Editorial

Surgery for mesothelioma: MARS landing and future missions

Keywords: Mesothelioma; Extrapleural pneumonectomy; Pleurectomy decortication

The first report of the Mesothelioma and Radical Surgery (MARS) trial appeared in the Journal of Thoracic Oncology [1]. The objective of MARS was to establish the possibility of allocating patients, at random, to have either extrapleural pneumonectomy (EPP) or no surgical resection. The target — 50 randomised patients — was reached in late 2008. Outcomes are not yet available; however, the trial was not powered to prove effectiveness but to address the question of feasibility.

In the MARS trial protocol (Fig. 1), patients were allocated to either trimodality therapy (chemotherapy, EPP and radical hemithoracic radiotherapy) or identical chemotherapy followed by any non-surgical treatment thought appropriate. The trial employed a two-stage consent process. Patients consented to participate in the study for completion of staging, chemotherapy and other work-up (N = 112). The 2–3 months required for chemotherapy between the first and second consent allowed patients and teams to come to terms with randomisation as a means of unbiased allocation. Of the 112 patients, 50 (45%) were eventually randomised. MARS has shown that unbiased allocation to surgery versus no surgery is not impossible — but it is far from easy.

The story of MARS goes back 5 years. Claims were being made that EPP had the potential to prolong life [2]. The data were derived from follow-up studies of multimodality therapy; one could not discern the effect attributable to surgery. There were no data concerning the denominator from which the cases were drawn, and it is likely that the EPP series include fitter patients with slower progressing cancer. Then, if only patients completing treatment are reported, it follows that these patients must be sufficiently well to receive the second and third modalities of treatment, further biasing the interpretation of outcome. These are some of the pitfalls in the reporting of follow-up studies [3]. It was against that background that the cancer epidemiologist Julian Peto urged European surgeons to put the question of radical surgery for mesothelioma to the test in the form of a randomised trial [4].

While MARS has been recruiting, claims for the benefit of EPP have moderated. The Boston group have raised a cautionary note in reporting the high burden of complications occurring in over 60% of patients [5]. This was echoed in the Mayo clinic follow-up study in which the authors report that more than 50% of EPP patients had major complications and a 3-year survival of only 14% [6]. An appealing argument for EPP was that it provided the best target for intensity-modulated radiotherapy but in 100 patients planned for this combination (37 did not have the radiotherapy) the median survival was 10.2 months [7]. Meanwhile the option of conserving the lung has received more emphasis. A report combining results of radical surgery for mesothelioma from three centres in the USA concludes 'patients who underwent pleurectomy/ decortication had a better survival than those who underwent extrapleural pneumonectomy' but the authors remind the reader 'the reasons are multifactorial and subject to selection bias [8].' The Leicester group in the UK have also shifted the emphasis towards lung-sparing procedures and report no detriment in their results from doing so [9].

The question that remains unanswered is whether either form of radical surgery offers a survival advantage over not having surgery. There are occasional individual patients who survive for some years after surgery but in the absence of much more data, preferably from randomised control trials (RCTs), these may have been long-term survivors irrespective of surgery.

On what outcome measure should we power a future trial? Prolonged survival has been the focus of EPP; the bold words 'curative surgery' were used in the pemtrexed (Alimta) trial. Only patients ‘not eligible for curative surgery’ were included. This indicates that the possibility of cure was in the minds of a wider oncological community as a goal in mesothelioma [10]. Cure is a small word on a big mission. It should only be claimed if the patient lives free of mesothelioma to die of something unrelated. It should be used with care and be based on evidence in the form of reliable data. The more moderate claim — that surgery prolongs life — can only be made if there is a reliable comparison group whose lives were shorter. With published survival curves rapidly approaching zero, the consensus emerging in the literature is that surgical ‘cure’ is not achievable.

If not cure, then does radical surgery offer palliation? Palliation is a longer word on a less clear mission. Strictly, it is the relief of present symptoms; it can be used to mean moderating or preventing predictable future symptoms such as chest wall pain and breathlessness; and it can also be used to mean extension of survival without prospect of cure.
Symptoms are poorly reported and there are no comparators: better data are needed to inform patients of their options. The hope of prolonged survival dominated earlier reports and therefore patients’ expectation and motivation. In planning a further trial of radical surgery for mesothelioma (provisionally called MARS-2) we will evaluate total pleurectomy and, as in MARS, we will include respiratory function and quality of life as measures of outcome.

An RCT is a very laborious way of perhaps answering just one research question and, in the design of a further MARS trial, it is critical to frame a relevant question. Asking the question in a persistent and determined way (and running an RCT is surely that) encourages others to reconsider their own answer. MARS has shown that random allocation of patients is possible but beyond that, for reasons of statistical power, may provide no definitive answer concerning the effect of EPP on survival but most important is the relentless search for secure evidence on which to base practice. In the words of Richard Lilford, ‘some unbiased evidence is clearly better than none.’