

Randomized controlled trials in malignant pleural mesothelioma surgery—mistakes made and lessons learned

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Randomized surgical trials are of the most difficult to design and recruit, however, they are the only robust method available to establish a new surgical procedure. Mesothelioma is a disease with a perceived poor prognosis for which surgical intervention has relatively high complications and not insignificant mortality. This review will consider the mesothelioma and radical surgery (MARS) 1 and 2 trials, SAKK 17/04 trial and the EORTC 1205 trial all aimed at assessing the potential benefit of radical surgery for malignant pleural mesothelioma. In addition, MesoVATS and MesoTRAP will be explored assessing the value of debulking surgery for malignant pleural mesothelioma. We also endeavour to identify the mistakes made and the lessons learned which will inform future randomized controlled clinical trials in the field of malignant pleural mesothelioma. Despite the insurmountable problems with randomized controlled clinical trials, we show that they are possible and continuing with uncontrolled experiments will perpetuate unproven and potentially harmful operations.

Keywords: Surgery; mesothelioma; radiotherapy; chemotherapy; randomized controlled trials

Submitted Dec 02, 2016. Accepted for publication Feb 23, 2017.

doi: 10.21037/atm.2017.04.05

View this article at: <http://dx.doi.org/10.21037/atm.2017.04.05>

Introduction

Randomized surgical trials are of the most difficult to design and to recruit. Patients are faced with two extreme options: a large, high-risk intervention or not. They may perceive that either they are being exposed to a dangerous, experimental procedure or that they are missing out on a potential “miracle cure”. However, randomized trials are the only reliable method to establish a new surgical procedure. The surgical literature is full of case series or phase II studies (1) which may show beneficial results but lose impact because of the inevitable weakness under accusation of selection bias. Their apparent benefit is based on completed treatments rather than on intention to treat; patients who do poorly do not complete the protocol and are thus not included in the final

analysis (2). Nevertheless, their results can be used to shape future surgical trial protocols by excluding poorly tolerated regimes i.e., European Organisation for Research and Treatment of Cancer (EORTC) trial 08031 which showed the difficulty in tri-modality therapy including extrapleural pneumonectomy (EPP) (3).

Mesothelioma is a disease with a perceived poor prognosis for which the surgical intervention has relatively high complications and not insignificant mortality. It is therefore imperative that surgery is justified and this can only be achieved by randomization. We have in the United Kingdom the ideal situation to satisfy the international requirements for mesothelioma therapy. We have an increasing incidence of the disease within a state-funded healthcare system where patient initiated treatment is both

expensive and difficult to access. We have therefore been able to conduct and construct an increasing portfolio of trials which have been complemented by trials from our European colleagues.

These trials have raised more questions than answers but have stimulated discussion and developed a continuing interest and future direction toward formulating an evidence-based treatment protocol for mesothelioma.

Radical surgery

Mesothelioma and radical surgery (MARS) trial

MARS was the first multicentre randomized controlled trial in mesothelioma (4), conducted in 12 UK hospitals of those with pathologically confirmed mesothelioma who were mediastinoscopy negative and were deemed fit enough to undergo tri-modality therapy. Over 3 years, 112 patients were registered of whom 50 were subsequently randomly assigned: 24 to EPP and 26 to non-EPP. The main reasons for not proceeding to randomization were disease progression (33 patients), inoperability (five patients), and patient choice (19 patients). EPP was completed satisfactorily in 16 of 24 patients assigned to EPP; in five patients EPP was not started and in three patients it was abandoned. Two patients in the EPP group died within 30 days and a further patient died without leaving hospital. One patient in the non-EPP group died perioperatively after receiving EPP off trial in a non-MARS centre. The hazard ratio (HR) for overall survival (OS) between the EPP and non-EPP groups was 1.90 (95% CI, 0.92–3.93; exact $P=0.082$), and after adjustment for sex, histological subtype, stage, and age at randomization the HR was 2.75 (1.21–6.26; $P=0.016$). Median survival was 14.4 months (range, 5.3–18.7 months) for the EPP group and 19.5 months (13.4 to time not yet reached) for the non-EPP group. Of the 49 randomly assigned patients who consented to quality of life assessment (EPP: $n=23$; non-EPP: $n=26$), 12 patients in the EPP group and 19 in the non-EPP group completed the quality of life questionnaires. Although median quality of life scores were lower in the EPP group than the non-EPP group, no significant differences between groups were reported in the quality of life analyses. There were ten serious adverse events reported in the EPP group and two in the non-EPP group.

Summary

It was concluded that in view of the high morbidity

associated with EPP in this trial that a larger study was not feasible. Furthermore, and controversially, it was concluded that the data, although limited, suggested that radical surgery in the form of EPP within tri-modal therapy offered no benefit and possibly harmed patients.

The thoracic surgical community certainly took notice and published a stinging critique of the trial (5,6). Fundamentally it was the fact that the tertiary end points, including survival, were based on a small pilot cohort, representing fewer than 10% of the required sample size for an adequately powered between-arm comparison which brought most criticism. They also felt that the conclusions were weakened by poor protocol compliance in that 6 of 26 patients in the non-EPP group underwent off-protocol surgery, whereas only 16 of 24 patients in the EPP group actually underwent EPP.

Quality control of the surgery in the MARS trial was questioned, mistakenly, since the main operating surgeons had cumulative experience of over 100 EPPs. The intent-to-treat morbidity (11/24; 46%) and mortality (3/24; 13%), and EPP-associated morbidity (11/16; 69%) and mortality (3/16; 19%), were much higher than reported in the literature. This was mistakenly used to question the validity of the results but reflected a series with no inherent selection bias. Indeed the EPP mortality of 2 of 19 (10.5% CI, 1.3–33%) lies within the range of reported data: 0–11.8% (7). The inferior post EPP survival compared to most previous reports was attributed, without evidence, to a disproportionate level of N2 or non-epithelial disease. Statistical analysis of comparative survival was corrected for these variables. Conversely, the reported 19-month median survival among chemotherapy-only (non-EPP) patients was said to be anomalous when compared with a vast prospective literature, although this was a highly selected cohort who were mediastinoscopy negative and had either responded to or at least remained resectable during three cycles of induction. The long-term outcome of the study cohort was not studied beyond 18 months and was therefore rightly criticized. However, the detractors were misguided in stating that these apparent deficiencies made drawing any conclusions from MARS 1 regarding the therapeutic efficacy of EPP impossible.

Mistakes

As one of the co-investigators I can reflect that the selection process was too complicated and including mediastinoscopy may not have been necessary and may have contributed to the slow accrual. The quality

assurance of the surgery was wrongly questioned but we were perhaps open to over-interpretation of the data. Could such strong conclusions be drawn from a pilot study? Nevertheless, this publication has had a striking effect on international practice stimulating an on-going debate about the relative merits of EPP versus radical lung-sparing surgery.

Lessons learned

We established that randomization between a large operation and no surgery was possible and a solid national research network was established. We learned the importance of good trials unit and the merits of the Principle investigator not being one of the operative surgeons, reducing accusation of bias in interpretation. Importantly we found that EPP was too radical for the majority of the population under study who were increasingly aged and infirm. A modified radical lung-sparing operation was standardized and used as the basis of the next randomized trial: MARS 2.

SAKK 17/04 (*ClinicalTrials.gov* NCT00334594)

This was a randomised, international, multicentre phase II trial of neoadjuvant chemotherapy and EPP of malignant pleural mesothelioma with or without hemithoracic radiotherapy (8). It was conducted in two parts at 14 hospitals in Switzerland, Belgium, and Germany. Patients with pathologically confirmed MPM, TNM stages T1-3 N0-2, M0; WHO performance status 0-1; age 18-70 years. In part 1, patients were given three cycles of neoadjuvant chemotherapy (cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 given every 3 weeks) and EPP; the primary endpoint was complete macroscopic resection (R0-1). In part 2, participants with complete macroscopic resection were randomly assigned (1:1) to receive high-dose radiotherapy or not.

The trial was slow to recruit, taking 7 years to recruit 151 patients to receive neoadjuvant chemotherapy, and of these only 75% proceeded to EPP. Surprisingly, complete macroscopic resection was achieved in only 96 (64%) of 151 patients. They enrolled 54 patients in part 2; 27 in each group. The main reasons for exclusion were patient refusal (n=20) and ineligibility (n=10). Twenty five of 27 patients completed radiotherapy. Median locoregional relapse-free survival from surgery, was 7.6 months (95% CI, 4.5-10.7) in the no radiotherapy group and 9.4 months (95% CI, 6.5-11.9) in the radiotherapy group. The most common grade 3 or

higher toxic effects related to radiotherapy were nausea or vomiting [3 (11%) of 27 patients], oesophagitis [2 (7%)], and pneumonitis [2 (7%)]. One patient died of pneumonitis.

Lessons learned

This trial further confirmed the difficulty in subjecting typical patients with mesothelioma to a radical trimodality regime. The findings did not support the routine use of hemithoracic radiotherapy for malignant pleural mesothelioma after neoadjuvant chemotherapy and EPP.

MARS 2 (*ClinicalTrials.gov* NCT02040272)

We are near to completion of the feasibility study to demonstrate the safety of comparing the addition of pleurectomy/decortication (PD) to cisplatin/pemetrexed chemotherapy in resectable pleural mesothelioma. The funding for the randomized phase III study is in place.

Mistakes

We are mindful of the problem with the operating surgeon consenting for the study. This can make both patient and surgeon uncomfortable as a demonstration of true equipoise is not quite what either is expecting. It may be better for the patient not to see the surgeon until after randomization. The surgeon then is in a more natural position of explaining the operation rather than trying to point out its deficiencies. The surgeon has to avoid giving advice which may induce bias and therefore the surgical consultation and the randomization meeting should be separated (9). We have adopted a more straightforward selection criterion to offer a more pragmatic all inclusive trial but the concern remains that the trial may not be sufficiently powered to allow for sub group analysis.

Lessons learned

We have developed an operation in extended PD (EPD) which is more suited to the target population (of the more elderly and infirm) therefore expediting recruitment. Learning from the criticism of MARS 1 we have taken careful measures to ensure surgical quality assurance. We have tried to balance the desire to spread the trial recruitment across the whole country against diluting the experience in each surgical centre. Careful measures are in place including: surgeon validation, operative photographic records or completion thoracoscopy and a specialist mesothelioma multidisciplinary team (MDT) to standardize patient selection.

Future randomized trials

EORTC 1205 (ClinicalTrials.gov NCT02436733)

EORTC are proposing a randomized phase II study of PD preceded or followed by neoadjuvant chemotherapy in patient with early stage malignant pleural mesothelioma. There should be less barriers to recruitment since both arms of the study end up with the same treatment. However, the results may be of limited value since it is really a trial of chemotherapy rather than surgery. The assumption is also made that EPD is an established treatment and rather assumes that MARS 2 has concluded.

MARS 3?

What if MARS 2 shows no OS benefit for the addition of EPD to chemotherapy? This may only become apparent after subset analysis of those “good actors” with node negative, epithelioid disease. A future randomized comparison will then be required in a more carefully staged population. The control arm may also need to be modified to include Bevacizumab on the basis of the findings of a randomized, non-surgical mesothelioma trial (10).

Debulking surgery

MesoVATS (ClinicalTrials.gov NCT00821860)

Following initial reports of the feasibility of video assisted debulking surgery for mesothelioma (11) there were reports of symptomatic improvement (12) and possible survival benefit (13). We, therefore, undertook a randomised, controlled trial in patients 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 video assisted thoracoscopic partial pleurectomy (VAT-PP) or talc pleurodesis, stratified by EORTC risk category (high *vs.* low) (14).

Due to an initial single-centre design it took nearly 9 years to randomly assign 196 patients, of whom 175 (88 to talc pleurodesis, 87 to VAT-PP) had confirmed mesothelioma. OS at 1 year was 52% (95% CI, 41–62%) in the VAT-PP group and 57% (95% CI, 46–66%) in the talc pleurodesis group [HR =1.04; (95% CI, 0.76–1.42); P=0.81]. Understandably, surgical complications were significantly more common after VAT-PP than after talc pleurodesis (which could be performed at the bedside), occurring in

31% of VAT-PP versus 14% who completed talc pleurodesis (P=0.019). Similarly, respiratory complications [19 (24%) *vs.* 11 (15%); P=0.22] and air-leak beyond 10 days [5 (6%) *vs.* 1 (1%); P=0.21], although not significantly, were more common in the VATS -PP group. Median hospital stay was longer at 7 days [interquartile range (IQR), 5–11 days] in patients who received VAT-PP compared with 3 days (IQR, 2–5 days) for those who received talc pleurodesis (P<0.0001).

Summary

VAT-PP was not recommended to improve OS in patients with pleural effusion due to malignant pleural mesothelioma, and talc pleurodesis was considered preferable considering the fewer complications and shorter hospital stay associated with this treatment.

Mistakes

The major mistake, I feel, was that OS was chosen as the primary outcome measure for a debulking operation in which inevitably tumour remained. The analysis in the manuscript focused on survival and played down the benefit in the secondary outcome of quality of life. There was a significant improvement in the EORTC low risk group which remained for 12 months.

Quality assurance in surgical method was lacking and required much post-hoc analysis. Too many surgical centres were needed due to poor initial recruitment. This highlighted the difficulty in the balance between spreading the net widely to promote recruitment whilst not diluting individual centre's experience. There was inevitably a variable degree of debulking introduced heterogeneity into the experimental arm.

The long duration of accrual introduced the additional variables of adjuvant chemotherapy, which was not taken into account initially, and a change in the method of talc administration during trial with the advent of medical thoracoscopy. The long-time delay in recruitment allowed for new treatments to become confounders in analysis.

Finally, the patient population was too heterogeneous. There was no specific analysis of those with symptomatic trapped lung versus those with lower volume disease and a fully expanded lung. The treatment was not stratified for tumour stage or volume.

Lessons learned

We needed a more accurate and robust method of standardizing surgical method with post-treatment operative video records. The patient population needed to

be more clearly defined and different clinical phenotypes or stages of disease described. It remained possible that debulking was beneficial in certain situations but the overall impression taken from the trial was negative.

MesoTRAP

In the MesoVATS trial there was no difference in survival between VAT-PP and talc pleurodesis. However, there was some evidence that VAT-PP improved EQ5D measured quality of life after 6 months particularly in the EORTC low-risk subgroup. At present the future role of VAT-PP is uncertain and may merit further investigation but this should be within the context of clinical trials. VAT-PP may also have a role to play in the specific situation of trapped lung.

The majority of the MesoVATS trial management groups have proceeded to propose a feasibility study (MesoTRAP) comparing video-assisted thoracoscopic partial PD with indwelling pleural catheter in patients with trapped lung due to malignant pleural mesothelioma (15). It will be designed to address recruitment and randomization uncertainties and sample size requirements for a Phase III trial.

Mistakes/lessons learned

MesoTRAP may struggle to recruit sufficiently quickly. Those of better performance status will hopefully be randomized in MARS 2 whilst those of poorer performance may not be fit for extensive surgery even if only by VATS.

Conclusions

Randomized trials in mesothelioma surgery are possible despite the perceived poor prognosis of the disease. The establishment of a coherent network of researchers and a robust trials unit are imperatives. In addition a robust multidisciplinary trial management group is desirable to administer a multimodality treatment protocol. Furthermore, the default position of the referring physician faced with a patient with mesothelioma should be not “there is nothing proven out there” but rather “which trial can I enter them into” (16).

As the operations are complex and potentially resource consuming only the highest grade of trial evidence will truly change clinical practice and secure healthcare funding. Furthermore, the successful conduct of one trial will boost subsequent derivative studies.

Unfortunately, the results of these trials may not be accepted if they contradict strongly held beliefs or strategies. The results in a randomized trial are rarely as good as those reported in uncontrolled case series since all patients allocated to the treatment remain under analysis with no selection bias. If the treatment is less than effective then the harmful effects will predominate.

The most useful and informative trials are the most difficult to complete. Randomized trials may present almost insurmountable problems but to persevere with only uncontrolled experiments will perpetuate unproven and potentially harmful operations (17).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Waller DA, Dawson AG. Randomized controlled trials in malignant pleural mesothelioma surgery—mistakes made and lessons learned. *Ann Transl Med* 2017;5(11):240. doi: 10.21037/atm.2017.04.05