Radical Pleurectomy and Intraoperative Photodynamic Therapy for Malignant Pleural Mesothelioma

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Background. **Radical pleurectomy (RP) for mesothelioma is often considered either technically unfeasible or an operation limited to patients who would not tolerate a pneumonectomy. The purpose of this study was to review our experience using RP and intraoperative photodynamic therapy (PDT) for mesothelioma.**

Methods. **Thirty-eight patients (42–81 years) underwent RP-PDT. Thirty five of 38 (92%) patients also received systemic therapy. Standard statistical techniques were used for analysis.**

Results. **Thirty seven of 38 (97%) patients had stage III/IV cancer (according to the American Joint Committee on Cancer [AJCC manual 7th Edition, 2010]) and 7/38 (18%) patients had nonepithelial subtypes. Macroscopic complete resection was achieved in 37/38 (97%) patients. There was 1 postoperative mortality (stroke). At a median follow-up of 34.4 months, the median survival was 31.7 months for all 38 patients, 41.2 months for the 31/38 (82%) patients with epithelial subtypes, and 6.8 months for the 7/38 (18%) patients with nonepithelial subtypes. Median progression-free survival (PFS) was 9.6, 15.1, and 4.8 months, respectively. The median survival and PFS for the 20/31 (64%) patients with N2 epithelial disease were 31.7 and 15.1 months, respectively.**

Conclusions. **It was possible to achieve a macroscopic complete resection using lung-sparing surgery in 97% of these patients with stage III/IV disease. The survival we observed with this approach was unusually long for the patients with the epithelial subtype but, interestingly, the PFS was not. The reason for this prolonged survival despite recurrence is not clear but is potentially related to preservation of the lung or some PDT-induced effect, or both. We conclude that the results of this lung-sparing approach are safe, encouraging, and warrant further investigation.**

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Malignant pleural mesothelioma remains an incurable cancer for which all treatments are palliative. Although the role of surgical procedures for mesothelioma remains investigational, the evidence is compelling that surgery-based multimodal treatments are the ones most likely to have the greatest impact on the course of the disease [1].

The goal of an operation in treating mesothelioma is to remove all gross disease, achieving a macroscopic complete resection (MCR). Other modalities are used to treat the residual microscopic disease that is always present. There are two surgical approaches, extrapleural pneumonectomy (EPP) and lung-sparing procedures. A lung-sparing operation results in more debrided surface area and, hence, almost certainly results in more residual microscopic disease.

EPP is defined by a standardized technique and nomenclature, whereas lung-sparing operations enjoy neither. Reported goals of lung-sparing operations range from a palliative debulking to an attempted MCR [2]. Some surgeons reserve lung-sparing procedures for patients who would not tolerate pneumonectomy. Some decide preoperatively, whereas some decide intraoperatively based primarily on the degree of invasion into the pulmonary fissures. There is even variability in the nomenclature used to describe lung-sparing operations: pleurectomy, palliative pleurectomy, radical pleurectomy, or pleurectomy/decortication.

In this study, all patients underwent lung-sparing procedures. This was a preoperative decision for every patient, even with evidence of extensive involvement of the fissures, bulky tumors, and patients who could tolerate pneumonectomy. The goal of every operation was to achieve MCR. Each operation included sparing of the lung and as much of the surrounding normal structures

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Abbreviations and Acronyms

EPP = extrapleural pneumonectomy
MCR = macroscopic complete resection
MPM = malignant pleural mesothelioma
PDT = photodynamic therapy
PFS = progression-free survival
RP = radical pleurectomy

as possible. Thus every effort was made to preserve the phrenic nerve and as much of the diaphragm and pericardium as possible, without leaving behind any visible or palpable cancer. When necessary, because of extensive full-thickness invasion, prosthetic reconstruction of the diaphragm, chest wall, or pericardium was performed. The term we use to define this procedure is *radical pleurectomy* (RP).

As part of a multimodal approach, our group has used photodynamic therapy (PDT), a light-based cancer treatment, as an intraoperative adjuvant. In PDT, a patient receives a nontoxic photosensitizing agent that is activated with visible laser light, triggering a variety of tumoricidal cascades. The currently known mechanisms of PDT include direct cell kill, destruction of tumor neovasculature, and provocation of a tumor-directed immune response [3]. Because the activating energy for PDT is visible light, and because visible light penetrates several millimeters into tissue, PDT will treat for a short depth below the surface.

Inspired by the intuitive appeal of lung-sparing operations, with respect to safety and quality of life, we conducted a small pilot study comparing two similar cohorts of patients with mesothelioma [4]. Half of the patients underwent EPP-PDT and half underwent RP-PDT. Our hypothesis was that PDT would be effective at controlling the increased residual microscopic disease in the group who underwent RP. As with the current study the decision to perform RP in the pilot study was a preoperative decision for every patient, regardless of tumor bulk or cardiopulmonary reserve. It was a small retrospective study with only 14 patients in each arm and, arguably, valid only for establishing trends rather than definitive conclusions. That said, we observed a significant difference in survival for the two groups. The median survival for the EPP group was 8.4 months, with the RP group not reaching median survival at a follow-up of 2.1 years. There was a higher percentage of patients with nonepithelial subtypes in the EPP group, but overall both groups were quite similar, with 86% AJCC stage III/IV disease. Stage adjusted, the survival for the EPP group was similar to that typically reported and the RP group survival was longer than that typically reported [2]. Interestingly, local control was far superior in the EPP group—the group with the shorter survival.

Our hypothesis was that despite poorer local control, there appeared to be a benefit to RP-PDT, at least with that specific photosensitizer. Expanding the RP cohort with another 24 consecutive patients to confirm or refute this hypothesis was the purpose of this study.

Patients and Methods

This study represents a retrospective review performed with the approval of the University of Pennsylvania Institutional Review Board under a protocol entitled "Treatment Parameters and Outcomes in Pleural Photodynamic Therapy (PDT)."

Patient Characteristics and Workup

From 2005 to 2010, 38 patients underwent radical pleurectomy and PDT for mesothelioma (median age 65 years, range 42–81 years; 28 men/10 women). The first 14 patients in this series are from a previous pilot study comparing lung-sparing to lung-sacrificing operations [4]. All 24 of the subsequent patients were consecutive. A multidisciplinary team evaluated all patients before enrollment.

Twenty-eight patients were treatment naive and went directly to RP-PDT, with the intention of following with four cycles of pemetrexed-based chemotherapy. Ten patients were referred after chemotherapy, primarily for progression, and underwent RP-PDT with individualized adjuvant treatment recommendations. Patient characteristics are summarized in Table 1.

The radiographic staging workup included positron emission tomography, computed tomography (CT) of the chest/abdomen, and brain imaging. Thirty-six patients underwent invasive staging with a bronchoscopy and laparoscopy ± contralateral thoracoscopy. All patients without a fused abdomen were taken to the operating room for an outpatient laparoscopy with peritoneal lavage to exclude radiographically occult peritoneal disease. Contralateral thoracoscopy was used only when there was concern for contralateral cancer. Mediastinoscopy was not performed because mediastinal metastases was not an exclusion criterion and had not proved significant in our pilot study. Enrollment was broad, including multiple patients with obvious nodal metastases, chest wall/rib invasion, or massive tumor bulk. In addition 2 patients with cancer detected on the invasive staging workup (one contralateral pleural/one abdominal) were enrolled after chemotherapy and repeated workup revealed no detectable extrahemithoracic disease.

Surgical Procedure

The operative technique was consistent by virtue of the same surgeon (JSF) performing all operations. The operative plan was established preoperatively and was to achieve MCR while preserving the lung, phrenic nerve, and as much of the diaphragm and pericardium as possible. A detailed and illustrated description of this technique can be found elsewhere [5], but the essential elements are as follows.

APPROACH. Because all patients were light sensitive, light precautions were taken throughout the operation. Patients were positioned in the lateral decubitus position and the chest was typically entered through a serratus-sparing thoracotomy through either the sixth interspace