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The Development of the Brigham and Women's Multimodality Treatment Plan for Malignant Pleural Mesothelioma: A Model for Improving the Treatment of Rare Diseases

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Mesothelioma of the pleural space is an uncommon disease. The current incidence within the United States is 2000 to 3000 cases per year as compared with esophageal and lung cancer, which are at least four and 50 times more common, respectively (1). Few physicians treat more than a handful of cases of malignant pleural mesothelioma (MPM) over the course of their professional careers. Even fewer academic centers in North America and Europe have been able to acquire a collective experience large enough to develop new treatment protocols for this devastating disease.

The Brigham and Women's Hospital (BWH) and Dana-Farber Cancer Institute (DFCI) in Boston, Massachusetts, are a combined cancer center with a large experience treating MPM. The diagnosis and management of this disease has become a major interest of the academic thoracic surgeons, medical oncologists, radiation oncologists, pathologists, pulmonologists, respiratory therapists, nurses, and educational house staff of our hospital over the past 20 years. Current treatments are based on two decades of research and experience, and new treatments are being developed.

This chapter traces the historical development of the current treatment of MPM at BWH, explains the development of our working paradigm of this disease, and serves as a template for other surgical innovators to design unique treatment algorithms for similarly uncommon diseases.

Improved treatment of a rare disease depends on three critical elements coexisting at the same place and time: a relative high frequency

of the disease, the commitment of a multidisciplinary research-oriented team and institution, and the ensuing dynamic growth of professional expertise. The BWH experience with MPM includes all three of these elements.

Historical Context

The distinctiveness of the BWH/DFCI experience with mesothelioma can be best appreciated within a historical context of the disease. The recognition of mesothelioma as a cancer and the development of treatment options are recent developments in the context of medical history.

In 1960, Wagner et al (2) published the first mesothelioma case series, reporting on 33 patients from a South African asbestos mining town with known occupational and environmental crocidolite exposure. In the 1970s, a landmark study by Selikoff (3) established a firm link between asbestos exposure and mesothelioma. The author followed 17,800 asbestos insulation workers in the United States and Canada for a period of up to 50 years and found that the incidence of mesothelioma within this group increased rapidly starting 20 to 25 years after the first exposure. Peak incidence occurred at 40 to 45 years after exposure. Seven percent of all deaths in this group of asbestos workers were due to mesothelioma, a shockingly high incidence for a rare cancer.

The association between mesothelioma and asbestos is well established (4). The causative role of asbestos exposure has been investigated extensively and its pathophysiology has been described in detail (3,5). Persons at the highest risk include those who work directly with asbestos in mines, mills, or shipyards. This risk extends to people residing in areas surrounding these sites. Family members of asbestos workers also have a substantial increased risk, termed "bystander risk," thought to be secondary to exposure to hair and clothes brought into the home (6).

Early efforts at surgical and nonsurgical treatments were disappointing. Worn (7) published one of the first series of patients undergoing extrapleural pneumonectomy in 1974, reporting a 5-year survival rate of 10% and a median survival of 19 months. Butchart et al (8) published their initial experience with extrapleural pneumonectomy for maximal surgical debulking of pleural mesothelioma in 1976. Extrapleural pneumonectomy had previously been used for tuberculous empyema, but was an operative technique that had always been associated with a high perioperative mortality. In Butchart et al's series, extrapleural pneumonectomy for MPM had a perioperative mortality rate of 31%, a 5-year survival of 3.5%, and a median survival of 10 months.

Initial studies investigating adjuvant chemotherapy and radiation therapy repeatedly showed little to no activity against the disease. These poor results were partly due to the lack of an accurate way to measure response rate prior to the advent of computed tomography (CT) scan for the chest. Furthermore, early trials were poorly designed, with too few patients and without stratification by histologic subtype.

Median survival of patients enrolled in therapeutic trials varied from 3 to 17 months, with the majority falling in the 6- to 10-month range (9).

Early attempts at radiation therapy were very limited as there was no way to avoid injuring the underlying lung parenchyma and nearby vital structures. Several early studies failed to show an added benefit when radiation was used in combination with surgery or chemotherapy (10).

Considering these relatively ineffective treatments and the seemingly persistently dismal prognosis, it is not difficult to see why there has been a fair degree of skepticism among physicians treating patients with mesothelioma. Fortunately, a few clinicians were not deterred, including a distinct group of health care providers at BWH/DFCI. This chapter describes the evolution of our institutions' current understanding and approach to MPM.

Frequency of Disease in New England

New England has had a rich maritime military history. In August 1776, regiments from Marblehead and Salem, Massachusetts, rowed George Washington's army to safety across Long Island Sound after the defeat on Brooklyn Heights. Three of the first six frigates built by the fledgling United States were built in New England or New York. The large whaling and cod fishing fleets from New Bedford, Nantucket, and Gloucester have provided sailors to the United States Navy for over 200 years.

The pace of production of United States naval ships during World War II reached one ship per week in the large shipyards of New England and New York. Asbestos slurry was sprayed upon the bulkheads of the ships to insulate the compartments against the cold of the North Atlantic and against fire within individual sections of the ship. Although quickly and easily applied to the bulkheads, this asbestos slurry would flake, and particles of asbestos dust would be suspended in the air once it had dried. Unaware of the long-term complications of this exposure, the shipyard workers did not wear protective clothing or masks. Many mesothelioma patients who served on these ships describe a cloud of white dust below decks whenever the large guns of the warship were fired. Thus, a large proportion of the New England population came into contact with substantial quantities of asbestos by either working within the New England shipyards or serving in the navy. Asbestos was also commonly used to insulate heaters within the home, exposing an even larger New England population. The consequence of this exposure is reflected in current geographical trends in the prevalence of mesothelioma (Fig. 47.1).

The long latency period from exposure to development of the cancer has contributed to the high frequency of pleural mesothelioma in the greater Boston area during the past two decades. Prospective studies following people with known asbestos exposure have demonstrated a rapid rise in the incidence of malignant mesothelioma beginning at 20 years postexposure and a peak incidence of approximately 0.6% per

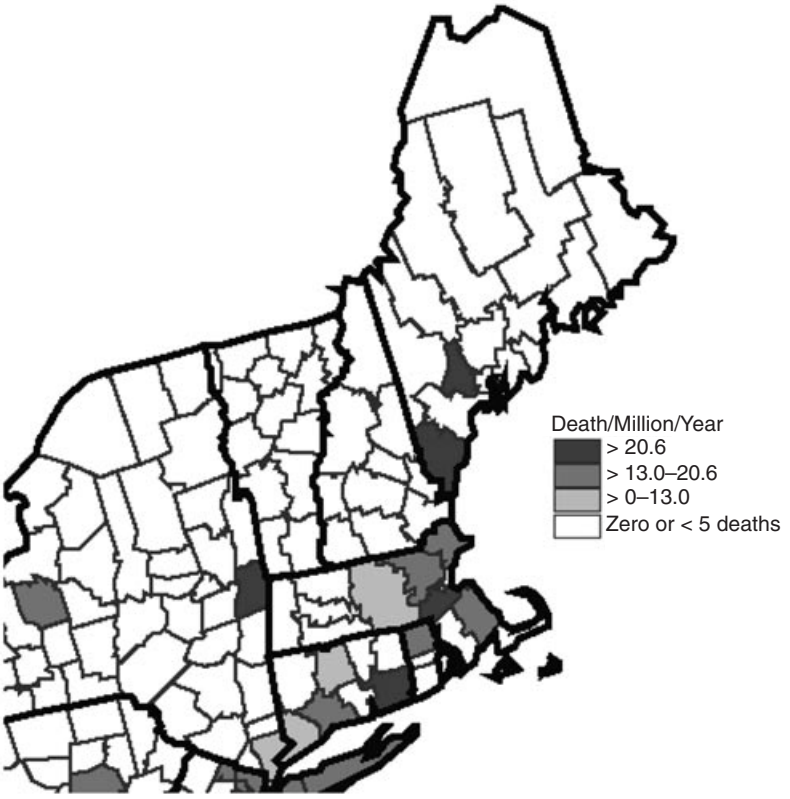

Figure 47.1. Malignant mesothelioma: age-adjusted mortality rates by county, United States residents age 15 and over, 1999. *Note*: Age-adjusted rates are not calculated for those counties with one to four deaths. (*Sources*: National Center for Health Statistics. Multiple causes of death data. Population estimates from U.S. Bureau of the Census. Work Related Lung Disease Surveillance Report 2002. Division of Respiratory Disease Studies National Institute for Occupational Safety and Health. U.S. Department of Health and Human Services. Center for Disease Control and Prevention. December 2002. http://www.cdc.gov/niosh/docs/2003-111/2003-111.html.)

year 40 to 45 years after exposure. As discussed above, asbestos mining and shipbuilding steadily increased to accommodate the war needs of the United States Navy during the late 1930s and 1940s. The Surveillance, Epidemiology, and End Results (SEER) Program data regarding the incidence of malignant mesothelioma between 1973 and 2000 (Fig. 47.2) depicts a trend that correlates with this exposure pattern and the known latency of disease.

Asbestos continued to be used in manufacturing for many years. In the United States, it wasn't until 1986 that the Toxic Substance Control Act addressed the health risks of asbestos, giving the Environmental Protection Agency (EPA) broad authority to regulate the manufacture, use, distribution in commerce, and disposal of the carcinogenic substance.

When one considers the timing of these federal regulations, the latency of the disease, the geographic distribution of asbestos exposure,

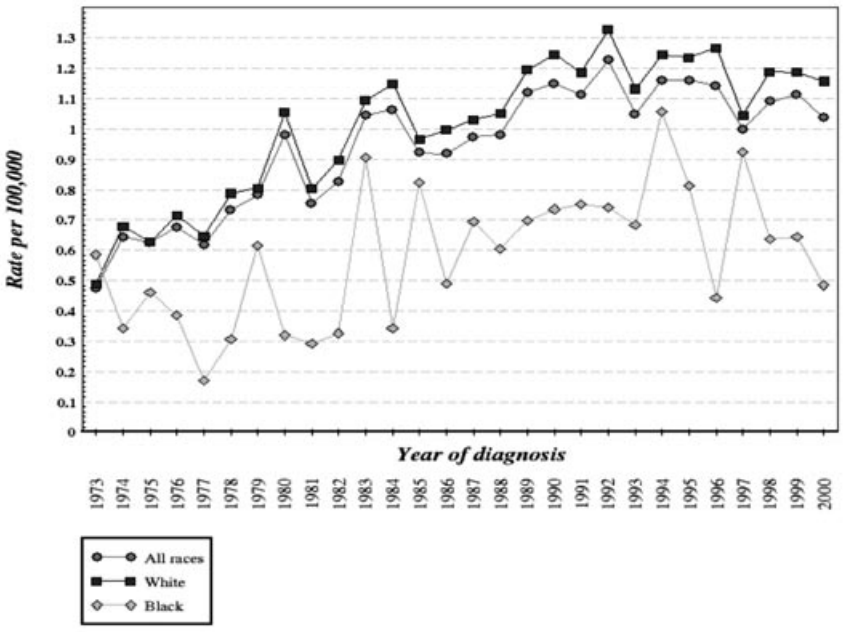

Figure 47.2. Surveillance, Epidemiology, and End Results (SEER) incidence age-adjusted rates for malignant mesothelioma, nine registries, 1973–2000. [*Source*: SEER Program (www.seer.cancer.gov). SEER Stat Database: Incidence—SEER Nine Registries Public Use, November 2002 submission (1973–2000). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the November 2002 submission.]

and the history of asbestos use, it is no coincidence that BWH has become an epicenter of treatment for MPM.

The 1980s: Diagnosis and Recognition of the Disease

The Sydney Farber Cancer Institute was founded in 1949, and originally treated only childhood cancers. In 1969 it expanded its mission to treat adult malignancies, and received federal designation as a regional comprehensive cancer center in 1973. It was renamed the Dana-Farber Cancer Institute in 1983. Located in Boston, Massachusetts, across the street from both the Peter Bent Brigham Hospital (which became the Brigham and Women's Hospital in 1980), and the Harvard Medical School, it soon became a major referral center for both aggressive and unusual malignancies within the New England area. Mesothelioma was among these cancers.

In March 1980, Karen Antman et al (11) published in the *American Journal of Medicine* the experience with the first 40 malignant mesothelioma patients treated at the Sydney Farber Cancer Institute. These patients had been treated between 1965 and 1978. Thirty-four of the patients had the pleural form of the disease and six patients had peritoneal mesothelioma. Sixty-three percent of these patients either

reported an asbestos exposure or were employed in New England shipyards, generally during World War II. In this series, Adriamycin (doxorubicin hydrochloride)-containing chemotherapy regimens induced a partial remission in 40% of the previously untreated patients. Yet, despite these remissions, the majority of patients (78%) ultimately died of local disease. Subtotal resection in this series and others (12) resulted in prolonged survival. Specifically, the 10 patients in Antman et al's review who underwent subtotal resections had a median survival of 15 months, compared to 8.5 months for the 20 patients who underwent only diagnostic operations and other treatments. Further analysis revealed that the median survival was a mere 4.2 months for patients who were diagnosed with limited disease but chose only supportive care.

Though Stout and Murray had distinguished mesothelioma from sarcoma in the 1940s, the treatment for the two diseases remained quite similar. Based on the findings published in their 1980 paper, however, Antman et al concluded that mesothelioma was sufficiently different from sarcomas to warrant treatment as a separate entity. Notwithstanding the biases inherent in this type of retrospective review, their evidence suggested an advantage to aggressive intervention. Therefore, the authors advocated a multimodality approach incorporating maximal surgical resection with adjuvant chemotherapy and radiation therapy.

In 1984, Antman organized a prospective multimodality protocol for malignant pleural mesothelioma at DFCI. This ambitious protocol started with an extrapleural pneumonectomy, as had been previously described by both Worn and Butchart. When possible, chemotherapy was started 4 to 6 weeks after surgery. Chemotherapy consisted of cyclophosphamide at a dose of 600 mg/m^2, combined with Adriamycin 60 mg/m^2, to a cumulative dose of 450 mg/m^2. After 1985, patients also received cisplatinum at 75 mg/m^2 (CAP chemotherapy). Radiation directed at previous sites of bulky disease was given to a dose of 5500 rad after the chemotherapy.

The accurate pathologic diagnosis of malignant mesothelioma also proved to be a barrier to treatment development. The distinction between lung adenocarcinoma and MPM is an important surgical issue, as surgical treatment of these two illnesses is radically different. Stimulated by the need to differentiate between these two histologically similar tumors, the pathology department of BWH drew on the large source of explanted tumors at our institution. In 1987, the department showed that staining for mucin and carcinoembryonic antigen and a predominantly peripheral pattern of staining for keratin proteins were highly characteristic of lung adenocarcinoma and allowed the distinction from malignant mesothelioma (13). In 1988, the department identified monoclonal antibodies to AE1/AE3 keratin proteins as being a sensitive method for the pathologic diagnosis of the sarcomatoid form of diffuse MPM (14). Further work in 1990 showed that the monoclonal antibody ME1 was reactive in frozen tissue sections with normal mesothelial cells and the epithelial type of malignant mesotheliomas (15). The ability to differentiate MPM from lung adenocarcinoma, sarcomas, and other pleural diseases made the BWH pathology depart-

ment a major referral center for tissue blocks from around the world. In turn, this process facilitated the additional accumulation of pleural mesothelioma cases from areas outside of New England.

The Early 1990s: Development of Multidisciplinary Expertise

Surgery Staff

The Brigham and Women's Hospital had a limited experience with extrapleural pneumonectomy for MPM from 1980 to 1987 (Fig. 47.3). Several cardiothoracic surgeons participated in these early efforts. Similar to other institutions, the initial experience with the operation was associated with high perioperative mortality and few long-term survivors. After the board of trustees created the Division of Thoracic Surgery at BWH in 1988, however, experience dramatically accelerated. This separate academic division was to be dedicated to the care of patients with noncardiac thoracic diseases. The work of this surgical division began with David Sugarbaker's return to Boston from his Toronto General Hospital thoracic surgical training. The Toronto program had become one of the most sought after thoracic surgical residencies in North America during the 1980s. A large and dynamic faculty, under the direction of Griffith Pearson, had developed a rich clinical practice, which included the first successful human lung trans-

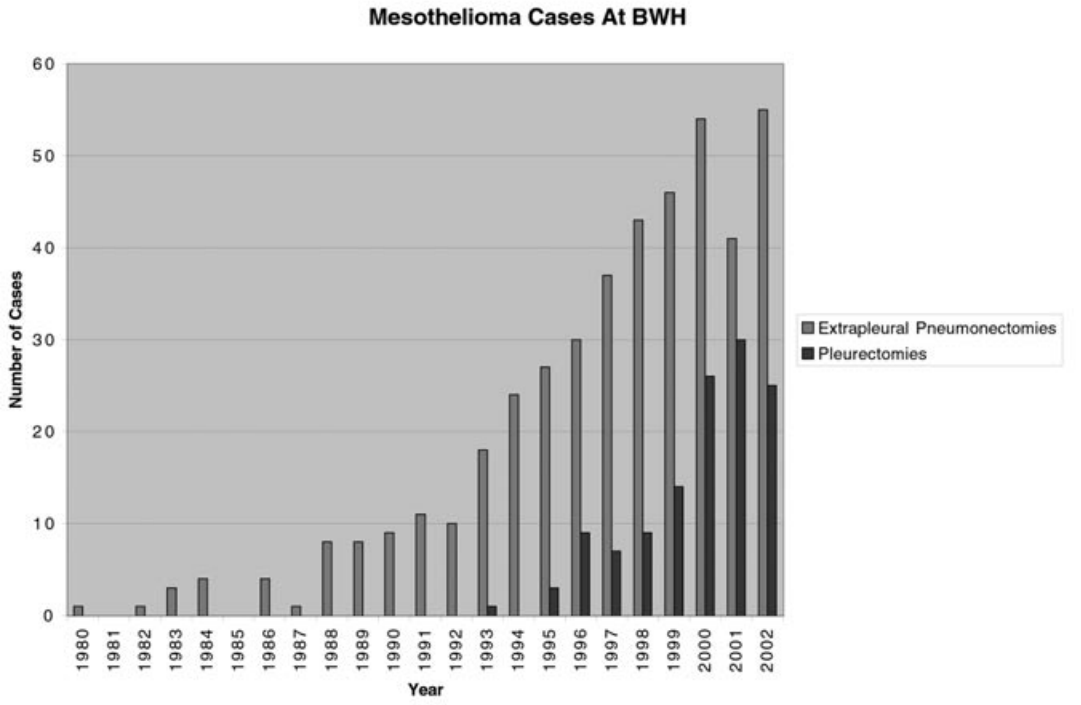

Figure 47.3. Mesothelioma cases at Brigham and Women's Hospital from 1980 to 2002 by type of resection.

plants, extensive esophageal surgery, lung cancer surgery, and the application of extrapleural pneumonectomy for MPM.

Steven Mentzer, a second alumnus from the Toronto program, joined Dr. Sugarbaker in 1990 and the two surgeons produced a dramatic increase in the volume of noncardiac thoracic operations performed at BWH, including extrapleural pneumonectomies. Over the next 12 years, they were joined by surgeons Malcolm DeCamp, Jr., David Harpole, Scott Swanson, Raphael Bueno, Jeanne Lukanich, Michael Jaklitsch, Yolonda Colson, Philip Linden, Lambros Zellos, and Michael Chang. Thus, only 12 surgeons have contributed to the BWH experience with extrapleural pneumonectomy, preserving the uniformity of the operation. At the same time, this group of surgeons congregating within a single institution sped the process of technical and clinical modifications, which reduced the expected operative mortality in a short period of time. Drs. Harpole, DeCamp, and Swanson currently lead thoracic surgical programs at other institutions, leaving nine full-time attending surgeons at BWH.

Intraoperative Expertise

Many contributions to the development of the modern extrapleural pneumonectomy as it is currently performed at BWH, were made through extensive discussions about surgical technique within the extended international thoracic surgical community. It has always been a goal of the members of this division to extensively describe potential pitfalls of the operation to all surgeons interested in learning this surgical technique. This information has been disseminated through written and oral presentations, with detailed illustrations. An early forthright discussion of our operative technique, as well as some of the technical difficulties with the operation, appeared in the 1992 publication by Sugarbaker et al (16).

As the operation begins, the patient, with a double-lumen endotracheal tube in place, is administered general anesthesia. The patient is placed in the lateral decubitus position. An extended posterolateral thoracotomy incision is made over the course of the sixth rib. A subperiosteal resection of the sixth rib is performed, and a plane is developed between the parietal pleura and the overlying rib cage.

The extrapleural dissection is begun superiorly toward the apex of the lung using both blunt and sharp techniques. Dissection is then begun in a similar fashion inferiorly and laterally to the sulcus between the pleura and the diaphragm (Fig. 47.4). The mediastinal pleura is then separated from the underlying structures down to the level of the azygos vein on the right and beneath the aortic arch on the left. Care is taken to prevent avulsion of the internal mammary vessels, the subclavian artery, and the azygos vein, as well as to keep the pleural envelope intact. During blunt dissection of the pleura in the left paravertebral sulcus, care must be taken to identify the correct plane. An incorrect retroaortic plane can produce bleeding from avulsing intercostal vessels.

The pericardium is opened and the serosal surface is inspected to ensure there is no direct invasion of tumor into the pericardial space.

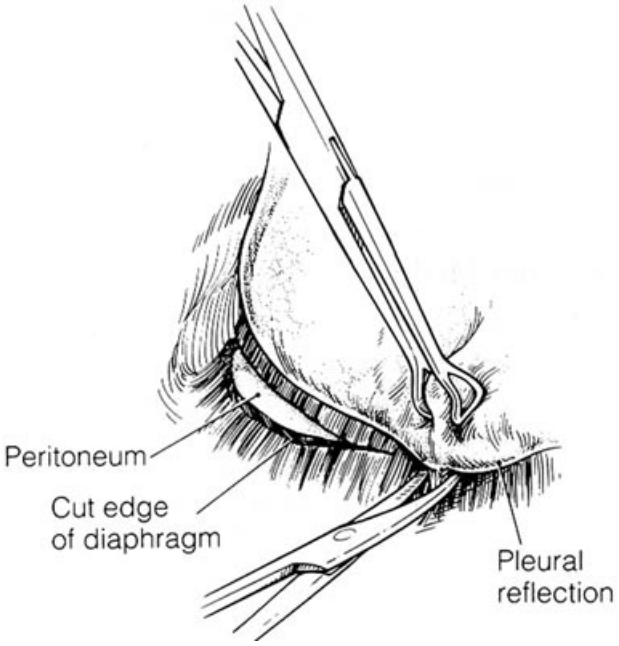

Figure 47.4. Extrapleural pneumonectomy: dissection inferiorly at the diaphragm (see text for details).

The diaphragm is divided in a circumferential fashion close to the chest wall. Care is taken when dividing the lateral bands of the diaphragm to preserve the underlying peritoneum. The diaphragm is separated from the peritoneum up to the lateral border of the pericardium. The crus of the diaphragm is divided in such a way as to prevent buttonholing of the inferior extent of the posterolateral pleura as it extends into the posterior diaphragmatic sulcus. The phrenic vessels are divided along the undersurface of the diaphragmatic crus.

The phrenic nerve is divided, and the pericardium is opened back to the level of the pulmonary vessels (Fig. 47.5). The pulmonary artery is dissected free from surrounding structures within the pericardium on the right, and just outside the pericardium on the left. Once the pulmonary artery has been divided, the pulmonary veins are likewise isolated from surrounding structures and divided. The posterior pericardium is mobilized to the level of the bronchus. The bronchus is divided with a heavy gauge bronchial stapler, and the specimen is passed off. A frozen section is obtained on the bronchial margin, and other areas of suspicion for margin involvement by tumor. A pericardial fat pad or pericardial flap is used to buttress the bronchial stump. The diaphragm and the pericardium are reconstructed with Gore-Tex patches.

Specific details learned through experience were highlighted in the 1992 description (16), including the importance of the careful dissection of the internal mammary vessels. These vessels, which are often tightly adherent to the pleura, can be inadvertently avulsed with posterior retraction of the tumor-filled parietal pleura. The placement of a

nasogastric tube to facilitate the identification of the esophagus was included. Specific dissection techniques to laterally divide the diaphragm while keeping the underlying peritoneum intact were described. The recommendation to divide the pulmonary artery trunk within the pericardium on the right and outside the pericardium on the left were included. Finally, specific details regarding the diaphragm and the structures piercing that muscle were given.

We have seen an evolution of the BWH techniques over the past decade. Early publications described the use of a running monofilament suture to anchor the prosthetic patches. This was abandoned when the beating action of a posteriorly displaced left atrium onto a Prolene knot produced an atrial laceration. The patches are now sewn into place with a soft braided permanent Ethibond suture leaving the knots outside the pericardium. Likewise, in our early experience, we would place a prosthetic pericardial patch only on the right side, since we believed that cardiac herniation was not possible on the left side. After a small number of cases of an entrapment syndrome of epicardial granulation tissue following heated chemotherapy, we changed our practice and now place pericardial patches for all patients (17). We observed a pattern of recurrence at previous chest tube sites, especially if the patient had been treated with talc poudrage in the past and the chest tube had been in place for greater than 2 days. In response, we added the prophylactic excision of all previous pleuroscopy and chest tube sites.

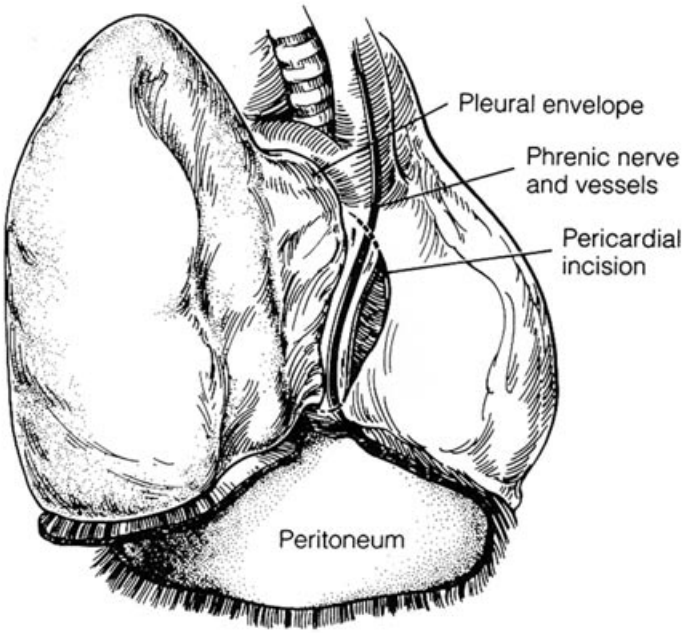

Figure 47.5. Extrapleural pneumonectomy: overall dissection (see text for details).

Diaphragmatic patch rupture has been a vexing problem that requires urgent reoperation as soon as it is recognized. In our earliest reconstruction attempts, we used O-Vicryl sutures anchored in the lateral remnant of the diaphragm muscle to loosely hold down the peritoneum; we placed an impermeable patch only if there was a peritoneal defect (16). The reefing technique was quickly abandoned in favor of patching all patients, with lateral sutures still in the lateral diaphragmatic remnant or around the lower ribs. Sugarbaker, using a leather-working awl that could easily be sterilized, developed a simpler and more reliable lateral anchorage system for the diaphragmatic patch. Loops of suture material passed through the lateral edge of the patch were then brought through the chest wall with the awl, where they were passed through a small postage stamp–sized patch of the same material and a sterile plastic button with the help of two angiocaths. The loop of suture was then tied down to itself onto the button, producing excellent lateral displacement of the patch. We have not recognized a lateral diaphragmatic rupture since adopting this system. Medial ruptures posterior to the pericardial edge and anterior to the thoracic spine have continued to be an infrequent problem. These have been minimized by three techniques: (1) a suture anchoring the patch to the anterior spinal ligament, (2) a tongue of extra patch material folded inferiorly along the lumbar spine in simulation of the diaphragmatic crus, and (3) a composite of two patches of 2-mm Gore-Tex stapled together in the middle with a TA stapler to create a dynamic patch at the center with less tension at the lateral suture lines. This last technique allows the prosthetic patch to "give" without rupture if the patient experiences abdominal distention.

The Division of Thoracic Surgery has extensively used the talent of Marcia Williams as a surgical illustrator, since accurate surgical atlas figures had not been developed for this operation. Illustrations were created from firsthand observation within the operating room. These illustrations have substantially contributed to the understanding of the magnitude of the operation for surgeons as well as nonsurgical care providers. The illustrations in this chapter are examples of her work.

Postoperative Care

The development of the BWH program for surgical care of the pleural mesothelioma patient has benefited from the input of all allied health professionals as well as the thoracic surgeons. Our division has always placed a high priority on a weekly quality assurance meeting attended by all members of the thoracic team. At this regularly scheduled meeting during the regular workweek, nurses, residents, fellows, nutritionists, surgical data managers, pharmacists, social workers, and attending thoracic surgeons discuss patient management issues. It has been our practice to close the operating rooms during this meeting to ensure that all members of the team are in attendance. This quality assurance meeting has significantly contributed to preoperative patient education, postoperative care, and intraoperative management.

Operative mortality following extrapleural pneumonectomy at BWH has consistently declined with increasing experience. This mortality was initially reported as 6% following the first 31 patients (18). This dropped to 5.8% after 52 patients (19), to 5.0% after 120 patients (20), to 3.8% after 183 patients (21), and to 3.4% after 328 patients (Sugarbaker, personal communication). Our nurses and residency staff have become experienced at recognizing complications early and differentiating a normal convalescence from an abnormal convalescence. This recognition of subtle early signs of complications has produced the statistical phenomenon of a simultaneously decreasing perioperative mortality rate with an increasing perioperative morbidity rate. The recognized overall postoperative morbidity rate rose from an initial report of 19% in 1991 (18), to 60.4% in 2003 (personal communication). This suggests that the entire multidisciplinary team had become more adept at recognizing morbidity, and intervening in an aggressive manner to stave off mortality.

The low perioperative mortality rate at BWH for an extrapleural pneumonectomy is dependent on several factors. Technical mastery of the operation has limited the operative time. Equally as important, anesthetic management has progressed sufficiently to anticipate perioperative hemodynamic changes, and reliably extubate the patient soon after emergence from anesthesia. Experience within the nursing staff and surgical residency staff has enabled the identification of postoperative complications early in their course. This latter aspect has been made possible by the close-knit physical location within the hospital of individual perioperative units. The thoracic surgical operating rooms are located within immediate proximity to each other, facilitating the intellectual input of more than one attending surgeon in a given case. We have a dedicated thoracic anesthesia staff and thoracic perioperative nursing staff. The thoracic intensive care unit, intermediate care unit, and postoperative wards are all located on the same floor of the hospital building. Thus, a skilled and experienced perioperative staff with extensive thoracic surgical experience has been developed. For instance, one of the identified perioperative management issues is the need for emergent reopening of a thoracotomy incision and open cardiac massage in the face of sudden cardiac arrest. Closed chest compressions are ineffective in patients who undergo extrapleural pneumonectomy, particularly right-sided resection, since the heart may be displaced away from the thoracic spine and the sternum.

Objective Results of Surgical Advances and Resultant Discoveries

In 1991, Sugarbaker and colleagues (18) published their first case series of patients receiving multimodality therapy for malignant mesothelioma. This retrospective review of 31 patients undergoing extrapleural pneumonectomy and subsequent adjuvant therapy demonstrated that the operation could be performed with acceptable rates of morbidity and mortality (19% and 6%, respectively), which was much improved from earlier series (45% and 31% in 1976, and 24% and 9% in 1986). No meaningful long-term survival assessment could be made.

These promising results of the BWH program reflected not only the refinement of surgical skill and improvement in perioperative care, but also the identification of prognostic variables with a consequent improvement in patient selection. As was recognized in 1976 by Burtchart et al (8), the success of extrapleural pneumonectomy was largely dependent on selection of the most appropriate surgical candidates. Sugarbaker realized the importance of this concept and focused much of his attention on improving staging and defining operative candidates. In the case series published in 1991 (8), the authors noticed trends toward improved survival in the subset of patients with negative histologic margins (Fig. 47.6). Though not statistically significant, this trend was encouraging. The determination of negative histologic margins required sampling at least 14 areas of the pleura in a protocol developed by Joseph Corson of the pathology department.

In 1993, Sugarbaker et al (22) updated their experience after 52 patients had been treated with extrapleural pneumonectomy in a trimodality setting. This analysis demonstrated significantly longer survival in patients with epithelial histology and node negative disease (Fig. 47.7A). Subset analysis of tumor size, gross residual disease, positive margins, and diaphragmatic tumor extension was still not statistically correlated with survival. Based on these findings, a BWH pathologic staging system was proposed.

The original BWH staging system had four stages. Stage I comprised tumors confined within the pleural envelope and without lymph node involvement. Stage II, which would be modified in a few years, also consisted of tumors within the pleural envelope, but with either intraparenchymal (N1) or mediastinal (N2) lymph nodes involved with tumor (22). Stage III disease was made up of locally aggressive and unresectable tumors beyond the pleural envelope that had invaded into the mediastinum or chest wall, or through the diaphragm, or involved contralateral (N3) nodes. Stage IV disease was defined by distant metastases.

The concept of a pathologic staging system quickly led to efforts to accurately stage patients clinically and radiographically prior to

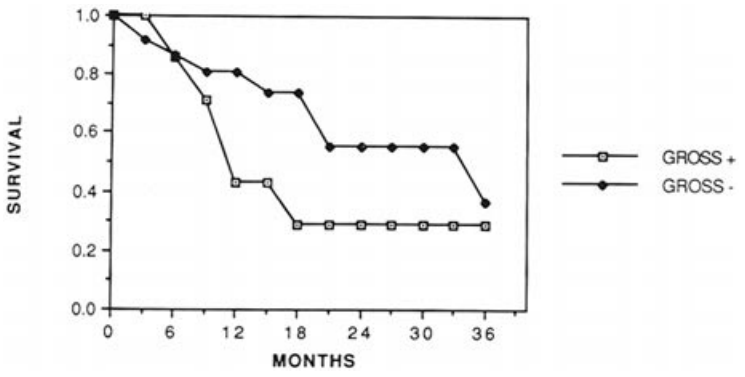

Figure 47.6. Impact of margin status on survival after extrapleural pneumonectomy (EPP) (8).

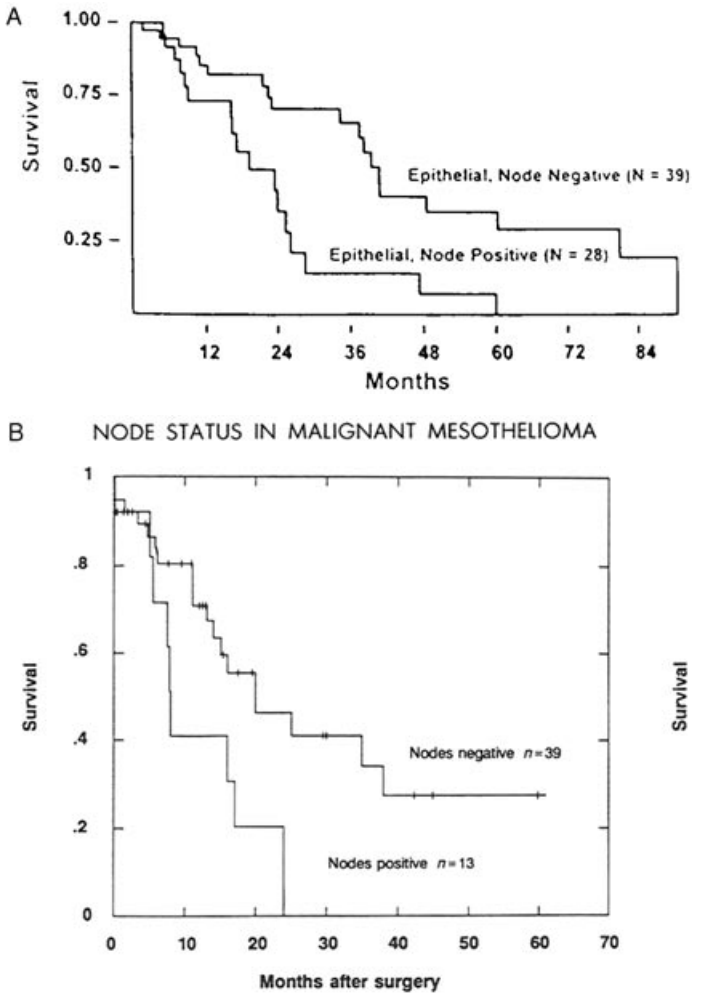

Figure 47.7. Impact of nodal status on survival after EPP in an early (A) (22) and later (B) study (20) from Brigham and Women's Hospital.

attempted surgical resection. A prospective study of chest CT and chest magnetic resonance imaging (MRI) to predict resectability of MPM recruited 34 patients referred for possible extrapleural pneumonectomy (23). All patients underwent both CT and MRI studies preoperatively. At the time of surgery, potential unresectable regions as determined by imaging were explored first and surgery terminated if resection was not possible. Scans that suggested transdiaphragmatic invasion were verified by minimally invasive imaging of the undersurface of the diaphragm in the operating room. Sensitivity for both CT and MRI was above 90% in all regions; MRI was found to be 100% sensitive in predicting unresectability due to diaphragmatic and chest wall involvement, whereas CT was less sensitive (94% and 93%, respectively). For mediastinal invasion, CT was 100% sensitive and MRI had a sensitivy of 92%. Advanced disease precluding extrapleural pneu-

monectomy in referred patients was a vexing problem at this time, as evidenced by the observation that only 24% of these 34 patients were found to be resectable. Since both CT and MRI contributed substantially to avoiding an extended thoracotomy incision in patients who were unresectable, both tests became part of our standard preoperative workup.

Our extrapleural pneumonectomy experience was reanalyzed in 1996, after 120 patients had been treated (20). This report confirmed the favorable prognostic factors of epithelial cell type and lack of nodal disease (Fig. 47.7B). The small numbers available for analysis did not yet allow differentiating a prognostic difference between N1 and N2 nodal disease. In addition, the previously published staging criteria were validated, with survival stratifying according to the BWH pathologic stage. Though there was no direct comparison made to a nonsurgical control group, the data suggested a survival benefit with trimodality therapy resulting in a median survival of 21 months as compared to 4 to 12 months in the untreated population.

Parallel with the ongoing development of surgical expertise, medical oncologists at BWH/DFCI were advancing knowledge and building on their experience. The initial adjuvant chemotherapy program for MPM at the BWH was a combination of 600 mg/m^2 cyclophosphamide, 60 mg/m^2 doxorubicin, and 70 mg/m^2 cisplatin (CAP) chemotherapy. This chemotherapy was planned for every 3 weeks for four to six cycles. It proved to be a difficult adjuvant regimen, however, and for the 88 patients who received this therapy, a median of four cycles was delivered, with a range between one and eight cycles (21).

In 1997, the CAP chemotherapy regimen was changed to a carboplatin and paclitaxel regimen, through the collaborative efforts of Gary Strauss of the medical oncology department, Elizabeth Baldini of radiation oncology, and David Sugarbaker of thoracic surgery. This treatment plan began with extrapleural pneumonectomy. Two cycles of chemotherapy given 3 weeks apart, with two cycles of Taxol (200 mg/m^2 as a 3-hour continuous infusion) and carboplatin [target area under the curve (AUC) 6 mg/mL $\times$ min, IV bolus following Taxol infusion] was started between 4 and 12 weeks postoperatively. Following these two cycles, the patient received thoracic radiation with concurrent weekly Taxol (60 mg/m^2 as a 3-hour continuous IV infusion) given weekly during radiation, for up to 6 weeks. Finally, two additional cycles of Taxol (200 mg/m^2) and carboplatin (target AUC 6 mg/mL $\times$ min) completed the adjuvant therapy (21). This multimodality treatment plan was better tolerated than the previous doxorubicin-based regimen.

Radiation therapy ideally started 3 to 4 weeks following cycle number two of chemotherapy. Radiation was given in five fractions weekly, once per day, to a total dose of 40.5 Gy. This was delivered in 1.5-Gy fractions over $5\frac{1}{2}$ weeks. If a boost dose was delivered to treat a focal positive margin was given, it was administered in 1.8-Gy fractions, yielding a total of boost dose of 14.4 Gy and total cumulative dose of 54.9 Gy. The initial clinical target volume was the entire hemithorax on the involved side. Field borders were defined superiorly by the clearing the first rib.

Laterally, the bony rib cage was cleared by 1.5 cm. Superolaterally the shoulder joint was blocked such that there was a 1.5-cm margin on the bony rib cage. The medial border was 3 cm over the midline to cover the mediastinum. Inferiorly, the field extended at least 1 cm below the diaphragmatic reflection of the pleura, often at the bottom of T12 or L1 vertebrae. A liver block was added at 30 Gy. The liver block extended at least 1 cm above the reconstructed diaphragm. A full bolus of radiation therapy was used to cover the incision as well as any drain or pleuroscopy sites. If a part of the incision or drain site was out of the photon field, that region was treated with a dose of 21 Gy delivered in three fractions (700 cGy × 3) with en face electrons to a depth defined by the thickness of the chest wall as measured by CT or MRI scan.

Although it took from 1980 to 1996 to accumulate 120 patients, 63 additional patients were treated over the next 3 years. The analysis of these 183 patients was published in 1999 (21). Four significant variables of improved survival were identified by log rank test: female sex (p = .03), epithelial cell type (p = .0001), negative resection margins (p = .02), and lack of extrapleural nodal involvement (p = .004). In this analysis, we considered metastases to the extrapleural peridiaphragmatic nodes as N2 disease, since they lay outside the pleural envelope and thus drained directly to the paraesophageal and internal mammary nodes and not through the lung hilum.

These four variables were then entered into a Cox proportional hazards model, which no longer identified gender as a statistically significant variable. The most important predictor of outcome became histologic subtype, followed by N2 nodal disease and positive resection margins (Table 47.1).

Our previously published pathologic staging system was applied to this large group of patients, and survival was significantly stratified by stage (p = .048). Median survival intervals for patients with stage I (n = 66), II (n = 41), and III (n = 69) disease were 25, 20, and 16 months, respectively. The identification of three main influences on survival by the Cox proportional hazards model led us to revise our previous staging system to account for positive margins and extrapleural nodes. In the revised staging system, stage I was unchanged, stage II included tumors limited by the pleural envelope but with tumor involving the resection margins or disease in the N1 intraparenchymal nodes, and stage III tumors either penetrated beyond the pleural envelope or involved the N2 mediastinal nodes (21). These revisions improved the survival stratification of our cohort of 183 patients (p = .0011, Fig. 47.8). This same group of patients was not stratified by the international

Table 47.1. Multivariate analysis of 183 extrapleural pneumonectomy (EPP) resections

Variable	*n*	OR	CI	*p* value
Mixed or sarcomatous cell type	**73**	**3.0**	**2.0–4.5**	**<.0001**
Positive resection margins	**110**	**1.7**	**1.2–2.6**	**.0082**
Metastatic extrapleural nodes	**40**	**2.0**	**1.3–3.2**	**.0026**

n, number of patients; OR, odds ratio; CI, confidence interval.

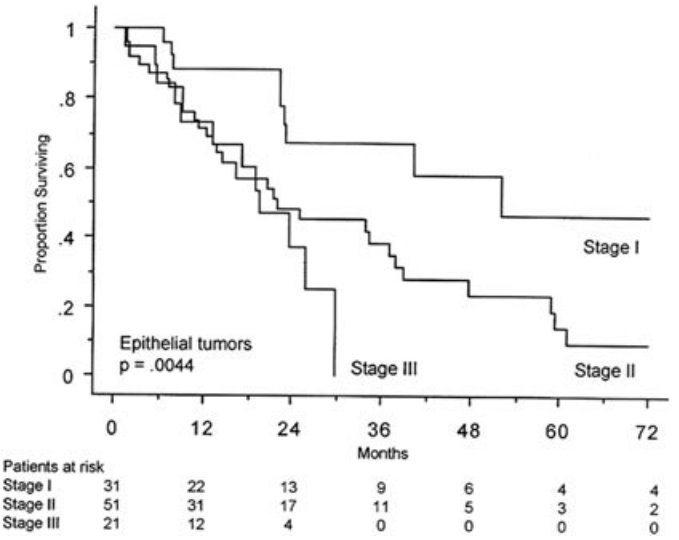

Figure 47.8. Results in malignant mesothelioma patients with epithelial histology having EPP at Brigham and Women's Hospital (21).

tumor, node, metastasis (TNM) staging system for mesothelioms (24) ($p = .31$) or by the Butchart staging system (37) ($p = .09$).

A subset of 31 patients within this group of 183 (17%) had the epithelial subtype, negative resection margins, and negative extrapleural nodal status. These stage I patients (by the revised Brigham staging system) had a 51-month median survival with a 2-year survival of 68% and a 5-year survival of 46%. This was encouraging data after more than a decade of treatment refinement.

The International TNM Staging System (24) and the Butchart staging system (8) failed to stratify survival when applied to our cohort of patients. The TNM staging system placed 8% of our cohort into the stage I category, 11% into stage II, 78% into stage III, and 3% into stage IV. Since the very large majority of patients were categorized as stage III, it becomes difficult to identify patients with different tumor characteristics, which is necessary to stratify survival. In addition, the T descriptor was not a statistically significant predictor of survival on log rank testing, reflecting the inability of this system to describe the biologic behavior of mesothelioma when applied to our patient population.

The staging system proposed by Butchart similarly did not significantly stratify survival in our patients. A small number of patients were categorized as having stage III disease ($n = 5$, 3%). The separate survival implications of pleural envelope penetration and nodal involvement are not taken into account by this early staging system, reflected by the majority of our patients being placed in the stage II category.

The revised Brigham Staging System has proven useful to us. This is an easy-to-use, surgically based staging system, and stratifies patients by ability to completely remove the tumor and involved regional lymph nodes. Observer bias may exist because this staging system orig-

inated at our institution and was based on an earlier cohort. Validation by other institutions is required to judge the utility of this clinical staging system.

Late 1990s: Development of Intraoperative Bicavitary Heated Chemotherapy

Despite these advances in surgical technique and refinement in prognostication and patient selection, the unfortunate fact remained that nearly all patients eventually died of their disease within 10 years of the operation. Recurrences appeared to result by direct extension from the ipsilateral hemithorax. Therefore, in the second half of the 1990s, the BWH group embarked on a new approach to multimodality therapy.

The major treatment plan of the previous 10 years had started with extrapleural pneumonectomy (EPP) because mesothelioma was predominantly a locoregional disease, and much of the early morbidity was from local spread. Since most patients died as a result of the primary cancer invading the diaphragm, chest wall, and mediastinal organs, initial surgical debulking was chosen prior to the initiation of chemotherapy in order to reverse the aggressive natural progression of this disease.

In 1997, Baldini et al (25) published a detailed retrospective review of 49 patients who underwent EPP and some combination of adjuvant chemotherapy and/or radiotherapy with a focus on defining patterns of failure. In this series, overall median survival was 22 months, and 34% attained 3-year survival. Resection margins were microscopically positive in 61% of patients and lymph nodes positive in 29%. Of the 54% of patients with recurrences, 67% percent had the first recurrence within the ipsilateral hemithorax, and 50% had recurrence at some time within the abdomen.

Three potential sources of tumor cells are positive resection margins, free intrathoracic cancer cells that have penetrated the pleura prior to resection, and spillage of tumor at the time of resection. In the abdomen, shed tumor cells have been detected on fluid cytology prior to dissection in 25% of patients amenable to curative resection (26). Surgical dissection causes a dramatic increase in the rate of intraperitoneal cancer cell shedding, up to 60% (27). These free cancer cells were shown to be viable and able to implant (28). These cells can become attached to the cavity surfaces within minutes, and cannot be dislodged with irrigation. They can be entrapped by fibrin accumulations, and their growth stimulated by healing wound growth factors (29). Delayed systemic chemotherapy may have no effect on tumor deposits embedded in fibrin. We considered the use of intraoperative chemotherapy as a potential solution to this problem.

The potential role of intracavitary chemotherapy as a method of improving regional control had been studied previously in a variety of abdominal malignancies. The local application of chemotherapy allows high cytotoxic levels to reach residual tumor cells by diffusion

without the side effects of high-dose systemic chemotherapy. Intracavitary chemotherapy with or without hyperthermia had been favorably reported in the literature.

In 1992, Markman and Kelsen (30) of Memorial Sloan-Kettering Cancer Center, reported the use of intraperitoneal (IP) chemotherapy in the treatment of MPM. Intraperitoneal cisplatin and mitomycin were infused through a peritoneal catheter left in place after surgical debulking. Cisplatin (100 mg/m^2) was given every 28 days and mitomycin (5–10 mg) was given 7 days after each IP cisplatin dose. A maximum of only five courses of cisplatin could be administered because of catheter failure or disease progression. While the median survival for the 19 patients treated in this manner was only nine months, 4 patients (21%) lived for more than 3 years from the initiation of therapy and two patients were clinically disease-free more than 5 years from the start of the intraperitoneal treatment.

Alberts et al (31) published a prospective randomized trial in the *New England Journal of Medicine* in 1996. Intraperitoneal cisplatin was compared to intravenous cisplatin in patients with stage III ovarian cancer following cytoreductive surgery. Among the 654 randomized patients, the estimated median survival was significantly longer in the group receiving intraperitoneal cisplatin (49 months) than in the group receiving intravenous cisplatin (41 months).

The Memorial Sloan-Kettering Cancer Center in New York has completed two studies of intrapleural chemotherapy following radical pleurectomy for MPM (32–34). Intrapleural chemotherapy consisted of cisplatin 100 mg/m^2 and mitomycin 8 mg/m^2. This treatment modality was well tolerated, with only two patients suffering grade 4 renal toxicity out of 28 patients treated. The pharmacokinetics of the drugs were similar to that seen with intraperitoneal chemotherapy. The most common site of recurrence, however, remained the ipsilateral hemithorax in these studies. In our analysis of this work, we felt that pleurectomy would leave more residual tumor than an extrapleural pneumonectomy, and believed that a higher dose of intracavitary cisplatin might be achieved.

The use of hyperthermia as an anticancer treatment stems from observations from about a hundred years ago and from tumor regression after high fever. Studies in the past 40 years have shown that tumor cells have a much higher sensitivity to heat than normal cells (35). Heat increases cell permeability, alters cellular metabolism, and increases membrane transport of drugs.

Stehlin et al (36) used hyperthermic melphalan to perfuse the limbs of patients with melanoma of the extremities. The 5-year survival of the 30 patients treated with hyperthermic melphalin compared favorably to the 27 patients treated with normothermic melphalin (80% vs. 20%). This observation has been confirmed by researchers at the National Cancer Institute of Milan, Italy (37). The 5-year survival of 140 patients with stage IIIA melanoma of the extremity treated with hyperthermic chemotherapy was 51%, compared to 16% for 297 patients with similar stage treated by conventional methods. This suggests a synergistic effect of hyperthermia and chemotherapy.

Van Ruth et al reported using doxorubicin and cisplatin in intraoperative heated chemotherapy protocols for malignant mesothelioma. They found that doxorubicin was able to penetrate into the intercostal muscle specimen. In their hands, intracavitary lavage with heated doxorubicin and cisplatin was a safe procedure with the advantage of high intrathoracic cytostatic drug concentrations, while having limited systemic side effects.

Paul Sugarbaker, the director of surgical oncology of the Washington Cancer Institute at the Washington Hospital Center in Washington, DC, and the older brother of David Sugarbaker, chief of the thoracic surgery division of BWH, had accumulated extensive experience with heated intraperitoneal chemotherapy for peritoneal carcinomatosis of gastrointestinal malignancies as detailed in Chapter 49. His data stimulated the thoracic surgeons in Boston, who saw multiple similarities between peritoneal carcinomatosis and malignant pleural mesothelioma.

The decision to design a phase I dose-escalation trial of heated intraoperative cisplatin at the time of EPP had been supported by BWH/DFCI and the leadership of all professional groups who would be involved in patient care. The obstacles to be overcome were formidable. Protocols to maximize both patient and staff safety were designed by a multidisciplinary "heated chemotherapy" team, which met once a week to develop guidelines for this novel therapy. Ideas were actively sought from surgeons, anesthesiologists, pharmacists, nurses, scrub technicians, medical oncologists, and respiratory therapists to design the method of drug delivery and disposal in the operating room. Safety courses were required for all staff participating in the protocol. Special isolation rooms with chemotherapy precautions were prepared in the intensive care unit (ICU) with guidelines for disposal of patient contact items, which might be contaminated by cisplatin. The institutional review board (IRB)-approved protocol was rewritten to clearly delineate responsibilities for the surgeon, scrub tech, circulating nurse, anesthesiologist, perfusionist, and ICU nurse. Instructions were also written for postoperative cleanup and handling of spills, based on guidelines from the Occupational Safety and Health Administration (OSHA) and the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO).

On September 17, 1998, representatives from the thoracic surgeons, thoracic anesthesia, operating room (OR) nursing and ICU nursing from BWH traveled to Washington Hospital Center to observe patients with peritoneal carcinomatosis treated with heated intraperitoneal chemotherapy infusion. This allowed multidisciplinary interaction with counterparts at the Washington Hospital Center. Technical points were learned, sketches were made, and extensive discussions about the safety and feasibility of this technique were held. This trip proved to be an invaluable source of information in the development of the intrathoracic heated chemotherapy perfusion protocol opened at BWH in the spring of 1999.

In this protocol, patients underwent EPP with the objective of complete cytoreduction of the cancer. Only 1 cm^3 or less residual disease

was permitted. A sodium thiosulfate bolus of $4\,g/m^2$ was given intravenously (IV) followed by a 6-hour infusion of $12\,g/m^2$. This drug is used to bind cisplatin that may have been absorbed into the vascular space to prevent systemic toxicity.

The diaphragm was removed during the EPP. This permitted access to both the abdomen and ipsilateral hemithorax for heated chemotherapy lavage. After the specimen was removed, but prior to reconstruction of the diaphragm and pericardium, a 1-hour lavage of escalating doses of cisplatin heated to 42°C bathed both body cavities. Urine output was maintained at 100 cc per hour during the lavage and for 1 hour afterward.

A temperature probe was placed in the esophagus, abdomen, and chest. A plastic sheet was sewn to the edges of the thoracotomy wound, draped over a retractor (Fig. 47.9). A slit in the plastic cover was made to allow the surgeon's double-gloved hand into the thorax to evenly distribute the perfusate. A perfusion circuit delivered the drug in heated peritoneal dialysate via a catheter in the pelvis, and a drain in the thorax collected the perfusate and returns it to the pump. A heat exchanger maintained the temperature of the lavage for 1 hour. A smoke evacuator was used to pull air from beneath the plastic cover

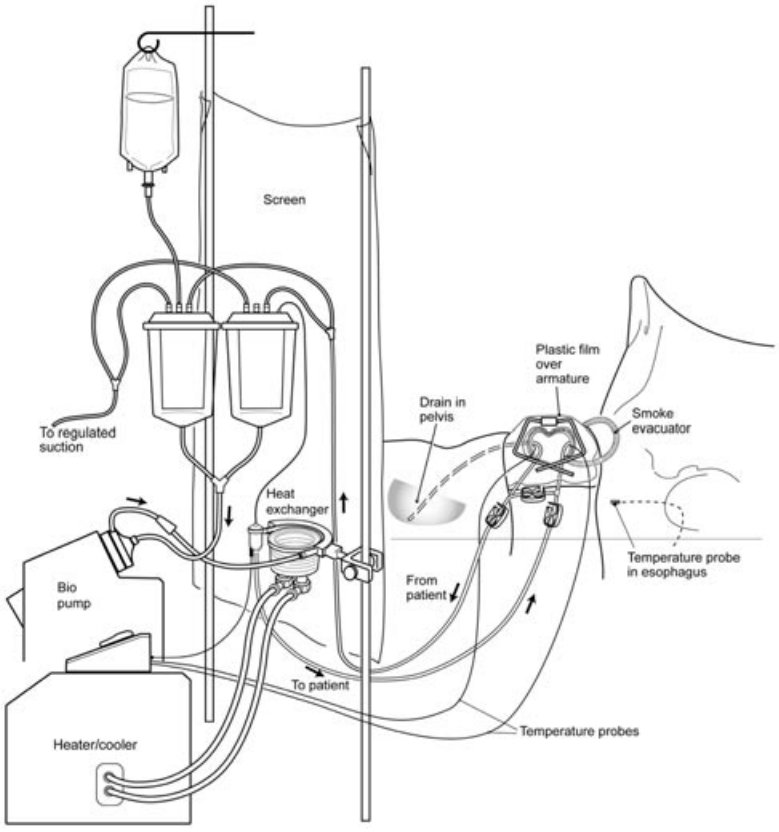

Figure 47.9. Technique of two cavity hyperthermic perfusion for malignant pleural mesothelioma (see text for details).

through activated charcoal, preventing any possible contamination of air in the operating room by chemotherapy aerosols.

Our initial circuit prototype used a roller pump. Overpressurization of the arterial tubing led to drug leakage. At the suggestion of our perfusionist, Daniel Fitzgerald, this circuit was modified to include a centrifugal pumphead.

The initial trial was a dose-escalation trial to determine the maximum tolerated dose (MTD) of heated bicavitary cisplatin. The dose started at 50 mg/m^2, and increased by 50 to 25 mg/m^2 after every three patients until two patients had an irreversible grade 1 renal toxicity. Pharmacokinetic blood and tissue specimens were collected every 10 minutes during the perfusion. Tru-Cut needle biopsies were obtained from the chest wall to determine depth of penetration.

Although final analysis of this protocol has not yet been published, preliminary observations were presented to the American Society of Clinical Oncology (ASCO) meeting in the spring of 2001. Unique aspects of this trial included the magnitude of surgery for cytoreduction (EPP), the bicavitary lavage (both abdomen and thorax), and the heating of the chemotherapy. Of the seventy patients enrolled, 50 completed the protocol. The MTD was significantly higher than in previous trials and the intrathoracic tissue levels of platinum obtained at the MTD were sixfold higher than at the commonly published dose of systemic chemotherapy. Operative mortality was 2%. Constrictive pericarditis was documented in 10% and required reoperation in 8%. Four of 50 patients had a prolonged intubation and 6% suffered grade II renal insufficiency. Grade II and grade III lymphopenia was noted in 33% and 8% of patients, respectively. Of note, 12% had technical complications including bleeding and patch failure. When compared to matched controls, there was an equivalent median length of stay of 9 days. When compared to a matched cohort of patients who underwent EPP alone, the data support the feasibility of the administration of intracavitary heated chemotherapy with comparable morbidity and mortality.

Influenced by Rusch et al (33), Roberts (39), and others, we began to offer radical pleurectomy for patients who were unsuitable for extrapleural pneumonectomy (Fig. 47.3). This included patients with a decline in their functional status and elderly patients. Furthermore, we would perform radical pleurectomy when the original operative intent had been to perform an EPP, but unresectable bulky tumor was found beyond the plane of resection. As a result, we gained experience with this operative alternative over the past decade.

Once our heated chemotherapy trial for EPP patients had been opened, and we had worked out many of the trouble spots, a second trial for pleurectomy patients was written. This also was a dose-escalation trial, but the doses were lowered for fear that there would be more intravascular absorption of the drug through the ipsilateral lung after the visceral pleurectomy.

In the spring of 2003, we presented our initial experience with intraoperative bicavitary hyperthermic cisplatin lavage at the time of radical pleurectomy for pleural mesothelioma at the meeting of the ASCO.

This was a phase I–II study that prospectively enrolled 60 patients with biopsy-proved extrapleural pneumonectomy, not considered to be candidates for extrapleural pneumonectomy. Forty-four of these patients underwent successful radical pleurectomy and a 1-hour lavage of the ipsilateral hemithorax and abdomen with dose-escalated cisplatin at 42°C. Sodium thiosulfate 16 g/m^2 was infused intravenously over 6 hours. The postoperative mortality was five of 44 (11%). The dose-limiting renal toxicity occurred at 250 mg/m^2, establishing the MTD at 225 mg/m^2. Significant cisplatinum was detected in lung and chest wall biopsies obtained at the time of lavage and was linearly related to the perfusate concentration. Interestingly, survival of these patients differed significantly depending on platinum dose. Low-dose patients (50–150 mg/m^2, $n = 9$) had a median survival of 6 months versus a median survival of 9 months for patients with middle doses (175–200 mg/m^2, $n = 8$), and a median survival of 19 months for patients treated at the MTD ($n = 23$, $p = .0017$). Neither age, preoperative forced expiratory volume in 1 second (FEV_1), nor adjuvant therapy accounted for the survival difference, suggesting that intraoperative bicavitary hypothermic cisplatin lavage may have a role to play for those unable to undergo extrapleural pneumonectomy.

The New Millennium and New Frontiers

Folate Antagonists

Despite the combined efforts of researchers throughout the world, the molecular events that ultimately led to the development of MPM still were not well understood by the year 2000. Our basic science laboratories applied screening differential display to explanted tissue samples preserved over the past decade in our tissue bank in an effort to identify how RNA expression in mesothelioma tumor cells differed from that of normal lung and pleura. These tissues were homogenized and the RNA extracted and amplified by the polymerase chain reaction. After electrophoresis, a display of bands of the gene products was displayed with the tissues lying side by side. This allowed the identification of 60 bands that were different between the tissues. One band, with 92% homology to the human α-folate receptor complementary DNA (cDNA), was highly expressed in 45 of 60 mesothelioma tissues studied.

The α-folate receptor is a glycoprotein on the cell membrane that binds folate and brings it within the cell for use in constructing the purines and pyrimidines, basic building blocks of RNA and DNA. Folate is essential for the rapidly dividing cell, and its absence may lead to megaloblastosis and premature cell death.

Other investigators had already noted that methotrexate, which is a chemotherapeutic agent that is a folate analogue and blocks folate metabolism, was one of the few agents that had a significant response to mesothelioma, a notoriously chemotherapy-resistant tumor (40). Two antifolate-based chemotherapy combinations emerged at the start of the new millennium: pemetrexed/cisplatin and raltitrexed/

cisplatin. In a phase I trial of pemetrexed/cisplatin, objective responses occurred in 5 of 11 (45%), and in a phase I trial of pemetrexed/carboplatin, responses occurred in 9 of 29 patients (31%) (40).

A phase III multinational trial randomized 456 patients with MPM to 75 mg/m^2 cisplatin with or without 500 mg/m^2 pemetrexed (41). This was the largest clinical trial ever conducted in the treatment of MPM, and the trial completed accrual in February 2001. Response rates were 41% in the pemetrexed/cisplatin arm, compared to 17% in the cisplatin arm ($p < .0001$). Median survival was significantly better when the antifolate was added (12 months vs. 9 months, $p = .02$). Pemetrexed is now marketed as Alimta by Eli Lilly, and has been approved in combination with cisplatin by the Food and Drug Administration for combination treatment of mesothelioma.

We have had the anecdotal experience of a patient who failed attempted EPP for MPM due to bulky tumor beyond the plane of resection. This patient was then treated in the Alimta/cisplatin trial at DFCI. The radiographic response was dramatic, and the patient successfully underwent EPP afterward. This experience may become a model for a multimodality treatment protocol using neoadjuvant Alimta/cisplatin for patients who appear radiographically unresectable.

Gene Ratios

Investigators at DFCI and in the Thoracic Surgery Division laboratories began to use gene microarrays to analyze mesothelioma tissues. Microarrays are cassettes that can simultaneously test for thousands of genes within a tissue sample. As an applied technique for diagnosis, however, we found it to have limited value in patient care because of the complex computational analysis required, the number of samples needed to draw statistically meaningful conclusions, the inability to independently analyze new samples without reference to additional samples, and the quantity of RNA required for such studies.

In 2002, Gordon et al (42), working within the Division of Thoracic Surgery, overcame these obstacles with the application of gene ratios. When a cell becomes neoplastically transformed (i.e., a tumor cell), changes typically occur in the expression of key genes. In simplistic terms, every cell can be thought of as expressing some benign and some malignant genes. The degree to which these genes are transcribed and subsequently translated into protein (i.e., expressed) can be quite different between normal and cancer cells.

Using a training set of 32 discarded MPM and lung adenocarcinoma samples collected in the tissue bank from 1993 to 2001, five genes were found to be highly expressed in MPM tissues and three genes were found to be highly expressed in lung adenocarcinoma (42). These eight genes can be used to express 15 pairs of ratios with an MPM-associated gene in the numerator and an adenocarcinoma gene in the denominator. Ratios >1 predict MPM and ratios <1 predict adenocarcinoma. These 15 pairs each proved to be between 91% and 98% accurate at predicting the correct histology of an additional 149 test tissue

samples. Accuracy was increased to 95% to 99% by using two or three ratios as a simple test.

The power of a gene ratio test extends beyond the ability to accurately differentiate between two tumor types. This test may be able to predict outcome in patients. To test this hypothesis, Gordon et al (43) defined two outcome groups (good and poor) based on known survival. They then used statistical methodology to correlate gene expression profiling data with survival outcomes to identify gene expression patterns that are markedly different between the two groups. From these data, they developed prognostic expression ratios that proved to be highly accurate in predicting treatment-related outcome in mesothelioma samples. A four-gene expression ratio test accurately predicted treatment-related patient outcome in mesothelioma independent of histology. This test may help stratify patients into treatment groups, which could optimize treatment strategies. It may limit the number of people who undergo radical surgery to those most likely to benefit. Finally, it may suggest a mechanistic pathway by which some tumors act more aggressively, and point the way to new therapies.

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