

Fifteen years in the evaluation of extrapleural pneumonectomy: Lessons to be learned

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From 2001 to 2010, a total of 447 patients were recorded in Brigham and Women's Hospital (BWH) International Mesothelioma Program Patient Data Registry as having had extrapleural pneumonectomy (EPP). Patterns of recurrence among 169 (38%) who had undergone initial EPP are reported. The remaining 62% of patients, treated initially with chemotherapy, were excluded as "a distinct cohort with poorer prognosis." Median survival was 15 months for the EPP-first patients, and evidently shorter¹ for the remaining 62%.

A 15-YEAR ERA OF EPP EVALUATION

In 1999 there were 3 landmark publications:

- Peto and colleagues² alerted us to an epidemic of mesothelioma in Europe, and we have seen the prediction fulfilled;
- BWH reported³ 19 months median survival in 176 hospital survivors of trimodal therapy with EPP, raising hopes of survival benefit;
- Butchart,⁴ who had reported an earlier experience, proposed that EPP, within multimodality treatment, should be the subject of multicenter trials.

The subsequent 15 years saw intense activity in the treatment of mesothelioma.

Understanding Efficacy and Effectiveness

When used in evaluating treatments, efficacy and effectiveness have distinct meanings.⁵ If intensity-modulated radiotherapy resulted in no recurrence within the radiation field, or heated intra-operated chemotherapy reduced local recurrence, that would be evidence of efficacy (Figure 1). When used in combination with EPP, intensity-modulated

radiotherapy was associated with 10 months median survival (intention to treat).⁶ Heated intra-operated chemotherapy with EPP gave a median survival of 13 months, 6 months shorter than before its introduction.^{3,7} Neither demonstrated effectiveness in lengthening survival in association with EPP. But how could we determine the effectiveness of EPP itself?

Seeing the Signal Within the Noise: What Should Be the Comparator for EPP?

When a mechanistically plausible intervention visibly, quickly, and reproducibly alters the course of events, we have traditionally relied on observation alone and should continue to do so, but with an appropriate degree of caution.^{8,9} Surgeons know examples: relieving tension pneumothorax, controlling exsanguinating hemorrhage, removing a cataract.

After Butchart's report⁴ in 1976, EPP had been dismissed because of a consistent pattern of early recurrence. To be reconsidered as part of multimodal treatment, what should be the comparator? Clearly not the 7 months median survival among patients fit only for supportive care.¹ Only a small minority of patients are ever candidates for EPP,¹⁰ and to receive 1, 2, or more other treatments, patients had to have a better than average inherent prognosis, introducing immortal time bias.¹¹ Being a survivor is an essential inclusion criterion for getting multimodal treatment; when survival is the primary outcome of interest, this will confound multivariate analyses.¹²⁻¹⁴

Intention to Treat, External and Impartial Monitoring, and Independent Analysis

It is important to recognize the principle of a "fair test."¹⁵ The comparison should be made with patients who are as similar as possible, accounting for known and unknown variables, ideally a randomly assigned control group. A well conducted randomized controlled trial requires an externally peer-reviewed protocol. It should be multicenter, impartially run, scrupulously monitored, and analyzed on intention to treat, which is how the mesothelioma and radical surgery (MARS) trial was set up.^{16,17} A cohort of patients was assessed as suitable for EPP, but were randomly assigned to not have it. Their median survival was 19.5 months.^{18,19}

Patient-Reported Outcomes

Quality of life and other patient-reported outcomes are not reported in the BWH study. In Lionel Shriver's novel *So Much for That*,²⁰ the husband of a woman with peritoneal

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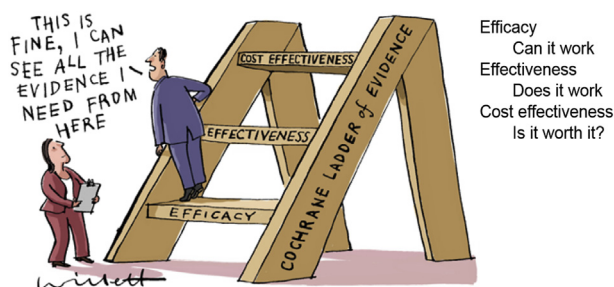


FIGURE 1. The Cochrane ladder of evidence. Reprinted with permission.⁵

mesothelioma, approaching the end of life and their \$2 million retirement fund, asks: “So what exactly did we buy? How much time?” The doctor replies: “Oh, I bet we’ve probably extended her life a good three months.” The husband returns: “No, I’m sorry Dr. Goldman. They were not a good three months.” We do not have the evidence that EPP in multimodality treatment buys time,²¹ and what time our patients do have should not be made worse by our treatments. We know that EPP is associated with a high rate of complications.²² In nonrandomized but well considered comparative studies, EPP resulted in more complications, poorer quality of life,²³ and shorter survival than lung-sparing surgery.²⁴

THE WAY AHEAD

These have been 15 years in which there have been 2 randomized trials.^{18,25} There should have been and still should be more. Otherwise, with a disease as variable as mesothelioma, with many possible but untested treatments, given in combination or in sequence, we will never see the signal for the noise. We need to distinguish between efficacy of individual elements of treatment and clinical effectiveness of treatment programs. To refine the questions and design the studies, we need independent analysis of all the data, rather than institutionally selected subsets. We need multicenter trials, impartially conducted, monitored, and analyzed.^{10,26}

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