Title page

Surgery for Mesothelioma: the evidence base and a pragmatic approach to surgical treatment.

Vasudev Baburaya Pai[1],
Kandadai Seshadri Rammohan[2],
Tom Treasure[3*]

Affiliations:
1. Kasturba Medical College, Manipal, Manipal University , India
2. Wythenshawe Hospital, University Hospital of South Manchester, Manchester, UK
3. Clinical Operational Research Unit, University College London, London, UK

*Corresponding Author:
Professor Tom Treasure
Clinical Operational Research Unit,
University College London,
London, UK
E-mail: tom.treasure@gmail.com

Compliance with Ethical Standards. The statements apply to VBP, KSR and TT

- The authors have no potential conflicts of interest.
- There is no original research reported in this paper.
- We only summarise and review clinical work already completed and published.

Note to editor

As you have put reference [1] after the abstract.

That is fine but shifts all the citation numbers along so in order to get these aligned I will but it in here. [1] However as van Zanwdwijk is retrievable on paper it is the

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Introduction:

Indian thoracic surgeons will be very well aware of malignant pleural mesothelioma so we will not dwell on the background more than just as a brief reminder. We will concentrate on the evidence concerning the clinical effectiveness of surgical resection. We will suggest a pragmatic approach to the problem which this disease presents and the important matter of prompt and effective palliation.

What is the present position?

Asbestos mining is prohibited in India, however it may not be well regulated. The Ban Asbestos Network of India (BANI) is a group of public health researchers, scientists, doctors, trade unions, activists and civil society groups who advocate immediate banning of the mineral. India changed her position in 2011 and agreed to add Asbestos to the list of Hazardous materials at the Rotterdam Convention. However, to date, Chrysotile asbestos remains off the list, a position supported by seven nations including India. In spite of the mining ban, India is the largest importer of Canadian Asbestos in the world. Asbestos continues to be used in roofing, cement pipes, gaskets, brake liners, clutch facings and insulation.[*]

To get an idea from an Indian perspective, VBP & KSR sought to discuss with at least four Indian regional cancer centres the magnitude of the problem facing India but no database which could be analysed was identified. There are several possible reasons

- This might reflect a low incidence of mesothelioma in the Indian subcontinent.
- It might be due to the absence of a well organised reporting system. There may be no mechanism for collecting and storing the data.
- It might be that in this population, mesothelioma is not regarded as a disease which is usefully treated by surgeons.

Most of the people affected by mesothelioma are the poor, for whom lung cancer and tuberculosis are seen as common problems rather than an occupational hazard. The Times of India reported in April 2016 that most asbestos related diseases are never diagnosed but simply labelled as tuberculosis or lung cancer.*

Aetiology

The aetiology of mesothelioma is asbestos exposure in the large majority of cases. However in Britain, given its widespread use in domestic building and building repairs, it is as likely to occur in jobbing tradesmen as in workers in large scale manufacturing or construction work. We know this from the work of Julian Peto.[2-4] There are pockets of the disease due to other material with a similar irritant structure (amphiboles) such as in the town of Biancavilla in

[*] http://timesofindia.indiatimes.com/home/environment/pollution/NGT-asks-5-mineral-rich-states-to-survey-all-asbestos-mines/articleshow/48039145.cms April 2016 accessed August 2017.

Sicily.[5;6] We are unsure how this compares with India but the general statements are likely to be applicable with the addition of probably more mesothelioma in unaware and unprotected workers.

Where it has been studied, asbestos exposure can be identified in up to 80% of cases. The development of Mesothelioma appears to be dose dependent – heavy exposure associated with earlier disease presentation, with an incubation period varying from 20 to 70 years.

Pathology

Malignant pleural mesothelioma is a relentless cancer which spreads along the pleura and invades the lung and the chest wall. It is this pattern of growth which makes resection with clear margins effectively impossible, other than in exceptional cases with an atypical behaviour.[7] Epitheliod Malignant Mesothelioma is the commonest histological subtype (50-70%) with sarcomatoid (10%–20%), and mixed (biphasic) being the other two categories. Epithelioid histology has a better prognosis than the other types.[8]

Reported outcome

The prognosis with malignant pleural mesothelioma is typically very poor. A median survival of seven months was found in the results of a recent analysis of the American Surveillance, Epidemiology, and End-Results (SEER) database which included 14,228 patients from 1973 to 2009 [9]. However, grouping the patients based on the number and type of treatment received, invites a comparison to be drawn, which could be misleading. (Figure)

This comparison neglects two important considerations:

1. The large majority of patients are never considered for extirpative surgery because it is evident that they are likely to die relatively soon; the extent of the pleural cancer and their poor general condition precludes surgery. The 50% of patients who die untreated within seven months (that is what 'median' indicates after all) are not relevant to an estimate of a treatment effect. Patients whose deaths contributed to the left hand of the graph, those who died soon after diagnosis, are not the ones offered surgical resection. These early deaths space out the lines on the graph in an eye catching way but it is determined by inherent prognosis not a treatment effect.

2. The flatter part of the graph to the right suggests a correlation between the number and radicality of treatments and survival: the more treatments patients receive, the longer is their survival. This too is flawed. Surviving patients, who are not only alive but well, are more likely to receive a second treatment. You can't treat the dead and doctors should rightly not treat patients with little prospect of benefit. Put bluntly, patients have to be alive to receive the treatments; they are not necessarily alive because of the treatment.

Review methods

To study the results of surgery for mesothelioma, electronic searches were performed using Ovid Medline, Embase, until January 2017. To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms "mesothelioma" with "surgery" including "pleurectomy" and "pneumonectomy" as either key words or MeSH terms. The latest and most complete articles were given preference. Reviews and meta-analyses were also retrieved for review. Expert opinions and commentaries of experienced researchers have also been studied. The data are very variable in how they describe the case mix, and were difficult to tabulate for outcomes measures. We have chosen to produce narrative summaries in the hope that this will be easier to follow, and more readable.

Surgical resection of mesothelioma

Since we like to have things well defined, the IASLC and IMIG group nomenclature is as follows: [10]

a. Extrapleural pneumonectomy (EPP): en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm. In cases where the pericardium and/or diaphragm are not involved by tumour, these structures may be left intact.

b. Extended pleurectomy/decortication (P/D): parietal and visceral pleurectomy to remove all gross tumour with resection of the diaphragm and/or pericardium. The IASLC Mesothelioma Domain suggests use of the term "extended" rather than "radical" in this instance as the latter implies a completeness of resection with added therapeutic benefit. There is currently insufficient evidence that resection of the pericardium and diaphragm provides either.

c. Pleurectomy decortication (P/D): parietal and visceral pleurectomy to remove all gross tumour without diaphragm or pericardial resection.

d. Partial pleurectomy: partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumour behind.

Macroscopic complete resection

The nature of mesothelioma makes it impossible to resect with clear margins. When the matter was formally studied prospectively by Arman Hasani working with John Alvarez in Western Australia, using an adequate method worked out with their pathologists, it was found that there was always cancerous tissue crossing the resection line.[11] Completeness of resection is a pathologist's judgement, made with a microscope. When it was evident that it was never being achieved in mesothelioma a new term 'macroscopic complete resection' was coined.[12] If complete resection is an evaluation made with a microscope, there is something oxymoronic about 'macroscopic complete' resection; it is tacit acceptance that the resection is *incomplete*. Let us not overlook that fact.

Surgery with 'curative intent': extrapleuralpneumonectomy (EPP)

There is only one operation that has been realistically proposed as possibly curative and that is EPP. 'Cure' in the context of mesothelioma is a small word on a big mission. Looking at the question chronologically, it was Eric Butchart in Britain in 1976, who first reported what he called pleuropneumonectomy for mesothelioma. The perioperative mortality was high and, when he wrote up the follow-up study he had only two survivors of 29 patients at 3.5 and 6 years.

It was thought by David Sugarbaker, then in Brigham and Women's Hospital in Boston, that resurrecting this operation and combining it with chemotherapy and radiation might meet with better results.[13;14] In 1999, Sugarbaker reported 183 patients who underwent extrapleural pneumonectomy followed by adjuvant chemotherapy and radiotherapy. There was no record of the degree of selection or the denominator from which these patients were drawn. The perioperative mortality rate was 3.8% (seven deaths) and the morbidity was 50%.[15] The deaths were excluded from the survival analysis thus immediately inflating the impression of benefit. Survival in the 176 remaining patients was 38% at 2 years and 15% at 5 years (median 19 months).

Sugarbaker vigorously promoted EPP. In Britain, David Waller and his team embarked on a programme of mesothelioma surgery and research.[16-18] After a systematic review published in The Lancet enabled a power calculation[19] a British group including David Waller and Julian Peto undertook the Mesothelioma and Radical Surgery (MARS) randomised trial which opened in 2004, initially to test feasibility.[20]

While MARS was in progress, Christopher Cao in Sydney[21] undertook a systematic review on EPP for mesothelioma analysing 34 of 58 relevant studies from 26 institutions. "The median overall survival for EPP varied from 9.4 to 27.5 months, and 1-, 2-, and 5-year survival rates ranged from 36 to 83%, 5 to 59%, and 0 to 24%, respectively. Whilst perioperative mortality ranged from 0 to 11.8%, the morbidity rates ranged from 22 to 82%. Quality of life assessments from three studies reported improvements in nearly all domains at 3 months postoperatively. Patients who underwent trimodality therapy involving EPP and adjuvant chemoradiotherapy had a median overall survival of 13 to 23.9 months."[21] The conclusion was that in a select group of patients with MPM, EPP may be of benefit, particularly when combined with chemotherapy and/or adjuvant radiotherapy. Importantly, these were all uncontrolled studies and included no patients who had lesser or no treatment. Also there is the trap of reverse causation explained above.

A report from the Memorial Sloane Kettering Cancer Center (MSK-CC) in 2007 where Raja Flores was working with Valerie Rusch provided valuable data on 945 patients. [22] The data were extracted from the publication by mathematicians in University College London (the author would not provide them) in order to define the upper limit of any survival benefit attributable to resection.[23] Patients who had no surgery, exploratory thoracotomy without resection, and those who had radical resection had similar survival of about 17 months. There

was no discernible benefit from resection itself. It was true that patients who had multiple treatments had lived longer but again there was the circular problem: were they alive because of multiple treatments or was it that their being alive gave an opportunity for further treatments to be given? The retrospective, observational, and uncontrolled nature of the MSK-CC study left us with no trustworthy answer.

These dubious claims for benefit from surgical resection of mesothelioma was the context for the only randomised control trial on the subject: the Mesothelioma and Radical Surgery (MARS) trial.[24] A total of 112 eligible patients recruited from 11 collaborating centres entered the trial to receive platinum-based chemotherapy. After chemotherapy patients were re-evaluated and those who had progressed on treatment and those who were deemed inoperable on review were not considered eligible for radical surgery and radiotherapy. Fifty eligible patients (45%) were randomized to EPP (24/50) or best nonsurgical care (26/50). In all, 67% (16 out of 24) in the surgery arm underwent EPP as the surgical intervention. The hazard ratio [HR] for overall survival between the EPP and no EPP groups was 1·90 (95% CI 0·92–3·93; p=0·082), and after planned adjustments for sex, histological subtype, stage, and age at randomisation the HR was 2·75 (1·21–6·26; p=0·016). Median survival (after induction chemotherapy) was 14.4 months for the EPP group and 19.5 months for the non-EPP group. The results showed that the non-operated control group, who had been eligible for EPP but were *randomly* assigned to *not* have surgery, had a survival similar to Sugarbaker's best surgical outcomes associated with EPP. Survival figures were poorer among patients randomly assigned to EPP.

Though not statistically significant in the diminishing numbers of patients, the median quality of life scores were lower in the EPP group. The high morbidity associated with EPP in this trial and in other non-randomised studies, led the researchers to conclude that a larger study was not feasible. The trialists concluded "These data, although limited, suggested that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients."

The MARS trial was published in Lancet Oncology[24] to be followed by vigorous and ongoing criticism[25]with resentment that continues. The critics rounded on the MARS trial in what was erroneously headlined as 'Clinical Guidelines' when it was in reality a position statement from the International Mesothelioma *Interest* Group.[26] Robust rejoinders came from the MARS investigators.[27;28] But other authors accepted that the evidence must be heeded.[29;30] Ugo Pastorino of Istituto Nazionale dei Tumori, Milan reviewed outcomes of EPP and concluded: "Our data suggest that patients with good prognostic factors had a similar survival whether they received medical therapy only, P/D, or EPP." [31] Median survival was 19 months among patients receiving medical therapy without surgery for those with favourable features - but those are the patients who would have been selected for EPP.[31] This supports MARS findings. Ottavio Rena and Catarina Casadio pointed out that EPP had never been shown to cure any patient[32] and found in their own study that the operation had impaired quality of life in many.[33]

There was some pushback. A group of EPP practitioners published an analysis from the International Association for the Study of Lung Cancer (IASLC) mesothelioma database.[34] They included 3101 patients from four continents, 1489 of whom underwent surgery with curative intent. 132 patients with stage I disease resected by EPP had a median survival of 40 months compared to 23 months for P/D, with no difference in survival at later stages. Patients undergoing any type of curative intent surgery had superior survival with multimodality therapy when compared to surgery alone (20 vs 11 months). The small number of stage I patients with adequate data made it difficult to draw strong conclusions regarding the differences in survival by procedure, and the authors acknowledged the potential contribution of institutional selection bias to the results.

Following the MARS trial findings the group in Marmara University in Istanbul changed their practice from EPP to PD and found that "Adoption of PD as the main surgical approach is not associated with survival disadvantage in the surgical treatment of MPM".[35]

More recently oncologists Abdel-Ghani Azzouqa and James Stevenson at the Cleveland Clinic, reflecting on the "diminishing role of extrapleural pneumonectomy in the surgical management of malignant pleural mesothelioma" commented on the 2012 IASLC (International Association for the Study of Lung Cancer) analysis: "The small number of stage I patients with adequate data made it difficult to draw strong conclusions regarding the differences in survival by procedure, and the authors acknowledged the potential contribution of institutional selection bias to the results." They recognise that MARS results "have prompted debate that EPP offers no survival benefit and possibly harms patients within the multimodality treatment setting".[36]

Subsequently Yamashita and colleagues reported a single instance of what looked like a true 'cure' by EPP five years after resection of a highly atypical mesothelioma[7] but as far as the typical pattern of mesothelioma is concerned EPP can reasonably be excluded from clinical consideration in the treatment of mesothelioma. The Yamashita case report looks like the 'exception that proves the rule'.[37]

The evidence for (extended) Pleurectomy/Decortication (eP/D)

Well before MARS had reported, there was a drift away from EPP. A series of comparisons were published. Let us consider them in chronological order.

In 2008,Raja Flores seems to have anticipated the move away from EPP.[38] With Harvey Pass and colleagues, he published a large observational study pooling outcome data for 663 patients undergoing EPP or P/D from 1990 to 2006 at three US academic surgical centres. He found longer median survival for P/D vs EPP (16 vs 12 months). After controlling for gender, histology, stage, and receipt of multimodality therapy, this was statistically significant ($P<0.001$). Compared to EPP, P/D was associated with lower operative mortality (3% vs 7%) and lower distant (35% vs 66%) but not local (65% vs 33%) recurrence rates.

In 2012, Loic Lang-Lazdunski who had been a principal surgeon in the MARS trial at Guy's Hospital in London published a comparison of their prospective institutional experience with 76 patients who underwent extended P/D or EPP as part of multimodality therapy. [39] Of 22 patients who received neoadjuvant chemotherapy and subsequent EPP, 17 received adjuvant thoracic radiotherapy; 54 patients underwent extended P/D and adjuvant chemotherapy. The 30-day mortality was 4.5% for the EPP group and zero for the extended P/D group. Whilst all the extended P/D patients completed the full multimodality treatment, only 68% of the EPP group managed to do so Survival was superior in the extended P/D group with a median OS of 23 months vs 12.8 months for the EPP group. The authors concluded that extended P/D should be the standard surgical procedure for MPM patients as part of multimodality therapy.

In 2014 Christopher Cao in Sydney reported about several studies, generating a total of 632 EPP patients and 513 P/D patients. [40] Both perioperative mortality and morbidity rates were significantly higher with EPP when compared with P/D - Mortality (6.8% versus 2.9%, P=0.02); morbidity (62% versus 27.9%, P<0.0001). Median survival trends favoured P/D patients – ranging from 13 to 29 months as opposed to 12 to 22 months for EPP patients. The authors cautioned that while these results are based on non-randomized comparisons of the two procedures, the available data suggest lower rates of perioperative morbidity and mortality and similar (and possibly superior) long-term survival with P/D.

Also in 2014, Bryan Burt working with Robert Cameron in Stanford, California reported the results of the STS database.[41]. A total of 225 patients underwent P/D (n=130) or EPP (n = 95) for malignant pleural mesothelioma at 48 centres. Patients undergoing EPP tended to be younger (63.2 $\pm$ 7.8 years vs 68.3 $\pm$ 9.5 years; P <0.001) and more likely to have received preoperative chemotherapy (30.1% vs 17.8%; P = 0.036) when compared to the P/D group. Other characteristics were statistically equivalent. Major morbidity was greater after EPP, including acute respiratory distress syndrome (ARDS) (8.4% vs 0.8%; P = 0.005), reintubation (14.7% vs 2.3%; P =0 .001), unexpected reoperation (9.5% vs 1.5%; P = 0.01), and sepsis (4.2%vs 0%; P =0 .03), as was mortality (10.5% vs 3.1%;P =0.03). Multivariate analyses revealed that EPP was an independent predictor of major morbidity or mortality (odds ratio, 6.51; P = 0.001). An increased incidence of ARDS was seen in low volume centres when compared to high-volume centres that performed EPP, (0% vs 12.5%; P =0.05). They concluded that EPP is associated with greater morbidity and mortality compared with P/D when performed by participating surgeons of the Society of Thoracic Surgeons-General Thoracic Database.

In 2015, EmanuelaTaioli working with Raja Flores, who had moved since his 2008 publication to Mount Sinai, New York[42], performed a meta-analysis of a total of 1512 patients treated with P/D, and 1,391 treated with EPP. There was a significantly higher proportion of short-term deaths in the EPP group versus the P/D group (4.5% vs 1.7%; p < 0.05). While there was no statistically significant difference in 2-year mortality between the 2 groups, the significant heterogeneity in the groups was noted. They concluded that P/D is

associated with less than half the short-term mortality (perioperatively and within 30 days) than EPP and recommended that P/D should be preferred when technically feasible.

So here were five big studies. Two other studies which we will not provide in detail can be added to the list. They are not controlled and there will be differences in patient selection for EPP and P/D. There was also the problem of poor definitions of operative techniques for P/D.[43] None of them has a non-operated control group. Most surgeons would guess that in the era in question, the presumed better prognosis patients would have been offered EPP and more 'salvage' cases would be in the P/D group. The bias therefore would favour EPP and yet in each case P/D came out better. But does that mean that P/D benefits patients?

Raja Flores has persuasively promoted the cause of P/D as the better operation for patients than EPP[44-46] but we cannot escape the conclusion that it might be because it does them less harm. It is hard to avoid the suspicion that if surgery of lesser radicality is associated with better survival, this does tend to suggest that surgery is not *the* beneficial factor that those trying to tackle mesothelioma with a knife might like to think. One thing that all agree on is that EPP carries a high burden of morbidity.[15;33]

Pleurectomy decortication is being compared with no surgical resection in the MARS-2 randomised controlled trial. (https://clinicaltrials.gov/ct2/show/NCT02040272).

Should there be more emphasis on palliative surgery?

In 2013, Cao et al studied 1916 patients who underwent pleurectomy. His group collated 12 studies on extended P/D, 8 studies on P/D and 14 studies on partial pleurectomy.[47] Perioperative mortality ranged from 0% to 11% and perioperative morbidity ranged from 13% to 43%. Median overall survival ranged from 7.1 to 31.7 months and disease-free survival ranged from 6 to 16 months. They concluded that perioperative mortality outcomes between different P/D techniques were similar. The extended P/D group had a trend towards a longer hospital stay with higher morbidity, but in their favour appeared to have a better survival, both overall and disease free.

With regard to palliation of pleural effusion in MPM, Rintoul's group performed a Phase III trial of video-assisted thoracoscopic partial pleurectomy (VAT-PP) versus talc pleurodesis in 196 MPM patients with a pleural effusion (the MesoVATS trial).[48] The primary end point was overall survival at 12 months, which was 52% in the VAT-PP group and 57% in the talc pleurodesis group (P=0.81). Surgical complications (31% versus 14%) and length of hospital stay (7 versus 3 days) were significantly greater in the VAT-PP patients, whereas the rate of complete resolution of the effusion at 12 months and the quality of life measures were similar in both treatment arms. Again, in an RCT, the more radical solution did not provide benefit over a lesser surgical intervention.

The single most effective palliative intervention is to achieve pleurodesis with the purpose of allowing the patient to breathe as well as possible for as long as possible. There is ample

evidence from randomised studies to prove the effectiveness of pleurodesis.[49] Talc is the best agent but it should be of the correct (larger) particle size. To replicate the good results achieved in trials, pleurodesis should be done to surgical standards. There is an ongoing trial (MARS-2) of eP/D versus pleurodesis with patients being randomly assigned.

Conclusions:

Reviewing the literature as it stands today, we would like to suggest that extirpative of any type is lacks evidence from randomised trials. [30] EPP can probably be set aside as a useful treatment for this disease. Surgery in the form of eP/D or P/D may have a palliative role and this is under investigation in MARS-2.

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