

Extrapleural Pneumonectomy Is the Preferred Surgical Management in the Multimodality Therapy of Pleural Mesothelioma: Con Argument

Robert B. Cameron, MD

Surgery, David Geffen School of Medicine at UCLA, Room 64-128 CHS, PO BOX 957313, Los Angeles, CA 90095-7313, USA

Malignant pleural mesothelioma (MPM) is an uncommon asbestos-related cancer with few good treatment options. Due to its low incidence/prevalence, frequent delay in diagnosis, and a strikingly short survival, few patients generally have been available for clinical trials. Because of a lack of therapeutic options, MPM historically has received little attention in many comprehensive cancer centers across the U.S. and throughout the world. In treatment centers that have specific programs for mesothelioma, treatment strategies often are remarkably different and based on considerable treatment biases.

Recently, one of the surgical strategies that some centers have adopted is that of extrapleural pneumonectomy (EPP). Although the use of EPP in this disease has been enthusiastically embraced at a number of centers, its superiority over a meticulous and complete radical pleurectomy and decortication (P/D) and even over non-operative treatment essentially remains unproven. In order to optimally and scientifically assess the place of EPP in the treatment armamentarium of MPM, this paper will review the theoretical and reported advantages of EPP compared to a lung-sparing approach such as P/D.

THEORETICAL CONSIDERATIONS

The following issues have been identified in the treatment of MPM with radical EPP.

Extent of Resection (R0 versus R1 versus R2)

The principle surgical problem in MPM is that the disease, by definition, is *diffuse*. Therefore, radical surgical strategies that are normally utilized for neoplasms manifesting as dominant tumor “masses,” do not apply to the diffuse “sheets” of malignant cells in MPM which literally abut/invade every surface in the hemithorax. Resection of a solitary malignant nodule (e.g., lung cancer, soft tissue sarcoma, etc.) can be performed with wide/radical margins following well-established surgical oncology principles (R0 resection; see Table 1), but an R0 resection cannot be accomplished in mesothelioma without completely removing all structures that are in contact with the pleura (see Table 2), a procedure which obviously is not practical. Clearly, the best resection that can be obtained with MPM, regardless of the procedure type (EPP or P/D), is an R1 resection. When one accepts this incontrovertible fact and acknowledges that in surgical oncology, outcomes are determined by the *closest*, not the most radical, margins, then one realizes that pursuing *locally* radical resections margins (i.e., pneumonectomy to establish a radical *lung* margin) in EPP while accepting minimal or no margins in other areas does nothing to change the overall R1 resection status of the operation and in no way achieves a *better* R1 resection than in P/D. Therefore, if the same meticulous surgical technique is used in all areas in both EPP and P/D, the best overall margins attainable are no different and are those of a R1 resection.

Radical Resection

When faced with a difficult problem, most surgeons (and physicians, in general) respond with a natural

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Address correspondence and reprint requests to: Robert B. Cameron, MD; E-mail: rcameron@mednet.ucla.edu

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TABLE 1. *Surgical resection classifications*

R0	No residual tumor; macroscopically complete removal by non-contaminated operation with wide or radical margins
R1	Microscopic residual tumor; macroscopically complete removal of gross disease but resection margin contains microscopically evidence of disease or disease-free margin is less than 1 cm (fixed) or 2 cm (vital)
R2	Macroscopic residual tumor
RX	Presence of residual tumor cannot be assessed

TABLE 2. *Tissues required to be removed in R0 resection of mesothelioma*

Ribs and intercostals muscle (all 12 on ipsilateral side)
Pleura ^a
Lung (intra-pericardial pneumonectomy) ^a
Trachea
Pericardium ^a
Diaphragm (complete) ^a
Esophagus
Superior vena cava (right side); aorta (left side)
Subclavian artery and vein
Nerves (phrenic, vagus, T1 nerve root, and sympathetic chain)
Vertebral bodies

^a Tissues currently removed with extrapleural pneumonectomy.

visceral desire to do “*everything*.” After all, surgeons can, and often do, conquer diseases with big operations; however, radical surgery in mesothelioma actually may be harmful. Mesothelioma is a soft tissue tumor, exhibiting many of the characteristics of soft tissue sarcomas. For instance, needle and surgical biopsies in both tumors frequently produce tumor wound seeding. Furthermore, surgery performed through the pseudo-capsule of a sarcoma (extrapleural plane of a mesothelioma) is incomplete and characterized by a high local recurrence rate. In these tumors in particular, the entire surgical wound is felt to be contaminated and at high risk for tumor dissemination. For this reason, it is generally logical and prudent to *limit* the surgical wound as much as possible. Yet in EPP, the wound is *extended* into the pericardium and into or at least adjacent to the peritoneum (and even the contralateral pleura) by full thickness resection of the pericardium and diaphragm. This may provide the surgeon with an initial sense that we “got it all,” but extension of the surgical field into adjacent body cavities may, simultaneously, contaminate a larger area not previously involved with the tumor and possibly adversely affect tumor control.

Radiation Therapy

Part of the rationale for the use of EPP is to provide a clear field for postoperative, adjuvant, high-dose radiotherapy (or possibly intensity modulated radiation therapy/IMRT) to improve local control.

However, areas of most concern (lower mediastinum and diaphragm) still have adjacent organs, such as liver (right), stomach (left), and heart (both), with potential for significant dose-limiting toxicity, even with IMRT. Furthermore, with radical resection of the diaphragm and pericardium, the true contaminated field, including the entire pericardial sac/heart and peritoneum, becomes prohibitive large for adequate coverage, even with the lung removed. Finally, detailed, computer-assisted techniques have been developed at a number of centers to deliver moderate doses of radiotherapy even with the lung in place. Thus, surgical resection of the lung for this reason theoretically is unjustified.

Disease Models

Disease models can be used to help predict successful therapies; however, there is no single disease that presents the same problems that occurs in mesothelioma. Lung cancer as a model was used in the IMIG staging system but the inadequacies of that staging system prove that it is a poor model for mesothelioma. Ovarian cancer is a more appropriate model since it generally is limited to spread within a body cavity with metastases to solid organs occurring late in the disease. In addition, this is the only cancer that benefits from “debulking” surgery, which is closer to P/D than to EPP and would suggest, at least theoretically, that EPP is not necessary.

History of Radical Surgery

It is clear that if nothing else, one should learn from history and not make the same mistakes. The history of radical surgical procedures is littered with abandoned operations (see Table 3). When surgeons learn more about the biology of the disease and develop rational rather than radical (visceral) strategies, almost all radical cancer operations have been abandoned in favor of more conservative approaches. While not precisely scientific, the history of radical surgery for cancer certainly does not favor long-term use of EPP.

TABLE 3. History of radical surgical procedures for cancer

Cancer	Radical procedure	Modern procedure
Lung	Pneumonectomy	Lobectomy/segmentectomy
Colon	Turnbull "no touch" colectomy	Standard colectomy
Breast	Halstead radical mastectomy	Lumpectomy
Sarcoma	Limb amputation	Limb-sparing resection
Mesothelioma	Extrapleural pneumonectomy	Pleurectomy and decortication

MEDICAL LITERATURE

The medical literature is strewn with a myriad of unsatisfying reports regarding the treatment of MPM. Many of the publications are case reports or small series. A few are larger series, most of which are retrospective. There are only a few prospective and even fewer randomized controlled clinical trials, none of which adequately addresses the issue of radical surgery. Recently, the literature was reviewed by the Cancer Care Ontario Program in Evidence-Based Care Lung Cancer Disease Site Group and by an International Consensus Panel of the IASLC, both concluding that there is (1) a tremendous paucity of useful information and (2) no convincing evidence to support the use of EPP (and surgery in general) in MPM, except possibly for in the palliation of pleural effusions.^{1,2} Instead of providing another comprehensive review of the literature on this topic, I will refer the reader to these reports and focus instead on the following key issues in an effort to more clearly reinforce the conclusions of the prior reviews.

Patient Selection

Clearly, patient selection introduces a strong bias toward favorable outcomes with EPP. Most series of EPP include only patients *without* significant comorbidity and with adequate functional lung reserve.^{3,4} Generally, younger healthier patients (mean age often < 60 years) are chosen for EPP, while older and more compromised patients (mean age often 60–70+ years) undergo P/D.^{3,5}

Operative Procedure

While the extent of an EPP described in most studies is relatively uniform (removing the parietal and mediastinal pleura, diaphragm, pericardium, and lung), the procedure of P/D is much more variable. Some surgeons utilize P/D in "early" disease with minimal visceral pleural findings, essentially leaving the visceral pleura intact.^{6,7} At UCLA, we discovered

that pathological examination of even normal appearing visceral pleural surfaces demonstrates complete tumor replacement with no remaining normal pleura requiring that a complete visceral pleurectomy be performed in order to avoid leaving gross residual tumor (R2 resection). Other surgeons utilize P/D as a palliative procedure in late stage disease when EPP cannot be performed, knowingly leaving behind gross tumor in the majority if not all cases.^{8–10} Neither of these uses of P/D attempts to achieve the same radical R1 resection that EPP does but instead are R2 resections. At UCLA we realized this and developed a straight-forward method of removing the entire visceral pleura and tumor completely almost regardless of the extent of disease and including complete removal from the pulmonary fissures, thereby equaling the R1 resection accomplished by EPP and overcoming a glaring shortcoming of P/D. Furthermore, because of the theoretical concerns of tumor spread as discussed above, we also uniquely limit our resection to the pleura itself and in the majority of cases can spare the pericardium and most of the diaphragm.

Adjuvant Therapy

Nearly all centers reporting EPP data also include intensive adjuvant therapies, including radiotherapy and frequently chemotherapy.^{4,11} Often patients who undergo P/D do not receive such aggressive therapies since P/D is viewed as only "palliative" therapy. This potentially further skews the results of the surgical procedures in favor of EPP. This is particularly true of radiotherapy as shown by Boutin et al.¹² who reported that moderate dose radiotherapy, e.g., using 21 Gy delivered in 3 days, reduced microscopic disease recurrence in procedure wounds from 40 to 0%. There is also the erroneous concept that postoperative adjuvant radiotherapy cannot be done following P/D. At UCLA, we have certainly not found this to be the case as long as the radiation is directed at a center knowledgeable in the treatment of mesothelioma.

Recurrence

One of the indications of success for EPP is that local recurrence rates are decreased with EPP with patients recurring more often with “distant” metastases. Yet, examining this claim one quickly detects the inconsistency of this finding. With resection of the diaphragm and pericardium, the pericardium and the peritoneum, in particular, become areas of *local* marginal failure not metastatic disease. Similarly, the contra-lateral pleura is at risk for local extension through the mediastinum and can also be a site of new primary disease due to a generalized field defect associated with asbestos exposure. When viewed in this light, 35 of 55 sites of metastatic disease reported by Rusch et al.⁴ would be reclassified as local recurrences and would indicate that local control is still poor even with EPP. Moreover, following a pneumonectomy, the generalized intra-thoracic tissue thickening that occurs can hide what would be obvious pleural tumor recurrence in a patient who underwent P/D due to an absent clear air-tissue interface, thereby further skewing the ratio of local to distant recurrences in EPP.

Survival

In reviewing the medical literature on surgery for mesothelioma, it becomes quickly apparent that there is no obvious survival advantage for one procedure over another, including EPP. In a variety of series an overall median survival of 17–22 months is noted, independent of the type of surgery.¹ This is despite a higher perioperative mortality rate for EPP (5.9–14% vs. 0–5.4% for P/D¹). In addition, there are reports of non-operative therapies, such as intra-pleural interleukin-2, showing a nearly identical median survival of 18 months¹³ versus 17–19 for both EPP and P/D.^{4,11,14} Creative patient selection in some series results in median survivals of over 50 months; however this clearly is achieved by manipulation of the patient cohort rather than any real improvement in therapy. This was recognized by the Consensus Panel in their statement: “lack of appropriately designed prospective trials means that it is difficult to be certain how much patient selection contributes to the results seen.”²

Benefits of EPP

There are several real *physician* benefits of EPP, including shorter operative time (due to the extensive decortication necessary with P/D), better reimburse-

ments (\$1,389–\$1,848 for EPP versus \$1,207–\$1,703 for P/D), and easier radiation therapy planning; however, currently there are no proven *patient* benefits.

CONCLUSIONS

Based on the above theoretical considerations and medical literature, there is no support for the use of EPP over organ (lung)-sparing P/D. In 2006, the only acceptable surgical approach, if any, is that of P/D, although surgery of any kind remains controversial. Both EPP and P/D should not be performed outside of experienced centers and preferably only as part of prospective randomized clinical trials. As has happened with numerous other diseases in the past, surgeons need to put down their knives and approach mesothelioma on a rational and scientific level rather than on a radical and visceral one. EPP should not become the (Sir Edmund) Hillary operation of thoracic surgery: being done simply because it is there and it *can* be done.

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