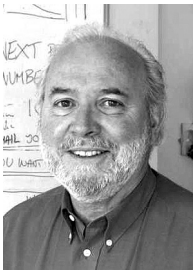
# Mesothelioma and Radical Surgery (MARS): a randomised controlled trial of extrapleural pneumonectomy for malignant pleural mesothelioma



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For many surgical interventions the benefits of surgery are self evident. These interventions can be characterised as having a clear mechanistic role in dealing with the problem: the surgical intervention which we employ clearly alters the course of events and corrects the problem. Thus in tension pneumothorax, relief of valvular stenosis, hip replacement, cataract surgery or the simple Thomas's splint for femoral fracture it is easy to distinguish the signal from the noise and reasonable people need no further persuasion [1]. Then we do not need randomised trials [2, 3].

In contrast in malignant pleural mesothelioma there is characteristically a long interval between the initiating asbestos exposure and the insidious first manifestations of the disease, and there is a variable course thereafter. After Butchart's work published 35 years ago [4] there was little take up of radical surgery; it was the results when the surgery was combined with chemotherapy which raised hopes once more [5]. From that time on it became increasingly difficult to see the signal from the noise. There was increasing knowledge about which cases survived longer after surgery [6] but whether survival was due to the selection as opposed to the intervention was unproven. Chemotherapy has been shown to improve survival in a randomised controlled trial [7] and when surgery and chemotherapy are combined, the effect of the surgery itself can no longer be clearly discerned. The "signal" of surgery cannot be distinguished from the "noise" of other therapies amongst the highly selected subset of patients put forward for operation. But results were not noticeably improving over time. The median survival in the Brigham and Women's series published in 2009 [8] was only 13 months – six months shorter than the survival of 19 months which raised hopes for some in 1999 [6]. In so far as one can make uncontrolled comparisons surely this should have signalled that things were heading in the wrong direction.

Thirty five years after the first series of extirpative operations for malignant pleural mesothelioma undertaken in the hope of cure [4] it was pointed out eloquently by Rena and Casadio that belief in cure flies in the face of the clinical evidence gained from years of experience with this disease [9]. Not only, as they argued, had their been no demonstrable cases of cure, and this is after a large number of surgical follow up studies [10] but the operation has consistently failed in it primary objective which is the eradication of the cancer [11]. The belief that extrapleural pneumonectomy might yet be shown to alter the course of events in mesothelioma was still held by many thoracic surgeon [12]. Against that background, published results of the MARS trial [13] were eagerly anticipated.

## Trimodality therapy including extra pleural pneumonectomy had a detrimental effect on survival and quality of life in the MARS trial

Patients in the Mesothelioma and Radical Surgery (MARS) Trial randomised to have extrapleural pneumonectomy (EPP) within trimodality therapy (chemotherapy, EPP and radical hemithoracic chemotherapy) gained no benefit but, on the contrary, died sooner and with less quality of life than similar patients randomised to not have EPP [13]. This difference was statistically significant ($P$ = 0.016) Patients who were randomised to go on to EPP and radiotherapy survived 18 months while those randomised to not have EPP survived a median of 22 months, both times being from the start of treatment with chemotherapy.

The existence of a control group is the key feature that sets MARS apart and, in terms of the reliability of the evidence, above all other reports of EPP of which we are aware. Furthermore the MARS control group was derived by random allocation, performed away from any clinicians or clinical centres, at the Clinical Trials & Statistics Unit of the Institute of Cancer Research, Sutton, UK. All imaginable means of biasing the allocation were rigorously excluded. Those patients allocated to not have EPP were equally likely to have been allocated to surgery.

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Those who set up the trial wanted an answer to the clinical question "Should we offer EPP to patients with mesothelioma?"[14]. On the present evidence the answer is "No" [13].

## The most important part of MARS is the control group

The purpose of a control group is to obtain a realistic estimate of what survival might have been if surgery had not been performed. No other report of EPP that we are aware of to date provides a control group of patients not undergoing EPP. Instead authors have relied on various sources of the natural history of the disease. For example in the important reference paper from Brigham and Women's in 1999 the opening paragraph states that the natural history for mesothelioma is 4-12 months [6]. The citations in support of this statement are an abstract and two papers published 10 to 19 year previously [15-17]. There is neither an explanation as to why these publications were selected for citation nor any analysis of whether the survival data were comparable with patients selected for and who had survived to leave hospital after EPP.

At the time of planning the MARS trial we were without any reliable contemporary estimate of the natural history of patients comparable with those being operated upon. These are basic data if we are to perform the necessary power calculations to design a trial. We therefore retrieved histology data on over 400 patients diagnosed with mesothelioma during the previous five years and then by tracking death certificates we were able to establish the natural history for contemporary patients. We had data from Guy's Hospital in London and Harefield Hospital, which lies a little outside the city. Patients diagnosed at Guy's had a median survival of 7 months while those diagnosed at Harefield lived nearly twice as long at 13 months [18]. Our inability to explain the difference resulted in our being unable to publish these findings as a research paper so Carol Tan's important study remains in abstract form. The 13 versus 7 month survival may have been due to earlier diagnosis at Harefield or a more rigorous threshold for defining the disease Guy's. It may have been that patients in the countryside around Harefield had better access to better doctors and had better general health care than ours in the inner city. However that there is a difference between two populations of patients with the same disease, apparently with similar management, and in the same time frame is what is most important even if we do not know why. If a hypothetical treatment under investigation at that time resulted in 12 months median survival that might be taken as evidence of useful benefit if we had compared it with 7 months or, conversely, treatment related harm if 13 months was regarded as the "control".

Patients in MARS allocated to not have EPP provide the best estimate of what would have happened to the EPP patients if they had not had surgery. There are no better data. The importance of a control group and a fair comparison has been recognised for many years: that was how the naval surgeon James Lind established how to cure and thus how to prevent scurvy more than 250 years ago, and so saved the lives of countless sailors [19].

## MARS surgical outcomes compared with other reports

It is fundamental to the credibility of MARS to compare its EPP outcomes with results achieved by others. We found five series in which EPP was part of the trimodality therapy with the sequence chemotherapy/EPP/radiotherapy and data that could be extracted for "intention to treat" outcomes. Median survivals were 14, 17, 18, 20, and 25.5 months [20-24]. Median survival in MARS patients allocated to EPP, similarly measured from the start of treatment, was 18 months, a finding in the middle of the range of other reports. MARS results are thus comparable with these clinical series.

The big institutional series of EPP reported in the MARS time frame are not directly comparable because of variable treatment protocols between and within studies and the differences in times frames, but they have appeared under the names of leading authorities in the most widely read international journals. The median survivals following EPP were shorter at 10, 12, 13 and 14 months [8, 25-27]. It appears that MARS surgical results are not worse than those published.

For further comparative data on EPP outcomes the systematic review by Cao and colleagues is valuable [10]. In the graphical display median survival for EPP reported is plotted against the number of patients in the series. This is a form of funnel plot derived by Egger [28]. It illustrates the wide dispersion of results and that the smaller the number of patients in the series, the wider the dispersion, hence the funnel appearance. It illustrates well the variation that might be expected in small series. However the graphical method also seeks out bias in reporting: in a wide world of surgical reporting, where the decision to report is made when the results are known, small series with good results are more likely to be reported.

It has been remarked that mortality in MARS is higher than expected [29] and no doubt it will be remarked upon again. In 34 studies including 2320 patients 30-day mortality ranged from 0% to 11.8% and was 6.0% overall [10]. There were two deaths within 30 days in patients undergoing EPP within the MARS trial which with a small denominator ($N$ = 19 for conventional event rate reporting) gives a death rate of 10.5% but with wide confidence intervals (1.3% to 33%). That is the nature of small data sets. To put it in round figures, if there are 20 patients in a set, event rates can only be 0%, 5%, 10% etc and for any given death rate, a single death, more or less, makes a 5% step change. To point to the death rate in MARS as if it were "significant" is simply a Type I (or alpha) statistical error.

## The setting up of the MARS trial

The MARS trial was not a shot in the dark; this randomised trial was set up specifically to test the belief in

EPP because the evidence for benefit available at the time was unconvincing. EPP alone was no longer being performed because there was a perception that the poor outcomes following EPP [4] results had improved when the surgery was performed in association with chemotherapy [30]. The possibility that any improvement might be attributable to the chemotherapy itself rather than any effect of the combination had not been tested. It was also considered by the late 1990s that better results were obtained with EPP within trimodality therapy [30]. But published results were all based on the analysis of patients who have completed all the modalities [31]. Interestingly at 17, 17, 18, 19, 24 and 35 months these survival times were longer than in more recent publications. Being alive and well enough to undergo the second and third element of trimodality therapy is a rigorous form of selection which inevitably selects for longer natural survivors. An implicit comparison was being made with expected natural history amongst all patients, many of whom would never be considered for surgery. Even with these major shortcomings in the nature of the evidence, the median survival times did not seem sufficient to justify the severity of trimodality treatment as far as we could discern from our systematic review of the literature [31]. But we could not be sure – there were no control groups against which to make a fair comparison.

There were many flaws in the nature of the "evidence" on which we were trying to base practice for mesothelioma [32]. Convinced by the arguments that we needed better evidence before undertaking such major surgery [33] we set out to design a randomised trial. The word "feasibility" was not one chosen by the founders of the trial but is an expression of caution by the funders. We wanted an answer to the clinical question and were prepared to start small if that was all the funding we could get [34].

## The nature of the MARS trial

That I was personally in doubt about the claims for effectiveness of EPP was well known [32]. As a result it was essential that MARS was a rigorously conducted randomised controlled trial. As its Chief Investigator I was not involved in the clinical care of any of the patients, played no part in the process of random allocation, and I did not see data while the trial was in progress - that was the duty of the trial's data monitoring committee. These are some of the steps taken to exclude the effect of inadvertent bias. Institutional follow-up studies, of their nature, cannot be implemented with any such rigour.

MARS was not only rigorous in its method but also innovative in its design. There were two distinct phases with separate consent processes [35]. 112 patients gave written consent to enter the first phase of the study. They agreed to have all their existing investigations reviewed and further investigations undertaken to establish whether they were suitable candidates for extrapleural pneumonectomy (EPP) and were planned to have three cycles of platinum based chemotherapy. When the chemotherapy was completed, and a post treatment CT

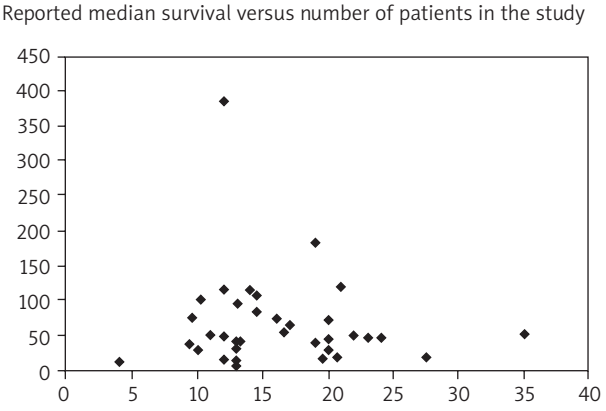


**Fig. 1.**

*Data from Cao et al. [10] for 34 series where median survival was available. Reported median survival versus number of patients in the study*

was performed, all the investigations were reviewed by the clinical team. Of the 112 patients in the first phase, 57 were considered to be potential candidates for EPP and consented to be allocated by randomisation. A multidisciplinary group including the oncologists taking care of the patient, the surgeon who would be called upon to offer EPP if that were the allocation, the trial radiologist, other members of the trial management group, and a representative of the of the trials unit met by teleconference, chaired by the chief investigator. If there was agreement that the patient was eligible the allocation was made independently at the trial centre and in due course 50 patients were randomised.

## Will MARS change beliefs?

When MARS had completed recruiting but before the results were known, three of the international societies of thoracic surgeons (EACT, ESTS and STS) conducted a joint survey of opinions and beliefs. Answers came from Europe, USA, and the rest of the world with a roughly 40:30:30 split from surgeons who did and did not perform EPP. In general they shared similar opinions. They believed that EPP was more effective than pleurectomy/decortication and that the addition of one and two adjuvant treatments incrementally increased benefit. So put simply, surgeons believe that their treatments work and the more treatment that is given the greater the good. Up to 80% believed that EPP within trimodality therapy could cure EPP. There were 217 of 802 surgeons who believed that EPP alone can cure EPP [12].

In an independent editorial on the survey Rena and Casadio commented:

"Great confusion about the meaning of the terms used to describe the surgical outcomes reigns among thoracic surgeons as well. When asked if surgery is able to cure MPM patients, about 30% of responders answered that EPP alone can cure MPM, and this is the belief of about 50% of thoracic surgeons in the USA. This shows that a large proportion of USA thoracic surgeons are convinced that surgery, and in particular EPP alone, is able to give the patient a postoperative

life completely free from MPM! This is strange, considering that to date there is no report of a single patient surviving a MPM. The problem is that the sense of the action 'to cure' is not clear to all or it is differently thought about in the thoracic surgeons community" [9].

Given the widespread belief in effectiveness of EPP, we realise that the MARS findings may not be welcome news. There may be a parallel to be drawn in history between radical surgery for breast cancer and for mesothelioma. Radical mastectomy was the standard of care for many years and for a minority of surgeons had escalated to include median sternotomy in pursuit of the internal mammary artery lymph node chain. The general acceptance that radical mastectomy does not favourably influence survival in breast cancer was a blessing for many women who could, from that date, be spared surgery that was both mutilating and unavailing. It would not have been welcomed by surgeons for whom radical mastectomy was the basis of practice for many years. We have recently been reminded of this episode in our surgical history by an article in the *Journal of the American Medical Association* [36]. According to the piece in *JAMA*, the evidence which called a halt to radical forms of mastectomy was a relatively small randomised controlled trial performed in Italy and published in 1981 in the *New England Journal of Medicine* [37]. My own recollections from the 1970s are of a less clear cut resolution of the beliefs around breast cancer surgery. During my general surgical training in the 1970s I was involved with, and personally performed, mastectomy in various forms depending on the beliefs of my surgical chiefs of the time. The move away from radical mastectomy antedated the trial. In support of my memory I found a published discussion from 1978 on what form of management was appropriate for breast cancer [38] which made no mention of radical mastectomy, nor did any of the correspondence that followed. The debate had already occurred and the RCT concluded it. Perhaps that will be seen in time as the role of MARS.

## Will MARS change practice?

Practice is already changed and the knowledge that MARS was in progress may have influenced the tone of publications in the last few years which has been more measured abut the benefits of EPP. Lung sparing operations are preferred over EPP in several publications from authors of high prominence in mesothelioma surgery [5, 26, 39-41]. The literature on pleurectomy decortication (P/D) however, when systematically reviewed is no better than it was for EPP [42]. Any apparent superiority of P/D over EPP may be because it is less harmful than EPP rather than it is at all effective in prolonging survival from mesothelioma. One could conclude that it does less harm rather than more good.

What is important now is to study carefully what is gained by lung sparing extirpative surgery compared with the patients outcome without surgery. A net gain in quality of life, predominately by maintaining breathing as far as possible, would be more important than trying to show survival gains measure in months at best.

It is already being argued that MARS was too small to change practice. It is true that the conclusion was based on the outcomes in 50 patients of whom 24 were randomly allocated to EPP and 26 to not have radical surgery but nevertheless the trialists were sufficiently confident in the reliability of the finding that any extension of this study or a further study of EPP was deemed inappropriate. The original proposal was that if "feasibility" was demonstrated the study would continue to a target total of 670 randomised patients [14]. With a hazard ratio in the MARS trial of 2.75 against EPP, to prove the result false an extended trial would have to accrue results in favour of EPP, pulling the result through the null point and out the other side to reverse the hazard ratio. EPP is an operation which has consistently failed in the primary intention of any cancer operations, that of clearing the cancer margins [11]. Taking all the evidence, it is improbable that the MARS finding against EPP is wrong. Since "some unbiased evidence is clearly better than none" [34] MARS may not be very big but it can reasonably be argued that it was big enough.

## Acknowledgements

I will be eternally grateful to the patients, nurses, doctors and scientists, too many to name individually, who made the MARS trial possible and made it a reality.

The "co-Founders" of the trial were Julian Peto, David Waller and Ken O'Byrne. Peter Goldstraw chaired the Trial Steering committee. I am also grateful to Walter Weder for very helpful conversations during and since the MARS trial which have helped me focus on the key points in the presentation of the process and results of MARS by provided a "reality check" on the reporting and implications of the MARS trial.

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