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Protocol - Thoracic general

The MARS trial: mesothelioma and radical surgery

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Summary

The increasing incidence of malignant pleural mesothelioma has demanded the attention of thoracic surgeons worldwide. Can radical surgery cure mesothelioma or add usefully to the length and quality of life for its victims? The MARS (mesothelioma and radical surgery) trial is open and recruiting in Britain. If the trial proves feasible we will seek to make an international study.

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Malignant pleural mesothelioma is not rare. In the UK it now kills more people than either melanoma or cancer of the cervix [1]. Deaths will peak between 2010 and 2015 [2]. Similar rates are anticipated elsewhere in Europe [3] and worse in countries where asbestos is unregulated. What should we be doing for these patients? There is little evidence on how best to manage mesothelioma [4]. A concerted effort is needed between physicians, surgeons, and oncologists. Diagnosis and palliation will be part of the surgeon's work throughout this epidemic but the big question is what is the chance of surgical cure? Surgery was introduced into practice in the 1970s [5] and our European Journal has published large series [6,7]. If operation by extrapleural pneumonectomy (EPP) had a clear role it would have been established. In the MARS trial (Mesothelioma and Radical Surgery) we think it is unproven – but to either side of us are believers and doubters.

The believers do not want to randomise patients because they see EPP as already of proven benefit, in selected patients. For evidence they point to the results of Sugarbaker [8] who analysed pathological findings in the 176 thirty-day survivors of EPP. A subset of 31 patients had all three of the prognostically favourable variables revealed in multivariate analysis: epithelioid histology, clear resection margins, and no positive extrapleural nodes. They had a median survival of 51 months. For the believers these results are sufficiently persuasive to argue that patients such as these should not be randomised to face a 50% chance of being denied a chance of cure. They want to do whatever they can for these patients. They argue that to take a nihilistic view is no longer acceptable to patients or doctors.

The doubters are not convinced that the case is made. Survival to four years in half of the patients in this small and retrospective subset may be a consequence of retrospective exclusion of the patients with unfavourable features. If one establishes favourable features from a data base, and redefines the groups on the basis of these significantly favourable and unfavourable features, there will be a difference in favour of the better group. That is a statistical inevitability; it is a circular argument. That is why in developing a risk model the data are randomly divided into a first test set to devise the risk model and the remainder are used to test its reproducibility [9].

Setting cold statistical argument aside for a moment, the believers see their position as giving patients hope. They see the doubters as nihilists who in turn argue that one thing is certain: that when a patient embarks on trimodality therapy, it will take six to nine months to complete the treatment. This is time during which the patient is in and out of hospital and sometimes travelling long distances from home. They admit they may indeed be nihilistic, but consciously so; it is not that they do not care. They see the prospect of useful addition of survival and quality of life as unlikely. For them treatments should not give false hope and needless suffering. The arguments based on compassion lead also to equipoise.

EORTC 08031 seeks to establish the feasibility of delivering EPP in selected patients. We support the implementation of trimodality therapy within well conducted studies – but there is no control group. We will be left with the question whether, in terms of quality adjusted life years, there is a useful gain over what might have been seen with a less severe treatment. We need better evidence. Why should a doctor with a particular point of view continue to deny active treatment to patients with lethal cancer without evidence? It is as unacceptable for an enthusiast to put

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patients through extreme treatments without evidence. Whichever of these two opposing points of view is espoused, however well intended, the evidence is simply not there to support either. At present the ends are polarised and neither pole has the evidence to shift those in the middle.

What seems incontrovertible is that to continue in the face of such uncertainty is, in health care terms, unacceptable. Clinical opinion based on 'experience' is insufficient in a disease with a variable course and where a gains in survival versus quality of life are competing objectives. A randomised controlled trial (RCT), although admittedly difficult, seems the only logical solution. In the MARS trial the operation (EPP) is sandwiched between induction chemotherapy and radical radiotherapy as that is the setting in which the best survival rates have been achieved. The control arm also offers full active trimodality therapy; every treatment is available to the patient, short of EPP. Specifically, those randomised to not have EPP will receive the same induction chemotherapy, are eligible for any palliative of debulking surgery considered appropriate, and radiotherapy should be given to any port sites or drain sites. Thereafter full supportive care will be given in both arms including any chemotherapy and or radiotherapy deemed clinically indicated.

One of the reasons for this complex and untidy design in the control group is to give (and to be seen to be giving) active treatment in both arms. The intention is that the trial surgeons will not offer EPP outside the trial. In Guy's Hospital it is agreed that EPP surgery is only funded within the trial by agreement with the Trust's Medical Director. There is precedent for this approach in the NETT trial of lung volume reduction surgery [10]. The MARS (Mesothelioma and Radical Surgery) trial is recruiting in the UK with

the intention that if its implementation proves feasible it will become an international trial. It is a difficult study but we did not choose surgery because it is an easy life. This is a serious question that we have to answer.

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