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Randomised pilot and feasibility study comparing video-assisted thoracoscopic partial pleurectomy-decortication with indwelling pleural catheter for trapped lung in pleural mesothelioma

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ABSTRACT

MesoTRAP aimed to provide preliminary data comparing the efficacy of indwelling pleural catheter (IPC) versus video-assisted thoracoscopic pleurectomy-decortication for trapped lung in pleural mesothelioma. Trapped lung prevalence was 11% (110/988). Over 31 months, 17 centres randomised 10 patients versus 38 planned. Thirteen non-randomised patients entered an observational substudy. Nine randomised patients reported daily visual analogue scale scores for pain and dyspnoea, but measurements varied substantially within and between patients, precluding meaningful analysis. Slow recruitment due to poor performance status precluding surgery prohibits a full trial. In the absence of high-level evidence, we conclude that the least invasive approach to trapped lung, namely IPC, should be considered in line with current guidance. Trial registration number NCT03412357.

INTRODUCTION

Trapped lung in pleural mesothelioma (PM) occurs when the lung fails to fully re-inflate following pleural effusion drainage, usually due to tumour on the visceral surface of the lung causing encasement. Without apposition of the visceral and parietal pleura, an effective pleurodesis is not possible. Re-accumulation of pleural fluid leads to repetitive cycles of breathlessness, drainage and fluid re-accumulation. As a challenging condition to manage with high morbidity, there is no clear management consensus. Some authorities recommend insertion of an indwelling pleural catheter (IPC) under local anaesthesia while others advocate video-assisted thoracoscopic partial pleurectomy/decortication (VAT-PD) to effect lung re-expansion.[1 2] Regarding VAT-PD there are no published studies addressing the management of trapped lung in PM. The Meso-VATS trial did not recruit patients with trapped lung.[3] The European Respiratory Society/European Society of Thoracic Surgery guidelines (2011) recommend that pleurectomy/decortication is considered for symptomatic patients with trapped lung and that a VATS approach is preferred.[4] The rationale for the MesoTRAP pilot trial was to obtain evidence for the optimal management of trapped lung in PM patients and provide preliminary data to develop a full phase III study to compare the efficacy of IPC versus VAT-PD for managing trapped lung with pleural effusion in PM.[5]

METHODS

MesoTRAP was a multicentre, open-label, parallel group, randomised pilot and feasibility study comparing VAT-PD versus IPC in a 1:1 ratio, in patients with trapped lung and pleural effusion due to PM. The protocol for the MesoTRAP study has been published.[5] We aimed to address uncertainties in recruitment and randomisation and to determine the sample size for a phase III clinical trial. The primary objective was to measure the SD of visual analogue scale (VAS) scores (0–100) for dyspnoea following randomisation and examine the patterns of change over time in each treatment group. Secondary objectives were exploration of the prevalence of trapped lung in PM; the ability to recruit and randomise 38 patients to either VAT-PD or IPC in 18 months; survival and adverse events; SD of VAS scores for chest pain; and quality of life at baseline, intervention; 6 weeks; and 3, 6 and 12 months. The primary inclusion criterion was presence of 'clinically significant trapped lung requiring intervention in the opinion of the clinical team' in patients with proven PM and pleural effusion, expected to survive at least 4 months and suitable for treatment with either VAT-PD or IPC. Main exclusion criteria were full lung re-expansion following pleural drainage and evidence of active pleural infection. Study-specific standard operating procedures for performing VAT-PD and IPC procedures were developed.[5]

The planned sample size of 38 randomised patients was a compromise between feasibility of recruitment in an 18-month period and ability to calculate the SD for VAS dyspnoea precisely enough to plan a definitive trial.[5] The planned primary analysis was to estimate (i) recruitment and randomisation rates within 18 months and (ii) the 70th percentile of SD for VAS dyspnoea, in each trial arm and overall, estimated as recommended in.[6 6] As planned, secondary analysis used descriptive statistics and graphical representations to summarise patterns of change in VAS over time, survival rates, quality of life and adverse events, with patients reported in their randomised group according to the intention-to-treat principle. In November

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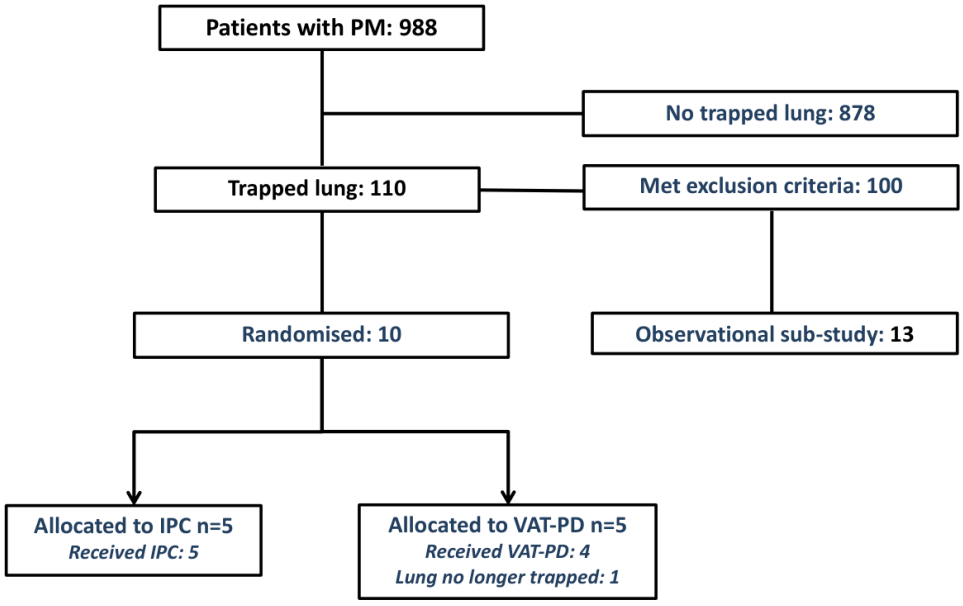


Figure 1 Consort diagram showing flow of patients through the randomised study and observational cohort. IPC, indwelling pleural catheter; PM, pleural mesothelioma; VAT-PD, video-assisted thoracoscopic pleurectomy decortication.

2018, an observational substudy for patients who declined the randomised study or who were unfit for surgery was opened.

The study was registered with the Clinical Trial registry NCT03412357 and funded by an NIHR Research for Patient Benefit grant PB-PG-1014-35050.

RESULTS

MesoTRAP was conducted at 17 surgical referral and non-surgical mesothelioma centres across the UK. Over a 31-month period between August 2017 and February 2020 (truncated by the COVID-19 pandemic), 988 consecutive patients with a new diagnosis of PM were screened, identifying 110 with trapped lung (11%) (figure 1). The median prevalence of trapped lung across centres was 9% (range 0% to 40%). Of the 110 patients, only 10 (9%) (mean age 71.0) were randomised to IPC (5) or VAT-PD (5), compared with the target of 38 in 18 months. Of the remaining 100 patients, the main exclusions to randomisation were unsuitability for surgery (35%), declined randomisation (21%), recruitment into another RCT (7%), previous (failed) pleurodesis (7%) and limited life expectancy (5%) (table 1). The predominant reason for unsuitability for surgery was poor performance status or being deemed unfit for surgery by a thoracic surgeon. Thirteen patients (mean age 79.6) from a group of 56, who were either not fit enough for surgery or who declined participation in the randomised study, were recruited to the observational substudy. Baseline demographics for randomised and observational cohort patients are shown in online supplemental table 1.

Table 1 Reasons for non-randomisation of patients with trapped lung

Criteria	N	%
Not fit for surgery or not equally suitable for both arms	35	35
Died before randomisation	3	3
Estimated survival <4 months	5	5
Previous pleurodesis	7	7
No pleural effusion	3	3
Declined participation	21	21
Recruited to another RCT	7	7
Reason not given	19	19
Total	**100**	

RCT, randomised controlled trial.

Nine randomised patients reported daily VAS scores for pain and dyspnoea, but measurements varied substantially within and between patients, and we could not estimate scores with any degree of certainty. However, most patients recorded low pain, but breathlessness was more prominent and persistent in both groups. There were no adverse events after IPC. Following VAT-PD, one patient had a prolonged air leak and one, a non-life-threatening arrhythmia. Fifteen patients died during follow-up, 3 VAT-PD, 2 IPC and 10 observational. Median overall survival was 274 days; 25% of people died within 105 days. Overall survival at 3, 6 and 12 months was 80%, 70% and 50% for randomised patients and 69%, 54% and 28% in the observational group (figure 2), reflecting the frailer status of the latter group. Completion of patient-related quality-of-life measures, particularly near the end of life, was poor, precluding meaningful analysis.

DISCUSSION

The failure of MesoTRAP to recruit to time and target indicated that a full-scale clinical trial to compare the role of VAT-PD with IPC in PM with trapped lung is not feasible. Main reasons for poor accrual were the lower than anticipated prevalence of trapped lung combined with high co-morbidity and unsuitability for surgery, excluding many patients from randomisation. At the time of study design (2016), the prevalence of trapped lung in PM was unknown. Several studies have reported on series of patients with trapped lung due to various malignancies, of whom up to 33% had PM.[7 8] To our knowledge, only Bibby *et al*[9] have reported the prevalence of 'non-expandable' lung (at some point

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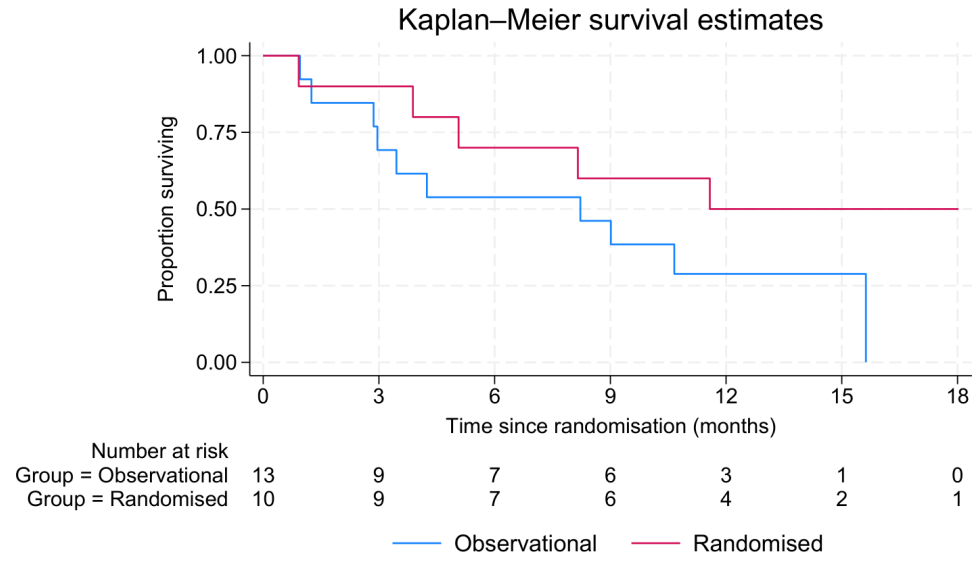


Figure 2 Kaplan-Meier survival curves for patients in the randomised study (both arms combined) and the observational substudy.

during the disease course) in 33% of 229 patients with PM.[9] Our figure of 11% in 988 patients across 17 centres is substantially lower and may reflect a more representative real-world experience outside of specialist centres, where a case-ascertainment bias may occur. We noted that the prevalence of trapped lung between centres varied widely between 0% and 40%.

Currently, there are no RCTs specifically investigating trapped lung across any malignancy type. MesoTRAP has demonstrated that despite attempting a multicentre study in a high-prevalence region for PM, it is not feasible to randomise patients to VAT-PD vs IPC in sufficient numbers. We found that PM patients presenting with trapped lung often have poor performance status. Forty-three of the 100 patients not randomised were unfit for surgery, had a prognosis of <4 months or died before randomisation. The small sample recruited meant that comparison between trial arms was not possible, and non-randomised analysis would not allow adequate adjustment for risk.

Given it is unlikely that this approach will be repeated, the question remains, what is the best treatment for management of trapped lung in this setting? MesoTRAP cannot fully answer this question. Although MesoTRAP cannot rule out benefit of VAT-PD in highly selected and otherwise fit patients, 12-month survival was low in both the randomised and observational cohorts (figure 2). Where choice of management is not clear, the least invasive approach in frail patients with limited life expectancy requiring symptomatic management would seem appropriate. This is in line with the current European Respiratory Society/European Association for Cardio-Thoracic Surgery statement on management of malignant pleural effusions which recommends placement of an IPC.[10]

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Contributors RCR conceived the study and designed it in conjunction with CF, LDS, NAM, NMR, ASC and JGE. Data interpretation was performed by LDS, CF and RCR. CF and RCR drafted the initial manuscript. All authors contributed to revisions and approved the final manuscript. RCR acts as guarantor for the MesoTRAP study.

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