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Extrapleural Pneumonectomy in the Multimodality Therapy of Malignant Pleural Mesothelioma

Results in 120 Consecutive Patients

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Objective
The authors examine the feasibility and efficacy of trimodality therapy in the treatment of malignant pleural mesothelioma and identify prognostic factors.

Background
Mesothelioma is a rare, uniformly fatal disease that has increased in incidence in recent decades. Single and bimodality therapies do not improve survival.

Methods
From 1980 to 1995, 120 patients underwent treatment for pathologically confirmed malignant mesothelioma at Brigham and Women's Hospital and Dana-Farber Cancer Institute (Boston, MA). Initial patient evaluation was performed by a multimodality team. Patients meeting selection criteria and with resectable disease identified by computed tomography scan or magnetic resonance imaging underwent extrapleural pneumonectomy followed by combination chemotherapy and radiotherapy.

Results
The cohort included 27 women and 93 men with a mean age of 56 years. Operative mortality rate was 5.0%, with a major morbidity rate of 22%. Overall survival rates were 45% at 2 years and 22% at 5 years. Two and 5-year survival rates were 65% and 27%, respectively, for patients with epithelial cell type, and 20% and 0%, respectively, for patients with sarcomatous or mixed histology tumors. Nodal involvement was a significant negative prognostic factor. Patients who were node negative with epithelial histology had 2- and 5-year survival rates of 74% and 39%, respectively. Involvement of margins at time of resection did not affect survival, except in the case of full-thickness, transdiaphragmatic invasion. Classification on the basis of a revised staging system stratified median survivals, which were 22, 17, and 11 months for stages I, II, and III, respectively ($p = 0.04$).

Conclusions
Extrapleural pneumonectomy with adjuvant therapy is appropriate treatment for selected patients with malignant mesothelioma selected using a revised staging system.

Approximately 2200 to 3000 new cases of malignant pleural mesothelioma will be diagnosed this year in the United States.[1-3] The etiology of this disease has been linked to asbestos exposure.[4] Geographic clustering of cases is observed in regions where industrial asbestos use was common in the United States between 1940 and 1970.[2] The incidence of this disease has been increasing steadily, and increased 50% during the 1980s.[1] Because of a long exposure-to-diagnosis interval, this trend is expected to continue until the next century, when the effects of industrial regulation of asbestos are manifest.

Diffuse malignant pleural mesothelioma is associated with a median survival of 4 to 12 months in untreated patients.[5-8] Three pathologic subtypes of malignant mesothelioma are recognized: epithelial, sarcomatoid, and mixed histology. Epithelial subtype tumors have been associated with better prognosis.[9,10] The clinical course is marked by relentless local growth of the tumor, with patients' deaths most commonly due to cardiac or pulmonary involvement. Approximately 10% of patients will die from complications of myocardial invasion. Approximately 33% of patients experience bowel obstruction secondary to transdiaphragmatic invasion into the peritoneum.[11]

Single modality therapy generally has been ineffective in treating this disease. Surgical resection using pleurectomy[12] or extrapleural pneumonectomy[13] has failed to demonstrate improved survival. Recent reports have noted reduced operative mortality of extrapleural pneumonectomy in modest series.[12,14,15] Although some tumors responded to single agent or combination chemotherapy,[16] no chemotherapeutic regimen has significantly affected outcome. Radiotherapy alone confers moderate palliative benefit at best.[17-20]

The failure of single modality therapy in treatment of this disease led investigators to consider cytoreductive pleurectomy followed by adjuvant chemotherapy and radiation. This less aggressive surgical approach substantially reduces treatment-associated mortality, with survival up to 17 months in one series.[21] The trimodality approach reported herein is based on the reasoning that if extrapleural pneumonectomy could be performed in selected patients with acceptable morbidity and mortality, a complete or near-complete resection might contribute to prolonged survival in this primarily locally recurring disease. Furthermore, the risk of radiation pneumonitis associated with high-dose radiotherapy can be avoided if radiation is given after extrapleural pneumonectomy.

We previously have reported on the efficacy of trimodality therapy, including extrapleural pneumonectomy, and proposed a revised staging system.[15] The purpose of this current study was to assess the efficacy of this treatment in a large patient cohort and to test the validity of the staging system previously published.

METHODS

We reviewed 120 consecutive patients with diffuse malignant pleural mesothelioma treated at the Brigham and Women's Hospital (BWH), the Dana-Farber Cancer Institute, and the Joint Center for Radiation Therapy (Boston, MA). The treatment plan consisted of extrapleural pneumonectomy followed by chemotherapy and subsequent radiotherapy. Long-term survival data were obtained by reviewing both hospital and office charts and by contact with patients and their physicians.

Patients with suspected malignant pleural mesothelioma were evaluated by a multimodality team consisting of a thoracic surgeon, medical oncologist, and radiation oncologist. Those who did not have a definitive diagnosis underwent pleuroscopy and pleural biopsy to obtain enough tissue for confirmation. If a pleural biopsy was obtained at an outside institution, the slides were reviewed by the Brigham and Women's Hospital pathology mesothelioma reference panel. Patients without medical contraindications who were clinical Butchart stage I[22] and believed to be completely resectable on the basis of computed tomography scanning or magnetic resonance imaging (after 1988) received trimodality therapy consisting of extrapleural pneumonectomy, CAP chemotherapy (cyclophosphamide, doxorubicin, and cisplatin), and radiotherapy to the ipsilateral empty hemithorax.

Patients were considered for trimodality therapy if they had good performance status with normal renal and hepatic function. Physiologic criteria for exclusion were compromised cardiac function, as evidenced by an ejection fraction of less than 45% by echocardiography; a preoperative partial pressure of carbon dioxide greater than 45 mmHg; a room air oxygen partial pressure less than 65 mmHg; or a predicted postoperative forced expiratory volume in 1 second (FEV_1) of less than 1 L. Patients with marginal FEV_1 underwent ventilation/perfusion scanning to accurately predict postoperative pulmonary function. Patients remained surgical candidates as long as there was no detectable mediastinal or transdiaphragmatic invasion detected on magnetic resonance imaging.

Surgical resection included *en bloc* removal of the lung, parietal pleura, ipsilateral pericardium, and ipsilat-

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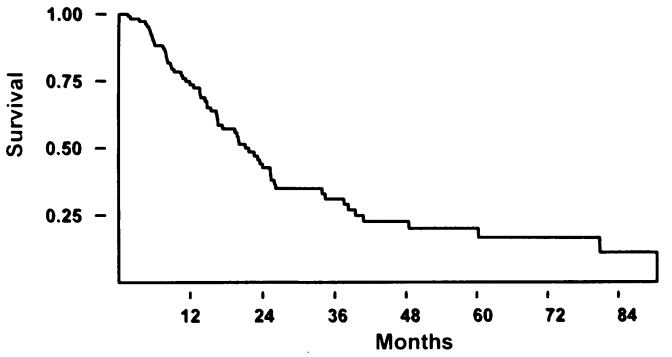

Figure 1. Kaplan-Meier survival curve for all patients surviving surgery (N = 114). Median survival = 21 months.

eral diaphragm. Careful attention was taken to ensure that previous biopsy sites or thoracoscopy ports were resected. The technical details of extrapleural pneumonectomy have been described previously.[23] In all cases, perioperative intravenous antibiotics and standardized postoperative care specific to extrapleural pneumonectomy patients were used. Postoperative complications were judged by standard criteria.[24]

Chemotherapy typically was initiated 4 to 6 weeks after surgery. Patients who were treated before 1985 (n = 9) received doxorubicin 50 to 60 mg/m^2 and cyclophosphamide 600 mg/m^2 for 4 to 6 cycles. Patients treated after 1985 had cisplatin added to the regimen at a dose of 70 mg/m^2.

After chemotherapy, external beam radiotherapy was delivered using linear accelerators ranging in energy from 4 MV to 10 MV. The first course treatment field included the entire ipsilateral hemithorax and mediastinum to a dose of approximately 30 Gy, followed by a boost dose to localized regions of previous bulk disease, when possible. The total dose to the boost volume was 50 to 55 Gy.

Statistical treatment included standard life-table analysis and assessment of possible prognostic factors. These factors included residual disease after resection (gross residual disease, histologic evidence of disease at resection margins, or histologically clear margins), epithelial *versus* sarcomatous or mixed cell type, and the presence of metastatic disease in regional mediastinal lymph nodes. Age, gender, asbestos exposure, smoking history, length of operation, side of tumor, and involvement of pericardium or diaphragm also were evaluated. Survival intervals were calculated from the time of resection to the time of last follow-up. Survival rates were compared using log-rank tests as well as uni- and multivariate regression analyses (Cox proportional hazards model).[25,26]

RESULTS

This analysis includes 120 consecutive patients undergoing extrapleural pneumonectomy at Brigham and Women's Hospital from 1980 to 1995 in this trimodality protocol. The median follow-up interval is 15 months (range, 2–91 months) and follow-up is complete through February 1996. The median age was 56 years (range, 31–74 years).The median time between onset of symptoms and diagnosis was 2 months (range 0.5–27 months). Sixty-seven percent (80 patients) had a smoking history and 78% (94 patients) had known asbestos exposure. Fifty-one percent (61 patients) had chest pain, and 73% (88 patients) reported a history of dyspnea.

The median postoperative length of stay was 9 days (range, 5–101 days). The morbidity rate was 22%, with 15 patients having major complications (12.5%), including intrathoracic hemorrhage (4), respiratory failure (4), pneumonia (5), disrupted diaphragmatic patch (1), perforated duodenal ulcer (2), empyema (1), upper gastrointestinal bleed (1), and deep venous thrombosis (3). There were six perioperative (30-day) deaths (5.0%). Two patients died of myocardial infarction, two of pulmonary embolus, one of respiratory failure, and one of cardiac herniation through the pericardial defect.

The overall median survival was 21 (1–96 months) months, with 2- and 5-year survival rates of 45% and 22%, respectively (Fig. 1). Clinical symptoms and computed tomography scan results were difficult to assess for the diagnosis of early recurrence, making the disease-free interval difficult to measure. The longest survival duration without known recurrence was 45 months. One patient survived 8 years and presented with scrotal and peritoneal recurrence.

In a multivariate Cox proportional hazards model, epithelial cell type (Fig. 2) and lack of hilar, mediastinal, or pulmonary node involvement (Fig. 3) were significant prognostic factors associated with prolonged survival. The 67 tumors (59%) of epithelial cell type were associated with 2- and 5-year survival rates of 65% and 27%, respectively. By contrast, the survival rate for the 47 patients with tumors of sarcomatous or mixed (n = 47) his-

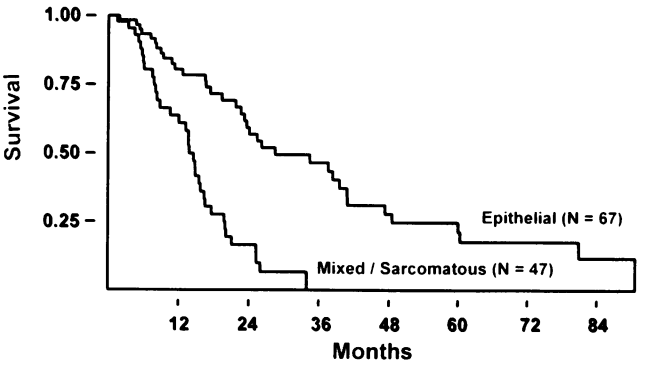

Figure 2. Kaplan-Meier survival curve for all patients with epithelial tumors *vs.* those with nonepithelial (sarcomatous or mixed) tumors. Patients with epithelial tumors had a longer survival (p = 0.0001)

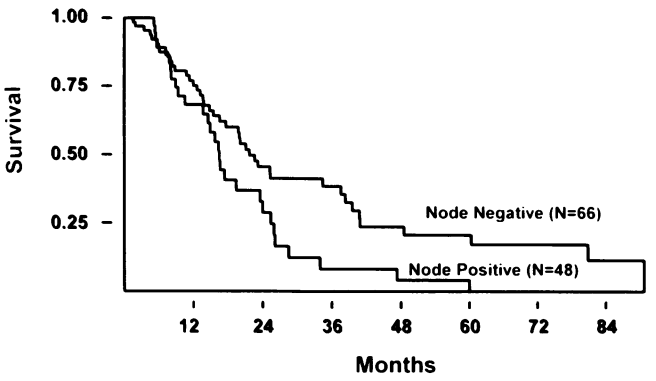

Figure 3. Kaplan-Meier survival curve for all patients with node-negative *vs.* node-positive pathologic specimens. Node-negative patients had a longer survival (p = 0.02)

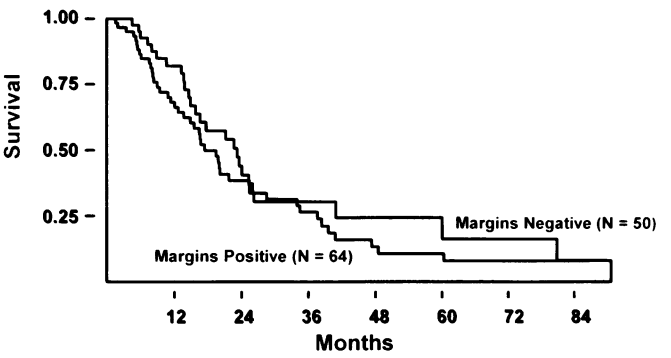

Figure 5. Kaplan-Meier survival curve for all patients with positive *vs.* negative surgical resection margins. Survival did not depend on margin status (p = not significant).

tology was 20% at 2 years with no 5-year survivors (p = 0.0001; Fig. 2). Similarly, the 66 patients with negative lymph nodes on pathologic examination had 2- and 5-year survival rates of 50% and 25%, respectively, whereas 48 patients with nodal involvement had a 2-year survival of 35% with no 5-year survivors (p = 0.02; Fig. 3). Node status also predicted survival within the epithelial cell type subgroup of patients (Fig. 4). Of the 67 patients with epithelial tumors, the 39 with negative nodes had a significantly better survival rate (74% 2-year; 39% 5-year) than the 28 patients with positive nodes (52% 2-year; 10% 5-year; p = 0.002).

Gross residual tumor, microscopically positive margins (Fig. 5), and tumor involving either pericardium or diaphragm (but not penetrating the full thickness) did not significantly affect survival. Microscopic transdiaphragmatic invasion, noted in a subgroup of 14 patients, was a significant negative prognostic factor (median survival 11 months) independent of cell type or node status. Age, gender, cigarette smoking, asbestos exposure, length of operation, and side of tumor were not significantly associated with the duration of survival.

We previously published a staging system based on an earlier analysis of a subset (N = 52) of the current cohort.[15] When classified according to this system, survival in the current cohort (N = 120) is stratified significantly by stage (Fig. 6). Median survival for stage I patients (n = 57) was 22 months, compared with 17 months for stage II patients (n = 43) and 11 months for stage III patients (n = 14; p = 0.04).

DISCUSSION

The results of the current study demonstrate that in a large series of highly selected patients, extrapleural pneumonectomy in the trimodality therapy of malignant pleural mesothelioma represents safe and effective treatment. It is associated with an overall median survival (21 months; Fig. 1) that is superior to reported results of single modality therapy. Furthermore, nodal status, cell type, and transdiaphragmatic invasion are prognostic factors capable of stratifying the survival of patients treated with trimodality therapy. These results would

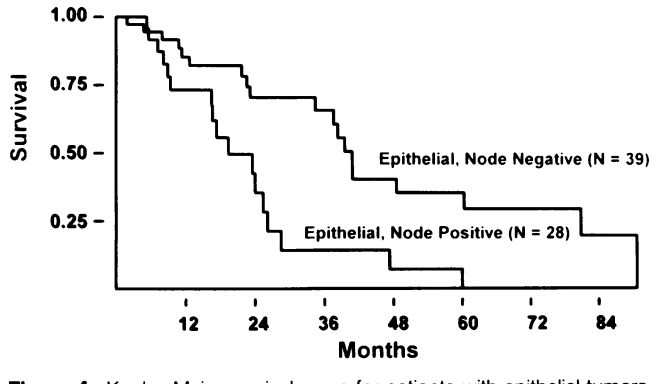

Figure 4. Kaplan-Meier survival curve for patients with epithelial tumors with node-negative *vs.* node-positive pathologic specimens. Patients with negative nodes had a longer survival (p = 0.002).

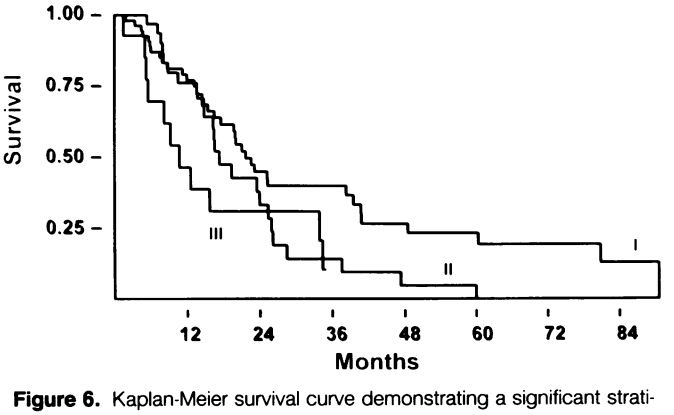

Figure 6. Kaplan-Meier survival curve demonstrating a significant stratification of survival when all patients are classified as stage I, II, or III according to our previously proposed staging system.[15]

suggest that selected patients with malignant pleural mesothelioma should be considered for aggressive management. Furthermore, these results validate a previously published staging system[15] that is based on resectability and node status. This clinically useful staging system may form the basis for new diagnostic and therapeutic approaches to this disease.

Historically, surgical resection alone was used initially as the sole treatment of mesothelioma, with disappointing results. Neither pleurectomy[12,27-29] nor extrapleural pneumonectomy[13,14,22] increased median survival, and operative mortalities with extrapleural pneumonectomy ranged as high as 31%.[22] Most patients who underwent surgical resection died of recurrent disease in the ipsilateral chest, with subsequent invasion of the mediastinum or peritoneum.

The role of chemotherapy alone in the treatment of malignant mesothelioma remains uncertain. Because many patients have mass lesions that are obscured by large pleural effusions and therefore do not have truly measurable disease, it often is difficult to determine response rates to chemotherapy. Chemotherapy in patients with measurable disease has resulted in approximately 20% response rates, although an increase in survival has not been demonstrated. Median survival intervals from 4 to 12 months have been reported in a number of series using single-agent chemotherapy (*e.g.* adriamycin,[30] cyclophosphamide,[31] cisplatin,[32] doxorubicin,[30,31] and mitomycin-C[33]).[16] Although doxorubicin–cyclophosphamide and doxorubicin–cisplatin combinations have been shown to have some activity against the disease, the results have not been found to be superior to single-agent therapy.[4] In patients with measurable disease, the response rate to combination regimens is approximately 26%.[4,34]

Radiation therapy as a single treatment modality also has been used without favorable results. Some studies have indicated that well-planned, high-dose radiotherapy produces response in some cases, but does not significantly alter median survival.[17] Radiation-induced injury to underlying pulmonary parenchyma has been a major cause of morbidity in patients treated with radiotherapy alone.

In other malignancies, response rates to chemotherapy escalate as tumor burden and stage are reduced.[35] Furthermore, chemotherapy alone or in combination with radiation has been shown to improve local control in esophageal cancer[36] and lung cancer.[37] Platinum-based chemotherapy has been shown to be most effective in epithelial malignancies, which may account partially for the survival advantage enjoyed by the epithelial histology subgroup. Future trials may entail therapeutic regimens tailored to sarcomatous *versus* epithelial histology.

With regard to prognostic indicators, the current results confirm our previous findings in a subset (N = 52) of the same cohort of patients.[15] Epithelial histology and negative node status both predicted significantly improved survival and were additive prognostic factors. Forty-two patients with epithelial tumors and negative nodes enjoyed a 39% 5-year survival. Given that mesothelioma primarily is a locally recurring malignancy, it is somewhat counterintuitive that resection margins positive for tumor do not predict poor outcome. One explanation for this finding is that the delivery of chemotherapy and radiation therapy to microscopic-positive margins contributed to improved local control, and thus, survival.

Several staging systems have been proposed for malignant pleural mesothelioma. However, they are of limited utility because previous treatment strategies have failed to result in stratification of survival. The usefulness of any staging system depends on its ability to stratify survival, to define the success of standard treatment, and to direct therapy. Given the recalcitrant nature of this disease to all standard modes of therapy, it is easy to understand how the development and validation of an accurate and predictive staging system has not been possible.

The most commonly used staging system was proposed by Butchart in 1976.[22] Based on the management of 29 patients treated with pleural pneumonectomy, this staging system divides patients into four groups. Included in stage I are those patients with disease confined to the capsule of the pleural envelope, lung, pericardium, and diaphragm. Stage II patients are those with tumors invading chest wall or mediastinal structures, namely the esophagus, heart, or contralateral pleura, with or without involvement of lymph nodes within the chest. Stage III patients are those with disease extending through the diaphragm into the peritoneum with lymph nodes positive outside the thoracic cavity. Stage IV patients are rare and are those with bloodborne metastases. Unfortunately, this system suffers from the inability to reliably distinguish the survival probability by stage.

An empiric staging system also has been proposed based on the international TNM staging variables.[38] This proposal has not been correlated to patient survival.[38] The tendency for tumors to extend far beyond their clinical stage makes preresectional T staging difficult at best. It is only in the setting of a complete gross resection (extrapleural pneumonectomy) that tumor extent can be assessed accurately. The precise designation of nodal status as N1, N2, or N3 is not possible in this disease, given the wide variation of tumor location and extent and the inconsistency of lymphatic drainage from different regions in the chest. This is unlike nodal designations in non-small cell lung cancer, which are based on lymphatic flow away from the tumor and therefore represent

disease progression. The paucity of metastatic disease in patients dying of mesothelioma renders M status irrelevant for the majority of patients.[39]

We previously proposed a staging system based on an analysis of a subset of the present cohort.[15] In this system, stage I includes resectable disease without lymph node involvement. Stage II patients include those with resectable tumors with involved lymph nodes. Stage III (combines Butchart stages II and III) tumors are deemed unresectable because of local extension of the tumor into the mediastinum or across the diaphragm. Stage IV includes patients with extrathoracic hematogenous metastatic disease at time of presentation.

This staging system is supported by the current analysis because the survival of 120 patients was stratified significantly according to stage (Fig. 6). This represents the only validated staging system in this disease. Resectability, histology, and node status provide possible tools for the preoperative assessment and selection of appropriate patients for aggressive therapy. The use of magnetic resonance imaging to assess transdiaphragmatic and mediastinal invasion has been investigated with favorable results.[40] New methods for detecting lymph node metastases, including positron-emission tomography scanning, combined with mediastinoscopy, laparoscopy, and thoracoscopy, could form the basis for more accurate preresectional staging.

These results appear superior to other combined modality series, and we favor further pursuit of extrapleural pneumonectomy combined with chemotherapy and radiotherapy. This study shows that an aggressive trimodality approach can extend survival in patients with node-negative epithelial tumors. The development of stage-specific adjuvant therapies may provide the basis for future clinical trials using this validated staging system.

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Discussion

DR. DAVID C. SABISTON, JR. (Durham, North Carolina): We have just heard an extraordinary presentation by Dr. Sugarbaker and his colleagues. I have followed this work for some time with great interest and appreciate their sending me a copy of the manuscript. They include very pertinent data and analyze them quite objectively.

I think the approach they have used has made quite an impact on the treatment of mesothelioma because it is a triple approach using chemotherapy and radiation after extensive surgical resection. It is remarkable that residual tumor in the pathological margins in some of these patients does not appear to affect the prognosis in terms of their survival. It is presumed that this is because of the effectiveness of the chemotherapy and radiation.

In the preoperative work-up, they have utilized computed axial tomography and magnetic resonance imaging scans quite effectively. There is also the role of positron-emission tomography (PET). I would like to ask if they have used the PET scan because it has the ability to demonstrate metabolic and biologic activity as well as to localize the site and extent of the residual tumor. Thank you.

DR. L. PENFIELD FABER (Chicago, Illinois): This is an outstanding series of cases and I would like to congratulate the authors on the results they have achieved. Diffuse malignant mesothelioma is a fatal disease and prior studies have all reported less favorable results.

Our experience at the Rush-Presbyterian–St. Luke's Medical Center consists of 49 patients who had an extrapleural pneumonectomy for malignant mesothelioma. Our mortality rate was 6.1%, which is similar to today's reported series, but our 5-year survival rate is not as good, at 12.2%. During this same period of time, we carried out 65 parietal pleurectomies and decortication for patients with less bulky disease, and they all received postoperative adjuvant therapy. We also carried out a multivariate analysis to determine what factors had an influence on survival. Similar to the present study, we defined that adjunctive therapy was statistically significant in enhancing survival. The epithelial histologic type of malignant mesothelioma was also statistically significant for enhanced survival. However, the analysis of positive nodes in our series did not have a statistically significant effect on survival. However, we did not do a systematic mediastinal lymphadenectomy, as we commonly do for lung cancer.

I would like to ask Dr. Sugarbaker his explanation for the finding that positive lymph nodes do have an effect on survival. When this tumor reoccurs locally, it becomes fatal by local invasion and rarely manifests itself by systemic metastatic disease. Why are lymph nodes an important prognostic factor when the disease usually remains local?

A new international TNM staging system for malignant pleural mesothelioma has recently been proposed. In this system, N2 or mediastinal lymph nodes place the tumor into stage III. This is at variance with Dr. Sugarbaker's proposed staging system, as N2 lymph nodes are categorized into stage II. In view of the fact that N2 disease carried a very poor prognostic implication in this series, would Dr. Sugarbaker now recommend that patients with N2 disease be submitted to extrapleural pneumonectomy for malignant mesothelioma? I would also appreciate hearing his comments about the new staging system, as randomized trials can only be conducted with uniform staging.

Our data demonstrated a survival trend in favor of extrapleural pneumonectomy when compared with pleurectomy. The pneumonectomy group had the largest tumor burden because patients at Rush without visceral pleural and fissure invasion underwent pleurectomy rather than pneumonectomy. The finding that the pneumonectomy patients with the larger tumor burden in our series had improved survival would imply that patients with the least tumor burden may benefit the most from radical extirpation for maximum local control followed by aggressive adjuvant therapy. This thesis would support Dr. Sugarbaker's approach to this aggressive tumor.