%	$p=0.98$
<b>Demographics</b>				
Mean (SD) age	69.9 (10.5)	67.1 (10.4)	72.3 (10.5)	$p=0.001$
Male	86.7%	83.3%	89.7%	$p=0.34$
Survival in days (diagnosis to death)	443 (197–743)	410 (186–753)	455 (197–743)	$p=0.52$
Days from diagnosis to pleurodesis	17 (0.0–63.0)	0.0 0.0–29.5)	54.0 (9.0–121.0)	$p<0.001$
<b>Subtype</b>				
Epithelioid	86	40	46	$p=0.21$
Sarcomatoid	9	8	1	
Biphasic	30	19	11	
Unclassified*	40	11	29	
Hospital admissions (episodes)	6.0 (2.0–9.0)	5.0 (2.0–9.0)	6.0 (2.5–9.0)	$p=0.51$
Hospital admissions (total days from diagnosis)	20.0 (12.0–31.0)	19.0 (12.0–28.0)	23.0 (13.0–35.0)	$p=0.36$
Hospital admissions (total days expressed as % of remaining lifespan spent)	5.1% (2.1–10.9%)	4.9% (2.1–12.1%)	5.1% (2.1–10.3%)	$p=0.96$

\*Patients with no histological subtypes defined (usually diagnosed by pleural fluid cytology).

Only 42% of patients with MPM underwent pleurodesis. Whether pleurodesis is underused, unnecessary or contraindicated in the remainder of patients deserves future investigation.

Surgical pleurodesis showed no advantage over bedside talc pleurodesis. This result is consistent with four randomised trials that have found no benefit of VATS talc poudrage over bedside pleurodesis using talc slurry or iodopovidone. Many believe that pleurodesis is more likely to be successful if performed early. In our study, surgical pleurodesis was often performed as early as the same time of the diagnostic thoracoscopy and in younger patients. Despite these biases, surgical pleurodesis showed no superiority over bedside pleurodesis.

This study was retrospective so clinical management and surgical approaches were not standardised. However, the use of a comprehensive statewide database over a significant period offered an unbiased view of current practice. Although not randomised, the comparison groups (eg, surgical vs bedside pleurodesis) were remarkably similar in their baseline demographics. As the largest study on MPM effusions, the results provide a platform to guide future prospective studies.

One recent study in which patients with MPM accounted for 47% of the cohort confirmed that indwelling pleural catheters (IPC) are comparable to pleurodesis in improving dyspnoea and quality of life,<sup>4</sup> and patients managed with IPC spent significantly fewer days in hospital.<sup>5</sup> The role of IPC in the management of MPM effusions needs exploration.

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**Competing interests** YCGL was a co-investigator of the British Lung Foundation Therapeutic Intervention of Malignant Effusion-2 trial for which indwelling pleural catheters were provided by Rocket Medical Ltd without charge. He has received an honorarium from CareFusion Ltd as an advisory board member.

**Ethics approval** Ethical approval was obtained from the Western Australia Department of Health.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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## DATA FOR ONLINE SUPPLEMENT

**Online Table A:** Characteristics of patient groups:

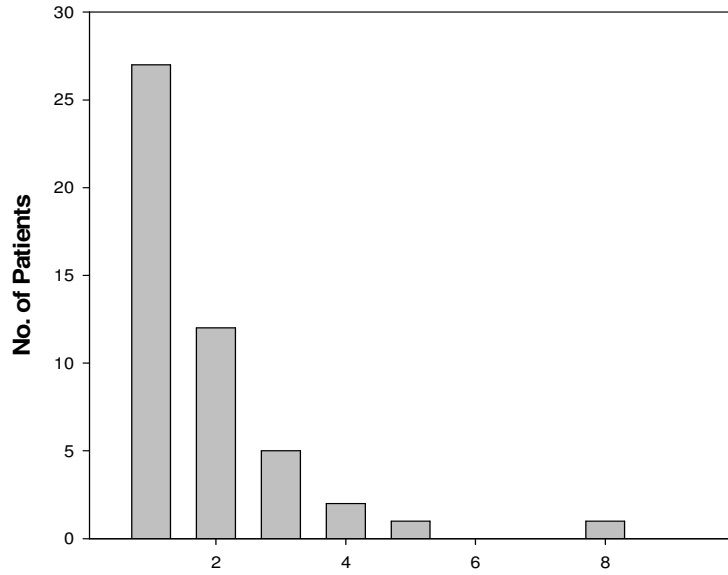
	<b>Overall (n=390)</b>	<b>Pleurodesed (n=165)</b>	<b>Non-Pleurodesed (n=225)</b>	<b><i>P</i> value*</b>
<b>Age: mean (SD)</b>	<b>70.0 (10.4)</b>	69.9 (10.8)	70.8 (10.1)	p=0.77
<b>Male</b>	<b>85.9%</b>	86.7%	85.3%	p=0.97
<b>Subtype:</b>				NS
<b>Epithelioid</b>	<b>195</b>	87	108	
<b>Sarcomatoid</b>	<b>39</b>	9	30	
<b>Biphasic</b>	<b>68</b>	30	38	
<b>Unclassified</b>	<b>88</b>	39	49	
<b>Survival (days from diagnosis)</b>	<b>351 (166 - 643)</b>	443 (197 - 746)	318 (128 to 574)	p=0.002
<b>No. of hospital admissions</b>	<b>5.0 (2.0 - 9.0)</b>	5.0 (2.0 - 9.0)	4.0 (1.0 - 9.0)	p=0.08
<b>Total inpatient days in hospital from diagnosis</b>	<b>17.0 (8.0 - 28.3)</b>	20.0 (12.0 - 31.3)	14.0 (5.0 - 25.0)	p<0.001
<b>% of remaining lifespan spent as hospital inpatient</b>	<b>4.9% (1.6 - 10.3)</b>	5.1% (2.1 - 11.1)	4.4% (1.3 - 10.0)	p=0.15

**Online Table B:** Comparison of patients by pleurodesis outcome:

	<b>Successful Pleurodeses (n=49)</b>	<b>Partial Success (n=64)</b>	<b>Failed Pleurodeses (n=52)</b>	<b><i>p</i> value</b>
<b>Age: mean (SD)</b>	73.1 (9.7)	68.7 (11.3)	68.2 (10.6)	p=0.04
<b>Time in Days (from diagnosis to pleurodesis)</b>	16.0 (0.0 to 49.5)	30.5 (0.0 - 83.5)	5.5 (0.0 - 61.0)	p=0.19
<b>Survival after Pleurodesis (days)</b>	275 (138 - 746)	428 (239 - 838)	300 (153 - 681)	p=0.21
<b>Survival in Days (from diagnosis to death)</b>	323.0 (142.5 to 742.5)	460.5 (314.3 to 946.5)	409.0 (197.5 to 719.0)	p=0.11
<b>No. of hospital admissions</b>	4.0 (1.0 to 6.8)	7.0 (2.0 to 9.0)	7.0 (3.0 to 10.0)	p=0.02
<b>Total days in hospital from diagnosis</b>	16.0 (10.0 - 28.0)	19.0 (11.5 - 32.8)	25.0 (16.3 - 31.8)	p=0.07
<b>% of survival time (from diagnosis to death) spent in hospital</b>	5.1% (1.8 to 13.0)	4.4% (1.8 to 8.2)	6.1% (3.0 to 13.5)	p=0.09
<b>Effusion Size (% hemithorax)</b>	50% (25 – 75%) (n=43)	50% (25 – 75%) (n=57)	50% (25 – 75%) (n=49)	p=0.67
<b>pleural fluid pH</b>	7.37 (7.30 - 7.54) (n=14)	7.37 (7.25 - 7.60) (n=19)	7.30 (7.21 - 7.37) (n=21)	p=0.09
<b>pleural fluid glucose (mmol/L)</b>	4.3 (2.5 - 5.3) (n=26)	5.1 (3.7 - 5.9) (n=16)	3.9 (3.3 - 5.4) (n=26)	p=0.27
<b>pleural fluid Lactate dehydrogenase (LDH) (IU/L)</b>	428 (342 - 669) (n=17)	361 (235 to 655) (n=18)	505 (233 to 961) (n=34)	p=0.48
<b>pleural fluid Protein (g/L) Mean (SD)</b>	44.9 (8.3) (n=28)	46.2 (8.7) (n=34)	44.8 (10.7) (n=36)	p=0.80
<b>Histological Subtype</b>				p=0.70
<b>Epithelioid</b>	25	37	25	
<b>Sarcomatoid</b>	2	3	4	
<b>Biphasic</b>	7	11	12	
<b>Unclassified</b>	15	13	11	

**Online Fig A:** Chart showing the number of procedures undergone by patients whose pleurodesis failed

**No. of Procedures in Patients who Failed Pleurodesis**



**Fig B:** Type and number of pleural procedures undertaken in patients with failed pleurodesis

**Type and no. of Procedures**

