



# Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial

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## Summary

**Background** Malignant pleural mesothelioma incidence continues to rise, with few available evidence-based therapeutic options. Results of previous non-randomised studies suggested that video-assisted thoracoscopic partial pleurectomy (VAT-PP) might improve symptom control and survival. We aimed to compare efficacy in terms of overall survival, and cost, of VAT-PP and talc pleurodesis in patients with malignant pleural mesothelioma.

**Methods** We undertook an open-label, parallel-group, randomised, controlled trial in patients aged older than 18 years with any subtype of confirmed or suspected mesothelioma with pleural effusion, recruited from 12 hospitals in the UK. Eligible patients were randomly assigned (1:1) to either VAT-PP or talc pleurodesis by computer-generated random numbers, stratified by European Organisation for Research and Treatment of Cancer risk category (high vs low). The primary outcome was overall survival at 1 year, analysed by intention to treat (all patients randomly assigned to a treatment group with a final diagnosis of mesothelioma). This trial is registered with ClinicalTrials.gov, number NCT00821860.

**Findings** Between Oct 24, 2003, and Jan 24, 2012, we randomly assigned 196 patients, of whom 175 (88 assigned to talc pleurodesis, 87 assigned to VAT-PP) had confirmed mesothelioma. Overall survival at 1 year was 52% (95% CI 41–62) in the VAT-PP group and 57% (46–66) in the talc pleurodesis group (hazard ratio 1.04 [95% CI 0.76–1.42];  $p=0.81$ ). Surgical complications were significantly more common after VAT-PP than after talc pleurodesis, occurring in 24 (31%) of 78 patients who completed VAT-PP versus ten (14%) of 73 patients who completed talc pleurodesis ( $p=0.019$ ), as were respiratory complications (19 [24%] vs 11 [15%];  $p=0.22$ ) and air-leak beyond 10 days (five [6%] vs one [1%];  $p=0.21$ ), although not significantly so. Median hospital stay was longer at 7 days (IQR 5–11) in patients who received VAT-PP compared with 3 days (2–5) for those who received talc pleurodesis ( $p<0.0001$ ).

**Interpretation** VAT-PP is not recommended to improve overall survival in patients with pleural effusion due to malignant pleural mesothelioma, and talc pleurodesis might be preferable considering the fewer complications and shorter hospital stay associated with this treatment.

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## Introduction

The incidence of malignant pleural mesothelioma continues to rise;<sup>1–3</sup> however, few evidence-based therapeutic options are available. Cisplatin plus pemetrexed chemotherapy has been shown to confer a slight survival advantage.<sup>4,5</sup> The role of surgical resection is uncertain, but several operative approaches have been described.<sup>6</sup> Extrapleural pneumonectomy (EPP) has been assessed in several studies—most recently in the MARS trial<sup>7</sup> as part of trimodality therapy. Lung-sparing approaches, including (extended) pleurectomy with decortication<sup>8–10</sup> and video-assisted thoracoscopic partial pleurectomy (VAT-PP), have also been assessed,<sup>11,12</sup> and might be particularly appropriate for patients with more advanced disease or comorbidities.

VAT-PP involves thoracoscopic debulking of the parietal pleura and visceral pleurectomy with decortication to release trapped lung.<sup>6</sup> Results of non-

randomised studies examining VAT-PP suggest that VAT-PP improved symptom control compared with EPP<sup>11</sup> and possibly increased survival compared with biopsies alone.<sup>12</sup> The standard approach to control pleural effusion in patients with malignant pleural mesothelioma is talc pleurodesis, either via a chest tube or, more recently, by thoracoscopy.

The MesoVATS trial was designed to establish whether VAT-PP improves survival in patients with pleural effusion secondary to malignant pleural mesothelioma when compared with talc pleurodesis, to provide a full economic analysis of these treatments, and to compare symptom control and quality-of-life outcomes.

## Methods

### Study design and participants

MesoVATS was an open-label, parallel-group, multicentre, randomised, controlled trial that recruited

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patients from 12 secondary or tertiary care hospitals in the UK. Eligible patients were those aged older than 18 years with confirmed (any subtype) or suspected (working diagnosis) malignant pleural mesothelioma who had a pleural effusion. Participants had to be fit enough to undergo VAT-PP and provide informed consent. Exclusion criteria were previous attempted pleurodesis and previous primary treatment for mesothelioma. Patients with previous malignancy were eligible if they were no longer receiving anticancer treatment and had a confirmed diagnosis of malignant pleural mesothelioma. Those with a history of malignancy but with only suspected mesothelioma were excluded because the relation of the pleural disease and effusion to the original cancer would have been uncertain. Patients with suspected malignant pleural mesothelioma who were found to have non-malignant disease or non-mesothelioma malignancy after randomisation were excluded.

The trial was coordinated by Papworth Hospital Clinical Trials Unit (Cambridge, UK) and approved by Huntingdon Research Ethics Committee. After sterile talc was re-designated as a medicinal product in April, 2011, the trial was registered with the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2011.

### Randomisation

Patients were recruited by a local principal investigator and were randomised in a 1:1 ratio to either VAT-PP or talc pleurodesis by a computerised random-number generator in blocks of ten (appendix) via a telephone randomisation line at Papworth Hospital, operated by staff who were independent of the study. Randomisation was stratified according to risk (high vs low) using the European Organisation for Research and Treatment of Cancer (EORTC) prognostic score.<sup>13</sup> Patients were defined as high risk if they met three or more of the following criteria: white blood cell count of greater than  $8 \cdot 3 \times 10^9/L$ ; non-epithelioid tumour type (or unknown cell type at randomisation); male sex; or Eastern Cooperative Oncology Group (ECOG) performance status of 1 or higher. The trial was open label, with patients, clinicians, and researchers all aware of the treatment allocation. The trial database was held at Papworth Hospital NHS Foundation Trust.

### Procedures

A detailed overview of the VAT-PP and talc pleurodesis techniques is described in the appendix. To ensure uniformity of approach, all surgeons discussed the VAT-PP procedure, and from Jan 13, 2009, they also recorded tumour extent and lung re-expansion before and after pleurectomy (appendix). At study outset, talc pleurodesis was done using talc slurry via an intercostal chest drain. From November, 2008, the protocol changed to allow talc pleurodesis by thoracoscopic poudrage.

Patients with confirmed mesothelioma at time of randomisation underwent either VAT-PP or talc pleurodesis (appendix). For patients with suspected (working diagnosis) mesothelioma randomly assigned to VAT-PP, two approaches were permitted: either diagnosis was confirmed by thoracoscopy before VAT-PP or VAT-PP was done directly. In the talc pleurodesis group, diagnosis could either be confirmed by thoracoscopic biopsy followed by subsequent talc instillation, or thoracoscopy with biopsy and talc poudrage were done as a single procedure (appendix).

Staging was determined by two radiologists independently using the International Mesothelioma Interest Group (IMIG) tumour stage and was based on the CT done before randomisation.<sup>14</sup> Differences were resolved by consensus.

Adverse events were documented and assessed by the local investigator for seriousness, severity, and causality, and were recorded on the case report forms at each follow-up visit.

After completion of the study treatment, ongoing management was at the discretion of the managing clinician. No restrictions were placed on the subsequent use of chemotherapy, radiotherapy, or other palliative control measures.

For the economic analysis, all data on resource use was patient-level and obtained at baseline and at 1, 3, 6, and 12 months on a bespoke data collection form (available on request). We multiplied resource use by costs and prices obtained from national sources (appendix). At baseline, data for type of procedure, days on a ward, days in intensive care, and complications were obtained by research nurses using information from hospital records. Follow-up information on hospital bed use, use of primary care services (eg, family doctor, practice nurse), radiotherapy, chemotherapy, hospice care, and diagnostic tests was obtained by researchers during patient interviews at 1, 3, 6, and 12 months. Some aspects were confirmed by hospital records—eg, dates of radiotherapy and number of chest radiographs. Information about consultations in primary care was patient-reported.

### Outcomes

The primary outcome was overall survival at 1 year after randomisation. At the end of the study, survival status for all patients was confirmed using the UK Office for National Statistics mortality register. Survival times were censored on June 17, 2013. Secondary outcomes were: presence or absence of apparent pleural effusion as assessed by the reporting radiologist on chest radiograph; quality of life measured using the EuroQol EQ-5D,<sup>15</sup> EORTC QLQ-C30 general cancer, and EORTC QLQ-LC13 lung cancer questionnaires;<sup>16</sup> lung function and exercise tolerance measured using spirometry and the shuttle walk test, respectively; complications; and cost to the health service measured by resource use retrieved from patient interviews and hospital records. For patients who

See Online for appendix

received their allocated treatment, each measure was assessed at randomisation (baseline) and 1, 3, 6, and 12 months after treatment. For patients who did not undergo their allocated treatment, follow-up visits occurred at 1, 3, 6, and 12 months after randomisation. Because of operational reasons, the shuttle walk test was only available at five of the 12 centres, and therefore was only undertaken by a subset of patients.

### Statistical analysis

On the basis of previous scientific literature<sup>17</sup> and a local audit,<sup>12</sup> we estimated 1-year overall survival to be 37% with talc pleurodesis and 59% with VAT-PP. To show this difference we needed 90 patients per group (5% two-sided significance) to give 80% power. Allowing for post-randomisation exclusions, we planned to randomly assign 196 patients.

We analysed the primary endpoint in the intention-to-treat population of patients with malignant pleural mesothelioma. We estimated 1-year overall survival with the Kaplan-Meier method, stratified for risk status, and compared differences between groups with a log-rank test. We used Cox proportional hazards models, stratified for risk group, to estimate relative risk of death in the 12 months after randomisation. We compared length of hospital stay using the Wilcoxon rank sum test, and complication rates, including persistent pleural effusion rate, with Pearson's  $\chi^2$  test. Because of the attrition rate in our study sample (due to death), the number of patients available for secondary outcomes decreased during follow-up. Therefore, we compared all repeated measures at each timepoint separately. We assessed overall survival, EQ-5D score, and quality-adjusted survival in high-risk and low-risk subgroups separately in the only preplanned subgroup analysis.

Initially, we analysed secondary outcomes separately at each timepoint in only patients who had completed an assessment. We did several sensitivity analyses for comparisons of EQ-5D scores, quality-adjusted survival outcomes, and costs using a missing-at-random assumption conditional on treatment group, risk group, and either survival status at each follow-up time or follow-up time in the study to death or censoring, and final survival status. For all other secondary outcomes, we restricted analysis to patients who completed each test.

The economic analysis estimated the costs and cost-effectiveness of VAT-PP versus talc pleurodesis up to 12 months after randomisation from a National Health Service (NHS) perspective. Resources were valued using NHS reference costs (Department of Health, 2011), unit costs of health and social care,<sup>18</sup> published literature, and the Papworth Hospital finance department. Costs are expressed in 2011–12 pounds sterling, inflated when necessary.<sup>18</sup> We converted the EQ-5D, valued using the UK social tariff,<sup>19</sup> to quality-adjusted life-years (QALYs) using the area under the curve method.<sup>20</sup>

Descriptive analyses show mean total costs by treatment group and differences between treatment group by category of cost for the original procedure and follow-up. We used non-parametric bootstrapping to estimate differences in mean costs with 95% CIs and incremental cost-effectiveness ratios. We represented uncertainty in cost-effectiveness acceptability curves and

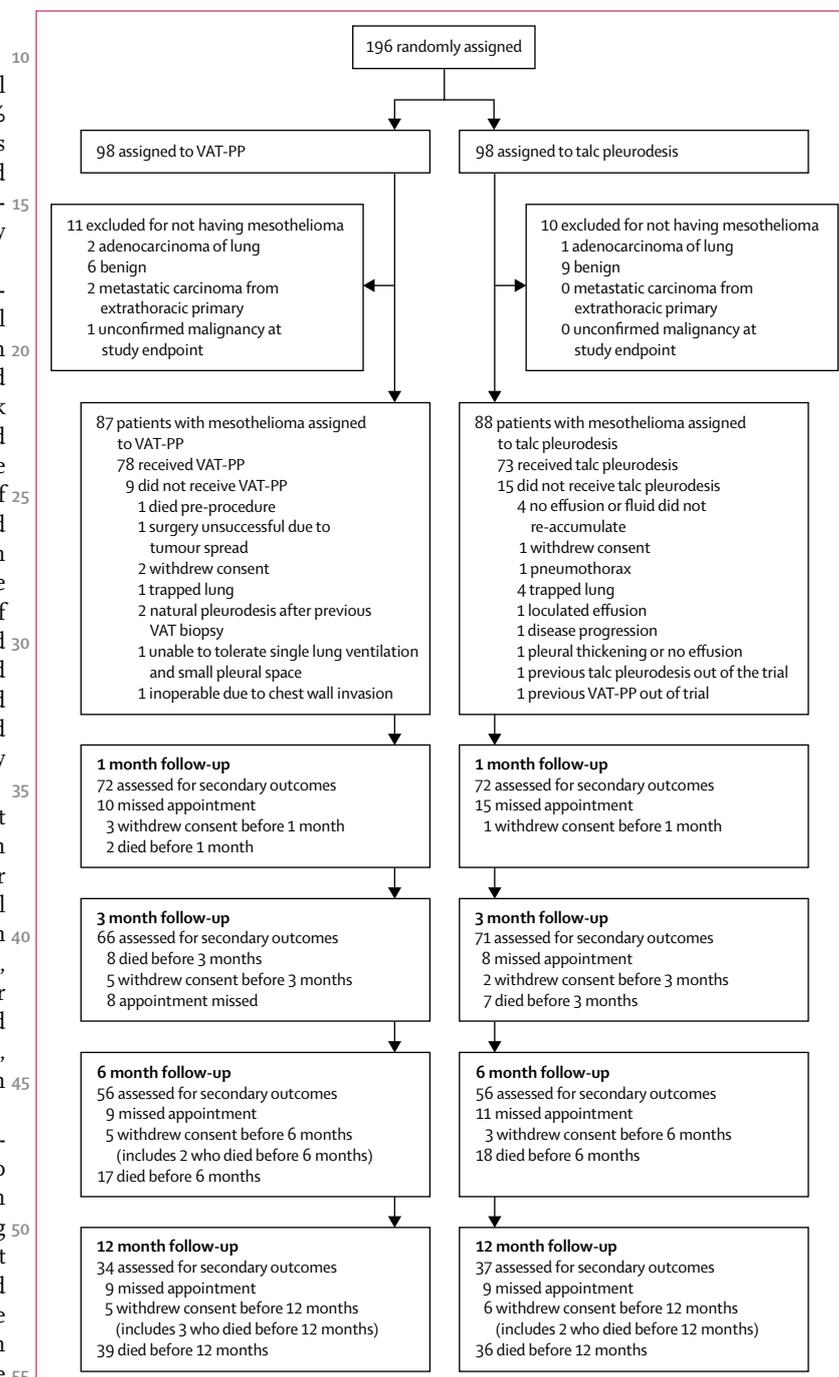


Figure 1: Trial profile

VAT-PP=video-assisted thoroscopic partial pleurectomy.

incremental net benefits for VAT-PP versus talc pleurodesis. Deterministic sensitivity analysis explored high-risk and low-risk subgroups, complications judged

	VAT-PP (n=87)	Talc pleurodesis (n=88)
Age, years	69.5 (7.5)	69.4 (7.3)
Sex		
Men	75 (86%)	76 (86%)
Women	12 (14%)	12 (14%)
EORTC risk status		
High	38 (44%)	47 (53%)
Low	49 (56%)	41 (47%)
FEV <sub>1</sub> , L*	1.60 (0.62)	1.67 (0.56)
FEV <sub>1</sub> , % predicted*	57.0 (18.2)	59.3 (17.6)
FVC, L†	2.21 (0.82)	2.35 (0.75)
FVC, % predicted†	60.8 (17.8)	64.2 (18.3)
BMI, kg/m <sup>2</sup> ‡	26.6 (3.9)	27.2 (4.4)
Shuttle walk test, m§	405.7 (154.3)	397.6 (163.3)
Tumour type		
Epithelioid	73 (84%)	73 (83%)
Sarcomatoid	10 (11%)	7 (8%)
Biphasic	4 (5%)	8 (9%)
IMIG tumour stage		
IA	2 (3%)	1 (1%)
IB	10 (13%)	7 (9%)
II	6 (8%)	9 (11%)
III	38 (49%)	34 (43%)
IV	21 (27%)	28 (35%)
Missing	10 (11%)	9 (10%)
ECOG performance status		
0	20 (24%)	16 (19%)
1	50 (60%)	53 (62%)
2	11 (13%)	14 (16%)
3	3 (4%)	2 (2%)
Missing	3 (3%)	3 (3%)
Smoking		
Current smoker	5 (6%)	4 (5%)
Ex-smoker	52 (61%)	45 (52%)
Never smoked	28 (33%)	38 (44%)
Missing	2 (2%)	1 (1%)
Asbestos exposure		
Yes	64 (74%)	66 (76%)
No	4 (5%)	1 (1%)
Not known	18 (21%)	20 (23%)
Missing	1 (1%)	1 (1%)
Dyspnoea		
Yes	67 (78%)	68 (78%)
No	19 (22%)	19 (22%)
Missing	1 (1%)	1 (1%)

Data are mean (SD) or number (%). VAT-PP=video-assisted thoroscopic partial pleurectomy. EORTC=European Organisation for Research and Treatment of Cancer. FEV<sub>1</sub>=forced expiratory volume in 1 s. FVC=forced vital capacity. BMI=body-mass index. IMIG=International Mesothelioma Interest Group. ECOG=Eastern Cooperative Oncology Group. \*n=76 in talc pleurodesis group; n=79 in VAT-PP group. †n=75 in talc pleurodesis group; n=79 in VAT-PP group. ‡n=74 in talc pleurodesis group; n=74 in VAT-PP group. §n=49 in talc pleurodesis group; n=53 in VAT-PP group.

**Table 1: Baseline demographic and clinical characteristics in randomly assigned patients with mesothelioma**

to be related to interventions, and the second half of the trial only (any patients randomly assigned after June 1, 2009) to account for changing clinical practice over time. We finalised these subgroup analyses after trial completion, and they were exploratory.

This study is registered with an International Standard Randomised Controlled Trial Number, 34321019; the European Clinical Trials Database (EudraCT), number 2011-001121-24; and with ClinicalTrials.gov, number NCT00821860

### Role of the funding source

The funder of the study had no role in study design, data collection, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

As planned, we recruited 196 patients between Oct 24, 2003, and Jan 24, 2012 (figure 1), and followed them up until Jan 31, 2013, with a further survival update on June 17, 2013. At randomisation, 120 (61%) of 196 patients had confirmed malignant pleural mesothelioma and 76 (39%) had suspected (working diagnosis) malignant pleural mesothelioma (appendix). 11 (11%) of 98 patients assigned to VAT-PP and 10 (10%) of 98 patients assigned to talc pleurodesis with suspected malignant pleural mesothelioma were subsequently found to have benign disease (n=15), adenocarcinoma of the lung (n=3), metastatic disease from an extrathoracic primary cancer (n=2), or unconfirmed malignant pleural mesothelioma at study endpoint (n=1), and were excluded (figure 1). We analysed the remaining 87 patients in the VAT-PP group and 88 patients in the talc pleurodesis group in the intention-to-treat analyses.

Within 12 months of randomisation, 42 (48%) of 87 patients in the VAT-PP group had died compared with 38 (43%) of 88 in the talc pleurodesis group; 14 (16%) patients in the VAT-PP group and 15 (17%) in the talc pleurodesis group either withdrew from the study or did not attend the final appointment (figure 1). Thus, at 12 months secondary outcomes were available for 34 (39%) of 87 patients in the VAT-PP group and 37 (42%) of 88 patients in the talc pleurodesis group, although some secondary outcomes were available for 72 (83%) of 87 patients in the VAT-PP group and 72 (82%) of 88 patients in the talc pleurodesis group. One patient withdrew following an MHRA decision, during the trial, to reclassify talc as a medicinal product, and the trial was suspended until MHRA registration. Other reasons for withdrawal from the trial are given in the appendix.

Baseline characteristics were similar between the two groups (table 1). Mean age was 69 years (SD 7.4) in all 175 randomly assigned patients with mesothelioma, and 151 (86%) were men. Most patients had epithelioid

tumours (table 1). Three patients had a history of cancer (one had breast cancer and another had bladder cancer in the VAT-PP group, and one had prostate cancer in the talc pleurodesis group). ECOG performance status was 0 or 1 for 139 (82%) of the 169 patients for whom data were available, and IMIG tumour stage was IA in three (2%) of 156 patients with available data, IB in 17 (11%) patients, II in 15 (10%) patients, III in 72 (46%) patients, and IV in 49 (31%) patients. Exposure to asbestos was reported by 130 (75%) of 173 patients with available data, and breathlessness was reported by 135 (78%) of 173, with a percent-predicted mean forced expiratory volume in 1 s (FEV<sub>1</sub>) of 58·1% (SD 17·8).

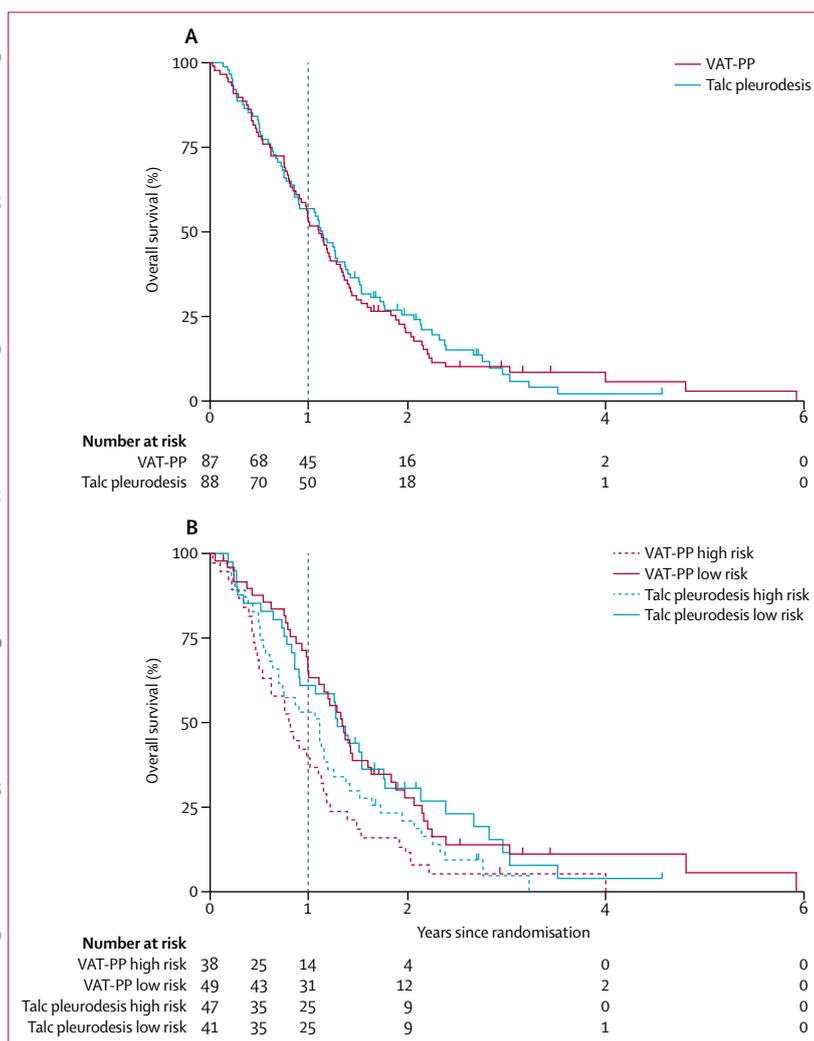
Nine (10%) of 87 patients in the VAT-PP group did not undergo their assigned procedure, compared with 15 (17%) of 88 patients in the talc pleurodesis group (figure 1). Talc pleurodesis commenced a median of 9 days (IQR 6–15) after randomisation in 73 patients, with 35 (48%) receiving talc slurry and 34 (47%) undergoing pleurodesis via thoracoscopy (data for the remaining four patients are unavailable). VAT-PP was completed a median of 14 days (IQR 8–21) after randomisation.

Overall survival at 6 months was estimated to be 78% (95% CI 68–85) in the VAT-PP group and 80% (70–87) in the talc pleurodesis group, and at 1 year was estimated to be 52% (41–62) and 57% (46–66), respectively (hazard ratio [HR] 1·04 [95% CI 0·76–1·42];  $p=0·81$ ; figure 2A). Median overall survival was 13·1 months (IQR 7·3–20·3) in the VAT-PP group and 13·5 months (7·3–21·1) in the talc pleurodesis group. Overall survival at 6 months was estimated to be 66% (95% CI 48–78) in patients in the VAT-PP group who were at high risk according to the EORTC prognostic score and 74% (59–85) in patients in the talc pleurodesis group who were at high risk; for patients who were at low risk, overall survival at 6 months was 88% (75–94) and 85% (70–93), respectively (figure 2B). At 1 year, overall survival was 37% (95% CI 22–52) in high-risk patients in the VAT-PP group and 53% (38–66) in high-risk patients in the talc pleurodesis group, and 63% (48–75) and 61% (44–74) in the low-risk group for VAT-PP and talc pleurodesis, respectively (figure 2B). Overall survival rates were not significantly different between the treatment groups (stratified log-rank test  $p=0·51$ ). The HR of death for the VAT-PP group relative to the talc pleurodesis group, stratified by EORTC prognostic risk, was 1·11 (95% CI 0·81–1·53;  $p=0·51$ ).

Pleural effusion was reported as apparently having resolved in 25 (37%) of 68 surviving patients in the talc pleurodesis group at 1 month, in 37 (60%) of 62 at 3 months, in 31 (57%) of 54 at 6 months, and in 27 (77%) of 35 at 12 months. Corresponding numbers in the VAT-PP group were 41 (59%) of 69 patients at 1 month, 36 (60%) of 60 at 3 months, 41 (77%) of 53 at 6 months, and 23 (70%) of 33 at 12 months. The proportion of patients with resolved pleural effusion was significantly higher in the VAT-PP group than in the talc pleurodesis

group at 1 month ( $p=0·008$ ) and 6 months ( $p=0·03$ ), but not at 3 months ( $p=0·97$ ) or 12 months ( $p=0·49$ ).

Of the 175 randomly assigned patients with malignant pleural mesothelioma, four patients withdrew within 1 month, of whom two did not provide baseline data and two did; a further two patients did not complete baseline quality-of-life questionnaires, and three had one or more missing baseline EQ-5D items, leaving 83 patients in the VAT-PP group and 85 patients in the talc pleurodesis group with baseline EQ-5D data. The pattern of missing data during follow-up, which was more frequent just before death, is shown in the appendix. EQ-5D results are shown in figure 3 and the appendix. Patients in the VAT-PP group had slightly worse EQ-5D utility index scores at 1 month than patients in the talc pleurodesis group (mean difference  $-0·06$  [95% CI  $-0·13$  to  $0·004$ ];  $p=0·07$ ), slightly better EQ-5D scores at 3 months (mean difference

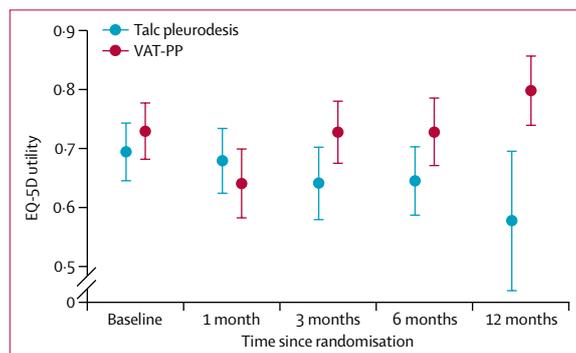


**Figure 2: Kaplan-Meier curves of overall survival, in all patients and by risk group**

Overall survival in all randomly assigned patients with mesothelioma, per treatment group (A) and in high-risk and low-risk patients, per treatment group (B). The vertical line crosses the x-axis at 1 year (primary endpoint). VAT-PP=video-assisted thoracoscopic partial pleurectomy.

0.04 [-0.03 to 0.12];  $p=0.27$ ), and significantly better EQ-5D scores at 6 months (mean difference 0.08 [0.003 to 0.16];  $p=0.042$ ) and 12 months (mean difference 0.19 [0.05 to 0.32];  $p=0.0003$ ). The mean number of QALYs in the VAT-PP group was 0.511 (95% CI 0.446–0.577) compared with 0.476 (0.418–0.534) in the talc pleurodesis group (mean difference 0.035 [-0.051 to 0.122];  $p=0.42$ ; **table 2**). Sensitivity analysis using a range of assumptions about missing data resulted in very similar estimates (appendix) and estimates of mean QALYs from all analyses were consistent.

Results of the analysis of some of the EORTC subscales (eg, global health, physical functioning, and role functioning) were similar to the results from the EQ-5D analysis (poorer function at 1 month and better function at 3, 6, and 12 months with VAT-PP than with talc pleurodesis), but results were not consistent between scales, nor were the differences noted between groups consistently significant (appendix).



**Figure 3: EQ-5D score during the 12 months after randomisation**  
Data are from patients who completed the ED-5D questionnaire at each timepoint (at baseline, 83 in VAT-PP group and 85 in talc pleurodesis group; 1 month, n=71 and n=70; 3 months, n=63 and n=71; 6 months, n=55 and n=56; and 12 months, n=33 and n=36). Datapoints show mean ED-5D utility (index-based value) and bars show 95% CI. VAT-PP=video-assisted thoracoscopic partial pleurectomy.

Patients in the VAT-PP group had higher mean FEV<sub>1</sub> at 1, 3, and 12 months after treatment than did patients in the talc pleurodesis group, despite lower baseline function, but differences were not statistically significant (appendix). Forced vital capacity did not differ between groups (appendix). Patients in the talc pleurodesis group recorded a greater mean distance in the shuttle test, and the difference was significant at 12 months (difference 103.5 m [95% CI 37.1–169.9];  $p=0.003$ ), although this analysis was based on data from only 36 patients because the test was only done in five of the 12 participating centres.

We did not note any significant interactions between risk group and treatment group, but high-risk patients had significantly worse overall survival than low-risk patients (HR 1.64 [95% CI 1.19–2.25];  $p=0.002$ ) and although some evidence suggested that high-risk patients who underwent VAT-PP had poorer overall survival than high-risk patients who underwent talc pleurodesis, the difference in overall survival between groups was not significant (HR 1.29 [95% CI 0.83–2.00];  $p=0.25$ ). The difference in mean EQ-5D score at 12 months in favour of patients with VAT-PP was significant for low-risk patients (mean difference 0.13 [95% CI 0.02–0.24];  $p=0.022$ ) and was large, but not significant, for high-risk patients (mean difference 0.32 [-0.04 to 0.67];  $p=0.08$ ).

The mean cost of VAT-PP treatment and follow-up care for 12 months was about £3800 more than the cost of talc pleurodesis (appendix). Differences were mainly attributable to the initial procedure and increased length of stay, followed by the cost of admissions during follow-up and treatment of surgical complications. The cost of gaining an additional QALY from VAT-PP is £109 000 (table 3). A potential willingness-to-pay per QALY of £30 000 is associated with a 5.4% chance that VAT-PP was cost-effective relative to talc pleurodesis, and a willingness to pay per QALY of £50 000 is associated with a 20% chance (figure 4).

Deterministic sensitivity analysis (table 3) shows that high-risk patients in the VAT-PP group had fewer QALYs

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	All patients	High-risk group	Low-risk group
<b>Total cost</b>			
Talc pleurodesis	10 436 (14.4)	11 408 (19.0)	9359 (21.6)
VAT-PP	14 252 (14.4)	13 688 (19.1)	14 663 (21.7)
<b>QALYs</b>			
Talc pleurodesis	0.476 (0.0005)	0.409 (0.0007)	0.555 (0.0007)
VAT-PP	0.511 (0.0006)	0.383 (0.0007)	0.607 (0.0009)
<b>Difference in cost</b>	3816 (20.7)	2274 (21.7)	5305 (19.1)
<b>Difference in QALYs</b>	0.035 (0.0008)	-0.026 (0.00085)	0.050 (0.0007)
<b>Incremental cost per QALY gained</b>	109 028	VAT-PP dominated by TP*	105 119
<b>Incremental net benefit at £30 000 per QALY</b>	-2766	-3054	-3805

Data are mean (SE) unless otherwise specified. Costs are presented in 2011 pound sterling (GBP£). This analysis uses bootstrapped estimates, not the imputed dataset (used in appendix). VAT-PP=video-assisted thoracoscopic partial pleurectomy. TP=talc pleurodesis. QALY=quality-adjusted life-year. \*An intervention (ie, VAT-PP) is dominated when it is less effective and more costly than the comparator (ie, talc pleurodesis).

**Table 2: Comparison of costs and QALYs gained from VAT-PP versus talc pleurodesis**

and were more expensive to treat than were high-risk patients who received talc pleurodesis, whereas the low-risk group had an additional cost of £105 119 per QALY gained for the VAT-PP group compared with the talc pleurodesis group. Using results from the second half of the trial only (after June 1, 2009; n=98), VAT-PP had a greater effect, with the incremental cost-effectiveness ratio falling to £68 600 per QALY gained (appendix).

Of the 78 patients who completed VAT-PP, respiratory complications were reported in 19 (24%) patients, cardiac complications in five (6%), and other (surgical) complications in 24 (31%). Of the 73 patients who completed talc pleurodesis, 11 (15%) had respiratory complications ( $p=0\cdot22$  for difference between treatment groups), three (4%) had cardiac complications ( $p=0\cdot84$ ), and ten (14%) had surgical complications ( $p=0\cdot019$ ). Some patients had more than one type of complication. Air leak beyond 2 days was significantly more common after VAT-PP than after talc pleurodesis, occurring in 19 (24%) of 78 patients in the VAT-PP group versus four (5%) of 73 patients in the talc pleurodesis group ( $p=0\cdot001$ ). Persistent air leak (>10 days) was more frequent in the VAT-PP group, but not significantly so (five [6%] vs one [1%];  $p=0\cdot21$ ). 21 serious adverse events were related to the trial medication or procedure; 13 (in 11 patients) were in the VAT-PP group and eight (in seven patients) were in the talc pleurodesis group ( $p=0\cdot35$ ; table 3). Full details of treatment complications are presented in the appendix. Median hospital stay after the procedure was 7 days (IQR 5–11) for the VAT-PP group and 3 days (IQR 2–5) for the talc pleurodesis group ( $p<0\cdot0001$ ). A similar proportion of patients in each group had chemotherapy after their study procedure (28 [32%] of 87 in the VAT-PP group vs 25 [28%] of 88 in the talc pleurodesis group), with a mean of 4·4 cycles (SD 2·4) and 4·5 cycles (3·2), respectively.

## Discussion

To our knowledge, our study is the first randomised controlled trial to compare VAT-PP and talc pleurodesis in patients with suspected or confirmed malignant pleural mesothelioma. Our results showed that overall survival was not improved by VAT-PP, and that this approach resulted in more complications, longer hospital stays, and was more expensive than was talc pleurodesis.

A study in a similar population of patients—the Mesothelioma and Radical Surgery (MARS) trial—compared extrapleural pneumonectomy (EPP) plus postoperative hemithoracic irradiation with no EPP in patients with mesothelioma who had received induction platinum-based chemotherapy. Although this feasibility study showed that recruitment and randomisation to EPP within the context of trimodality therapy was achievable, the adjusted HR in favour of not having EPP was 2·75 (95% CI 1·21–6·26;  $p=0\cdot016$ ). In view of the high morbidity associated with EPP, a larger study was not undertaken.

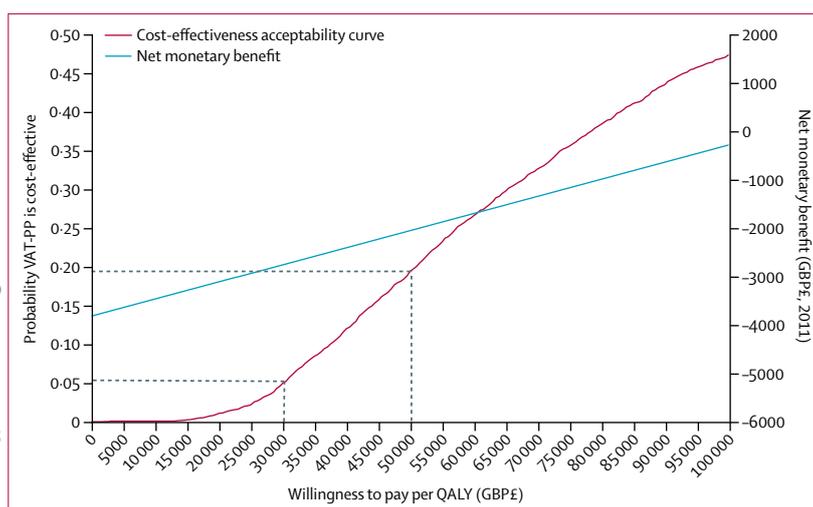


Figure 4: Cost-effectiveness and net monetary benefit of VAT-PP

QALY=quality-adjusted life-year. VAT-PP=video-assisted thoracoscopic partial pleurectomy.

	VAT-PP (n=78)	Talc pleurodesis (n=73)
Serious adverse events	13 (17%)	8 (11%)
Death	1 (1%)	0
Extended hospital stay		
Renal failure	1 (1%)	0
Surgical emphysema	1 (1%)	0
Repeat VAT-PP and subsequent CVA	2 (3%)	0
Fever and dyspnoea	0	1 (1%)
Re-admissions		
Leaking drain	3 (4%)	0
Persistent pleura effusion	1 (1%)	3 (4%)
Hydropneumothorax	1 (1%)	0
Empyema	1 (1%)	1 (1%)
Infected drain site	0	2 (3%)
Thorcotomy with decortication	0	1 (1%)
Symptom control	1 (1%)	0
Other		
Awareness under anaesthesia	1 (1%)	0

Data are number of events (% of patients). VAT-PP=video-assisted thoracoscopic partial pleurectomy. CVA=cerebrovascular accident.

**Table 3: Deaths and serious adverse events possibly or probably related to treatment**

In recognition that many patients with mesothelioma present with advanced disease and comorbidities, MesoVATS assessed VAT-PP—a less arduous surgery than EPP. However, we found that this approach does not confer a survival advantage over talc pleurodesis and resulted in longer hospital stays. Median overall survival was 13·1 months in the VAT-PP group and 13·5 months in the talc pleurodesis group (compared with 14·4 months reported in the EPP group of MARS<sup>7</sup>) and was at the upper end of the range of 7–14 months reported in the systematic review of 14 observational studies and

case series of partial pleurectomy.<sup>21</sup> 1-year overall survival in the VAT-PP group in our study (52%) was similar to our pre-trial estimate of 59%; however, our pre-trial estimate for the talc pleurodesis group of 37%, which was derived from audit data, was very different to the actual result (57%), and was probably based on less carefully selected patients than those put forward for VAT-PP. This result shows the bias inherent in many non-randomised comparisons.

So far, few studies into partial pleurectomy for malignant pleural mesothelioma have been published (panel). Since most patients with malignant pleural mesothelioma present with advanced disease, the findings from MesoVATS could be generalised, because 78% of patients with a final diagnosis of malignant pleural mesothelioma were at IMIG stage III/IV and most had an ECOG performance status of 1. These results contrast with the more highly selected patients in the MARS trial who were predominantly IMIG stage II and had an ECOG performance status of 0 or 1.<sup>7</sup> The

#### Panel: Research in context

##### Systematic review

We searched Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library for articles comparing talc pleurodesis with video-assisted thoroscopic partial pleurectomy (VAT-PP) in patients with mesothelioma, using the keywords “mesothelioma”, “pleurect\*”, “thoracic surgery”, and “talc pleurod\*”. We screened the relevance of studies by assessment of titles, keywords, abstracts, and full texts. We used a Critical Appraisal Skills Programme checklist to assess the quality of the evidence. We found a few published studies that were similar to our own; however, surgical approaches that aim to remove all macroscopically visible tumour (extrapleural pneumonectomy and extended pleurectomy decortication) are not directly comparable with techniques such as partial pleurectomy, in which the aim is to partially remove parietal or visceral pleura for diagnostic or palliative purposes.<sup>6</sup> Second, high-level evidence for partial pleurectomy is scarce in this setting. No randomised trials involving partial pleurectomy have been reported. Cao and colleagues<sup>23</sup> reported a systematic review of safety and efficacy of pleurectomy (extended pleurectomy with decortication and partial pleurectomy) in patients with malignant pleural mesothelioma. Of 14 studies identified as containing patients who had undergone partial pleurectomy (assigned retrospectively on the basis of International Mesothelioma Interest Group or International Association for the Study of Lung Cancer criteria), most were retrospective, none assessed quality of life, and data completeness was variable. Surgical approaches varied between thoracotomy and video-assisted thoroscopic surgery. Since all studies were non-randomised case series involving selected patients, spanning a wide timeframe (1958–2008), with variable methods and reporting, we found it difficult to draw conclusions other than noting that median survival ranged from 7 to 14 months.

##### Interpretation

Our trial is the first, to our knowledge, to compare VAT-PP and talc pleurodesis in a randomised controlled trial. With regard to future clinical practice, our results show that VAT-PP does not offer a survival advantage over talc pleurodesis and is associated with more surgical complications. However, we found some evidence that low-risk patients who are expected to survive at least 6 months might benefit in terms of quality of life from VAT-PP. Future randomised studies of lung sparing (extended) pleurectomy with decortication at thoracotomy should examine whether more extensive pleural resection confers benefit in terms of survival and quality-of-life measures.

advanced stage of disease at randomisation in our trial might explain why VAT-PP did not confer a survival advantage over talc pleurodesis; the more limited excision of tumour by VAT-PP than by EPP might have been insufficient to have an effect on overall survival. Future randomised studies examining lung-sparing (extended) pleurectomy with decortication at thoracotomy will establish whether more extensive resection provides a survival benefit with acceptable morbidity.

In the VAT-PP group, EQ-5D-assessed quality of life for surviving patients at 6 and 12 months was significantly better than that in the talc pleurodesis group. From a patient perspective, this finding is important because quality of life is a primary concern in the final months of life. Although the clinical significance of the observed improvements in EQ-5D is unclear since no pre-trial minimally important difference was posited, Pickard and colleagues<sup>22</sup> suggest that a difference in EQ-5D utility in the range of 0.07–0.12 is important for patients with lung cancer. Differences of this order were achieved at 6 and 12 months in the VAT-PP group compared with the talc pleurodesis group. However, the EQ-5D results were at odds with two cancer-specific quality-of-life questionnaires that did not show consistent improvements in the VAT-PP group. Further studies examining the reasons for the variation in outcomes between the quality-of-life questionnaires in this scenario are required.

Historically, control of pleural effusion has been by talc pleurodesis, either using talc slurry via an intercostal drain, or by talc poudrage at thoracoscopy. During the study, practice shifted from administration of talc slurry via a chest drain towards increasing use of talc poudrage at thoracoscopy in line with contemporary practice (appendix). Previous studies of talc pleurodesis efficacy have shown effusion control rates (partial or complete) between 60% and 84%, but these were in heterogeneous populations containing few patients with mesothelioma.<sup>23,24</sup> Studies of talc pleurodesis efficacy focusing specifically on patients with mesothelioma seem to have lower success rates than studies in heterogeneous populations, probably because extensive visceral disease, common in mesothelioma, mitigates against successful pleurodesis because of failure of visceral and parietal pleura apposition combined with a paucity of normal mesothelial cells.<sup>25,26</sup> A retrospective study<sup>27</sup> of 165 patients with malignant pleural mesothelioma who underwent pleurodesis reported that pleural effusion was not controlled in 31% of patients, with no difference between talc slurry and talc poudrage. At the inception of our trial, the predominant method for assessing pleural effusion was chest radiograph—a less sensitive method than ultrasound, which is now widely used. In some cases, pleural tumour or pleural reaction after pleurodesis or pleurectomy might have been mistaken for a small recurrent pleural effusion. This factor should be taken into account when interpreting the results relating to fluid control. Others have defined failure of pleurodesis

as the need for further pleural intervention for fluid control.<sup>28</sup> Data for subsequent pleural interventions were not routinely obtained in our study.

In the economic analysis, VAT-PP cost an additional £3800 per patient compared with talc pleurodesis. The additional 0.035 QALYs gained per patient (equivalent to 12.5 days of full health) could be bought at a rate of £109 000 per QALY. Due to the prolonged recruitment period and changes in management over time, we estimated cost-effectiveness in only patients recruited in the second half of the trial (98 patients randomised after June 1, 2009). For this group, the cost per QALY was £68 600, which is closer to, but in excess of, the highest cost per QALY of a drug (£50 000) accepted by NICE in previous decisions for end-of-life treatments.<sup>29</sup> The reason for the improvement in cost-effectiveness is multifactorial. After study midpoint, trial patients undergoing VAT-PP had a slightly lower median hospital stay than did earlier patients (7 days [IQR 5–7] vs 8 days [6–11]) whereas patients with talc pleurodesis had a very similar but slightly higher median hospital stay than did earlier patients (4 days [2–7] vs 3 days [2–5]), resulting from greater use of thoracoscopy and talc poudrage in the second half of the trial (appendix), which is more expensive (talc pleurodesis cost £1129 in the first half of the trial and £2649 in the second half). Additionally, we noted some evidence of a greater difference between the groups in EQ-5D score at 6 and 12 months in the second half of the trial, whereas survival remained similar for the two groups (appendix).

Since VAT-PP was both more expensive and less effective than talc pleurodesis in the high-risk subgroup, there seems to be little rationale for this procedure in these patients. However, treatment of low-risk patients with VAT-PP might have some economic justification if the end-of-life willingness-to-pay threshold is raised to £68 600 per QALY or if future studies show that the costs of VAT-PP relative to talc pleurodesis continue to decline further. Further refinement of risk classification systems might also help to identify patients who might benefit most from each treatment.

During the 10 years of study recruitment, several changes in the clinical management of malignant pleural mesothelioma occurred. With regard to staging, MesoVATS used CT, although recent research has shown that although CT remains the first-line investigation method, PET-CT, and in certain circumstances, MRI, might improve the accuracy of staging.<sup>30,31</sup> NICE guidance (2008)<sup>29</sup> on cisplatin plus pemetrexed chemotherapy for mesothelioma resulted in more patients in the second half of the study receiving chemotherapy after study treatment. Because similar numbers of patients in each group had post-procedure chemotherapy, we felt the use of chemotherapy in the clinical management of the disease did not unduly bias the results.

The poor prognosis and high morbidity in this group of patients meant that secondary outcomes were available

for less than half the population by 12 months, although results were robust to a range of missing data analyses. Because the study was open label with group allocations available to patients, clinicians, and researchers, we cannot exclude bias in secondary outcomes as a result of a patient or clinician having a strong preference for one of the treatments.

In conclusion, VAT-PP had no effect on overall survival, resulted in more complications, longer hospital stay, and was more expensive than talc pleurodesis in patients with pleural effusion due to malignant pleural mesothelioma. However, significant improvement in EQ-5D score at 6 and 12 months in the VAT-PP group suggests that this treatment might have a role in patients expected to survive at least 6 months. Subgroup analysis suggests that patients in the EORTC low-risk prognostic group might benefit most from VAT-PP, and further work in this subgroup might be appropriate.

#### Contributors

RCR was the chief investigator for this trial (2009 onwards). AJR was one of the original instigators of the study. RCR, AJR, DAW, JGE, and ASC were involved in recruitment, clinical care, and data collection. The trial was coordinated by RCR and VH, and data analysis was done by LDS, MB, EL, and JAF-R. RCR, LDS, and JAF-R interpreted the data and wrote the first draft of the manuscript, and all authors contributed to subsequent editing. All authors reviewed and approved the final version of the paper. The authors accept full responsibility for the overall content of the paper. Day-to-day running of the trial was undertaken by RCR, VH, and LDS under the guidance of the trial steering committee.

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#### Declaration of interests

RCR has been a member of an advisory board for Lilly UK. JGE has received honoraria from Lilly UK. All other authors declare no competing interests.

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