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Newer therapies may extend survival of some patients with malignant mesothelioma.

Malignant Pleural Mesothelioma: A Comprehensive Review

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Background: *The incidence of malignant mesothelioma continues to increase, but the disease remains difficult to detect early and treat effectively.*

Methods: *The authors review the pathogenesis, incidence, clinical presentation, diagnosis, pathology, and both standard and experimental treatments for mesothelioma.*

Results: *When possible, surgery (video-assisted thoracoscopy, pleurectomy/decortication, or extrapleural pneumonectomy) is utilized. Effects on underlying structures limit application of radiation therapy, but some systemic agents are beginning to enhance survival.*

Conclusions: *The disease is expected to increase in incidence till 2020, so awareness of this entity as a possible diagnosis should be heightened. In patients with advanced disease, several newer antitumor agents are already showing a capability of extending survival so it is not unreasonable to expect further progress in this area.*

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Submitted April 20, 2006; accepted July 10, 2006.

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Dr Simon receives honoraria from Eli Lilly and Co and Genentech, Inc. No significant relationship exists between the other authors and the companies/organizations whose products or services may be referenced in this article.

Abbreviations used in this paper: MPM = malignant pleural mesothelioma, CT = computed tomography, VATS = video-assisted thoracoscopy, P/D = pleurectomy/decortication, EPP = extrapleural pneumonectomy.

Introduction

Mesothelioma is an uncommon neoplasm arising from the mesothelial cells lining the pleura. Rarely, pleural mesothelioma is localized, benign, and readily resectable for cure. A variant of localized pleural mesothelioma is a fibrous tumor of the pleura that probably arises from a different layer of cells in the pleura, and it also is usually completely resectable. For the purposes of this review, only the more common and aggressive diffuse malignant pleural mesothelioma (MPM) will be discussed. MPM is usually associated with history of chronic asbestos exposure. Despite its relatively rare incidence, there is a great interest in this disease as it

has spawned many legal battles and consequently has led to the elimination of asbestos in all the industrial sectors, particularly in shipping and construction.

Incidence

In the United States, MPM occurs in approximately 2,500 persons per year, with nearly 200 individuals diagnosed in Florida annually, and 19% are women.¹ Almost 72,000 cases are expected to occur in the United States in the next 20 years. In Western Europe, 5,000 patients die of the disease each year. Worldwide, the incidence is increasing and it is expected to peak in the year 2020.² Nevertheless, most physicians will encounter MPM only a few times in their careers. Historically, the untreated median survival has only been 6 months, which explains the palliative approach taken by the oncologists treating patients with MPM.

Malignant mesothelioma was first recognized in 1870,³ but the link between asbestos and MPM was not discovered until 1960 in South Africa when the first convincing evidence of a link between malignant mesothelioma and both occupational and incidental asbestos exposure was reported.^{2,4} It was not until the second half of the 20th century that mesotheliomas and lung cancer were considered separate entities.² Due to the extraordinary fire-resistant properties of asbestos, this substance was widely used in the United States and Europe in an uncontrolled fashion, mostly in the shipbuilding and construction industries, between the 1940s and 1979 when the US government curtailed its use. During that time, an estimated 40% of the entire workforce, or about 27 million individuals, were exposed to asbestos. Although its industrial use was largely eliminated, asbestos is still present in countless buildings where it was commonly used as insulation and a fire retardant. Manmade and natural disasters that destroy these buildings could therefore still expose millions to asbestos. An estimated 10 million New Yorkers were possibly exposed to this carcinogen during the World Trade Center disaster on September 11, 2001, where dust laden with asbestos filled the air.

Pathogenesis

Of the two basic types of asbestos, the larger amphibole fibers are the most carcinogenic. Their greater biopersistence and higher iron content catalyze the production of reactive oxygen radicals. When inhaled, the fibers are too large to be phagocytized by pulmonary macrophages, and over the years they burrow back into the serosal surfaces of the pleura, pericardium, and peritoneum. Asbestos may lead to a variety of other conditions such as benign pleural plaques, diffuse

pleural thickening, benign pleuritis with effusion, and asbestosis. However, it is unknown why MPM occurs in the relatively few individuals within the large total population exposed to asbestos. Only 2% to 10% of individuals with heavy, prolonged asbestos exposure develop MPM. Conversely, up to 80% of MPM patients have a history of asbestos exposure.⁴

Due to the lack of asbestos exposure in some patients with MPM as well as its failure to produce the neoplasm in all exposed individuals, investigators have been looking for other etiologies or cofactors for MPM. Genetic predisposition for MPM may play a strong role, such that even minimal or apparently inconsequential asbestos exposure may lead to tumor development. An intriguing and controversial putative cofactor linked to MPM development is exposure to the tumorigenic simian vacuolating virus 40 (SV40), one of over 40 viruses that infected *Macacus monkey* kidney cells that were used to prepare early batches of live polio vaccine. SV40 viral gene sequences have been demonstrated in a variety of malignancies including certain brain cancers, sarcomas of bone, non-Hodgkin's lymphoma, and in over 50% of epithelial MPM.^{5,6} Of the estimated 62% of the 92 million US residents who received the potentially SV40-contaminated Salk polio vaccine for the 8 years it was used (1955-1963), at least one fifth may have received live, infectious SV40-containing vaccine. Despite numerous and quite compelling studies of the possible role and malignant transformation capacity of SV40 virus *in vitro* and in animal studies of MPM,⁵ epidemiologic studies of age-specific trends in the US incidence of MPM are not consistent with an etiologic effect of exposure to SV40-contaminated polio virus.⁷ Although testing for SV40 was done rigorously, not all cohorts born after 1963 were SV40-free. A major eastern European manufacturer used a procedure to deactivate SV40 that did not fully inactivate SV40 in oral poliovirus vaccine; these SV40-contaminated vaccines were produced from the early 1960s to about 1978 and were used throughout the world.⁸ This remains a highly controversial aspect of MPM etiology and pathogenesis.

Clinical Presentation

The initial clinical presentation for most patients with MPM is progressive dyspnea and/or steady chest wall pain.⁴ Dyspnea is usually the result of a large pleural effusion, and the nonpleuritic chest pain is generally caused by significant chest wall invasion. There also may be a dry cough, weight loss, fever, fatigue, or night sweats. The disease is more commonly found unilaterally (95%) located in the right chest (60%), and it occurs predominantly in men, usually presenting in the 6th through 8th decades. Eighty percent of patients will

have a definite asbestos exposure history, often with a 20- to 50-year latency between asbestos exposure and development of the malignancy. The symptoms of MPM may be insidious and nonspecific such that the time from initial presentation until diagnosis is often 3 to 6 months. Common prior occupational exposures include pipefitters, plumbers, steamfitters, heavy construction or shipbuilding industry workers, and those working aboard ships, especially in the boiler room.

Diagnosis

The physical examination and chest radiographs will demonstrate a large pleural effusion in 80% to 95% of patients with MPM.⁵ Conversely, 10% to 29% have little or no fluid. As the disease advances, there tends to be less pleural fluid present. Initially, the fluid is free flowing and layers out on decubitus chest radiographs, which may be similar in appearance to the effusion seen in heart failure, early empyema, and other benign causes. Later, as MPM progresses, the effusion becomes loculated. Localized chest pain and a palpable chest wall mass indicate chest wall invasion and nonresectability.

Computed chest tomography (CT) with contrast is a much more sensitive examination. CT scans will show the pleural effusion, the size of the lymph nodes in the hilum and mediastinum, and the presence of pleural masses, especially as the tumor tends to form a rind of tissue that encases the lung and often extending into the fissures and along the mediastinal pleura and diaphragm. Although chest wall invasion and transdiaphragmatic spread of tumor may be visible or suspected on chest CT scans, magnetic resonance imaging (MRI) of the chest with contrast, which includes coronal and sagittal views, is more sensitive in illustrating this and is especially important when a potentially curative surgery is being considered for the patient. Fig 1 illustrates some of the findings typically seen on imaging studies in MPM. Positron emission tomography (PET) may offer some additional information in the staging of MPM since it reliably detects contralateral chest involvement and extrathoracic metastases such as supraclavicular nodal disease. In some cases, it may be difficult to differentiate the primary tumor from N2 mediastinal lymph node involvement because of their close anatomic proximity.

Pleural fluid cytology may yield a definitive diagnosis of MPM in 20% to 33% of patients. A blind core

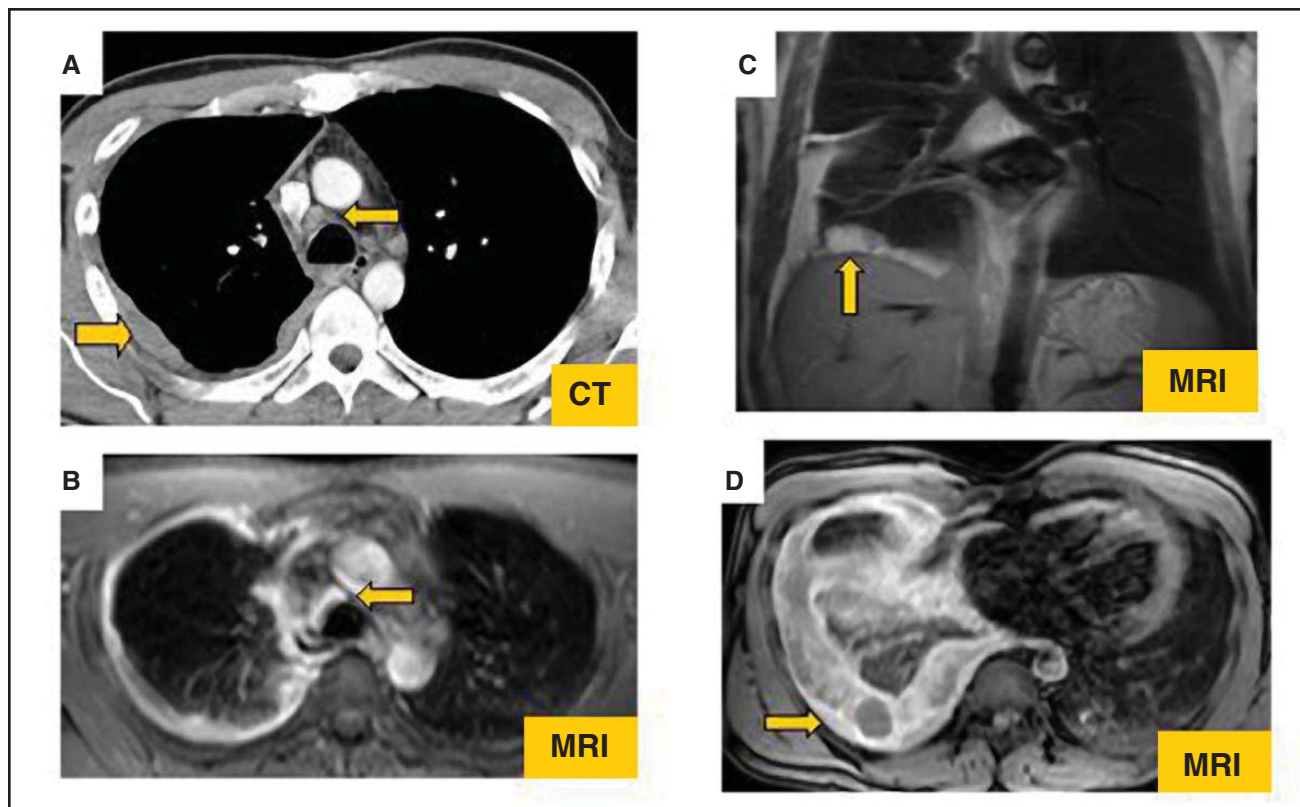


Fig 1. — Typical radiographic appearance of pleural mesothelioma. (A) Chest CT showing (small arrow) borderline enlarged right paratracheal lymph node in right-sided mesothelioma (large arrow). (B) Axial T2-weighted MR image at the same level showing (arrow) enhancement (white) of this lymph node, which was found to contain metastatic mesothelioma on mediastinoscopy. (C) Coronal T2-weighted MR image of same patient showing enhancing right-sided pleural tumor with arrow showing the sharp line of the diaphragm indicating no definite tumor invasion. (D) Axial T2-weighted MR image at the level of the heart showing (arrow) typical thick pleural tumor and some fluid pockets in right-sided MPM. Images provided courtesy of *OncoView: Current Opinions in Thoracic Oncology*, a publication of the Moffitt Cancer Center's Thoracic Oncology Program. February 2005;2(1). www.MoffittCancerCenter.org.

needle biopsy of the pleura modestly improves the yield. A CT-guided core needle biopsy of one of the pleural masses is more sensitive (87%) in making a diagnosis. Diagnostic accuracy of greater than 95% is possible using video-assisted thoracoscopy (VATS), which allows directed pleural biopsy and drainage of the effusion after breaking up loculations. Intrapleural talc, which yields the highest pleurodesis rate in MPM, can then be instilled to prevent reaccumulation of the effusion. One disadvantage of VATS in mesothelioma is the possible seeding of tumor along the surgical incisions and chest tube tracts, which ultimately results in tumor growth in the chest wall in up to 20% of patients.⁹

In addition to standard histology, special immunohistochemical stains of the biopsy tissue may be necessary to make a definitive diagnosis of MPM because of its histomorphologic similarities to adenocarcinoma. Mesothelioma is characterized by staining for calretinin in 88% and vimentin in 50% of patients. However, adenocarcinoma usually lacks these markers and instead stains positive for carcinoembryonic antigen (84%), CD15 (77%) and Ber-EP-4 (82%). A complete array of immunostains must be performed to make a reliable diagnosis. Electron microscopy, although more costly, may be needed in equivocal cases to make the distinction between the two neoplasms.

Adequate tumor tissue not only allows a definitive diagnosis but also helps to determine which of the histologic subtypes is present. Epithelial mesothelioma is the most common, is found in approximately 50% of cases, and has the best prognosis. The more aggressive sarcomatoid type is seen in 16%, and the mixed type is seen in 34%.

Recently, investigators in Australia have discovered a new serum marker called soluble mesothelin-related protein (SMRP) in 84% of patients with mesothelioma.¹⁰ This protein, which is detected with a simple blood test, may offer not only a useful diagnostic test for MPM, but also a means of monitoring treatment responses. It could also be a method for screening at-risk individuals. SMRP is elevated in only 2% of patients with other pleural diseases. A commercial SMRP tumor marker assay test kit should be available soon.

In a recently published study, serum osteopontin levels were found to be significantly higher in patients with pleural mesothelioma than in patients with exposure to asbestos or those patients who have fibrosis alone.¹¹ Immunohistochemical analysis revealed osteopontin staining of the tumor cells in 36 of 38 samples of pleural mesothelioma. This indicates that osteopontin levels may help us in the near future in early diagnoses of patients who have a known history of asbestos exposure.

Despite the ready availability of multiple diagnostic techniques with this neoplasm, a definitive diagnosis of MPM is often delayed due to a low clinical suspicion for this disease. Hence the clinician must have a high

index of suspicion, especially in a patient with a history of asbestos exposure who has a pleural effusion or atypical noncardiac chest pain to ensure that a timely diagnosis is made.

Staging

As with all malignancies, proper staging is crucial in MPM for rational treatment planning. Over the years, many staging systems have been proposed. The most widely accepted is the TNM-type system of the International Mesothelioma Interest Group (IMIG).¹² The IMIG system is the most comprehensive classification, albeit somewhat more detailed. A brief explanation of the classification follows:

Stage I includes lymph node-negative patients with minimal tumor confined to the parietal pleura (stage Ia) or with minimal visceral pleural involvement (stage Ib).

Stage II includes lymph node-negative patients with confluent superficial tumor on all pleural surfaces or involvement of the diaphragmatic muscle or lung parenchyma. Stage I and II patients have potentially resectable tumor.

Stage III is the most common presenting stage and includes patients with metastasis to hilar (N1) or ipsilateral mediastinal (N2) lymph nodes, or those with extension of tumor into the soft tissues of the chest wall, the endothoracic fascia, mediastinal fat or pericardium (T3 tumor).

Stage IV includes patients who have locally advanced tumor invading the spine or ribs, the chest wall extensively, transdiaphragmatic spread, or contralateral pleural spread. Patients with stage IV disease also may have contralateral or supraclavicular lymph node involvement (N3) or distant metastases.

Treatment

MPM does not have one widely accepted treatment modality since none reliably results in cure. Moreover, there is a striking lack of randomized, clinical trials comparing treatment regimens in this disease, due in part to the relatively low incidence of this neoplasm. Clinical series generally are either at best phase II trials of one treatment regimen or retrospective reviews of a small number of patients treated over a long period of time. Despite these shortcomings, significant improvements in therapy for MPM offer a ray of hope in this aggressive malignancy.

Surgery

Complete surgical resection is theoretically the most effective treatment. However, with the usual diffuse spread of MPM throughout the hemithorax, complete

resection of this neoplasm with histologically negative margins is rarely achieved. Hence, the term cytoreduction was coined to describe the type of resection usually employed in MPM, which results in removal of the vast bulk of the tumor, but generally at least microscopic tumor is left behind.

Three surgical procedures may be used with MPM for palliation and/or treatment: (1) VATS talc pleurodesis, (2) pleurectomy/decortication (P/D), or (3) extrapleural pneumonectomy (EPP). There are no randomized studies comparing these techniques, and results are generally found in retrospective series that often used different staging systems, further confounding comparisons.

Video-Assisted Thoracoscopy

VATS plays an important role in MPM by permitting directed biopsy to obtain diagnostic tissue. Then at the same procedure, the effusion is drained, loculations are lysed, and pleurodesis is accomplished usually with aerosolized talc. Although no cytoreduction of tumor is performed, this technique is effective in creating a pleurodesis that relieves the dyspnea caused by the commonly seen effusion in this disease. However, this procedure does not prevent the occasional patient from undergoing subsequent EPP. VATS pleurodesis by itself does not prolong survival, but it is preferred in patients with comorbidities or advanced-stage disease, who then may undergo systemic chemotherapy.

Pleurectomy/Decortication

One therapeutic surgical option that is intended to cytoreduce actual tumor burden is P/D. This procedure is performed through an open thoracotomy and consists of removing the parietal pleura including the portion over the mediastinum, pericardium, and diaphragm (often requiring removal of part of the diaphragm) and stripping off of the visceral pleura to decorticate the lung. Compared with EPP, this procedure poses some-

what less physiologic stress on the patient since it leaves the lung in place, and it has a slightly lower operative mortality rate of 1.5% to 5%.¹² Common disadvantages of P/D are the large postoperative air leak, empyema, hemorrhage, the frequent inability to remove all of the tumor from lung fissures, impairment or lack of diaphragmatic (or phrenic nerve) function, and the obvious limitation on any postoperative radiotherapy because the lung is still present. Macroscopic tumor is left in the chest at the end of the procedure almost 80% of the time.¹³ By itself, P/D provides good palliation and prevents return of a symptomatic effusion, but there is usually a high locoregional recurrence (80% to 90%),¹⁴ and generally it is not considered a potentially curative procedure.

Extrapleural Pneumonectomy

The most aggressive surgical procedure is EPP, which involves en bloc resection of the parietal and visceral pleura along with the involved lung, mediastinal lymph nodes, diaphragm, and pericardium. The diaphragm and pericardium are then reconstructed with Gortex or Marlex mesh. Although this procedure has a profound physiologic impact on the patient since the lung is removed, it may be performed in experienced centers with less than a 5% mortality.^{12,15} This is the most complete cytoreductive procedure and essentially the only procedure with which long-term survivorship is seen.

Selection of the appropriate subset of patients for EPP is crucial. Table 1 lists the patient selection criteria used at our institution for EPP. Aside from the obvious selection criteria listed, prior coronary bypass grafting usually precludes performing an EPP since at least one bypass graft on either side is usually located out in the pleural cavity encased by tumor, and the tumor cannot be separated from the graft. Patients with nonepithelial-type mesothelioma have an aggressive tumor that EPP does not control. Chest wall pain usually is found where there is unresectable tumor deeply invading the chest wall. Prior pleurectomy generally precludes the technical performance of EPP since any potential resection planes are obliterated and only an incomplete resection is possible. In the patient population seen at our institution, only approximately 10% to 15% of all MPM patients seen may qualify for EPP. In view of the documented lack of survival benefit of cytoreductive surgery in patients with metastases to often normalized mediastinal nodes in MPM,¹⁴ we favor routine mediastinoscopy in all patients considered for EPP.

Radiotherapy

Unlike most tumors, MPM grows as a diffuse sheet of tumor throughout the pleural cavity, enveloping the lung. As a result, it is difficult to deliver to the entire neoplasm the radiotherapy needed to be tumoricidal (>60Gy) because of the limitations on dose to the underlying structures (lung 20 Gy, liver 30 Gy, spinal

Table 1. — Patient Selection Criteria for EPP

<p>ECOG performance status 0–1.</p> <p>Stage I or II (rarely stage III) mesothelioma (International Mesothelioma Interest Group staging system).</p> <p>No prior coronary bypass surgery.</p> <p>Cardiac ejection fraction >45%, and no significant cardiac arrhythmias or dysfunction.</p> <p>Adequate pulmonary function to tolerate a pneumonectomy.</p> <p>No significant renal or liver disease or other comorbidities.</p> <p>Minimal or no chest wall pain.</p> <p>Epithelial subtype mesothelioma.</p> <p>No prior pleurectomy (but VATS talc pleurodesis does not disqualify the patient).</p>
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cord 45 Gy, heart 45 Gy, and esophagus 45-50 Gy). Radiation pneumonitis, myelitis, and hepatitis have been well described in early series attempting primary treatment with whole chest radiotherapy. Some recent reports have shown promise for the use of the more complex technique of intensity-modulated radiothera-

py (IMRT) to treat the unresected tumor.¹⁶ This conformal technique requires three-dimensional treatment planning that delivers a homogeneous dose to the tumor with good protection of organs at risk.

Currently, radiotherapy in MPM is used effectively to treat localized chest wall recurrences such as those

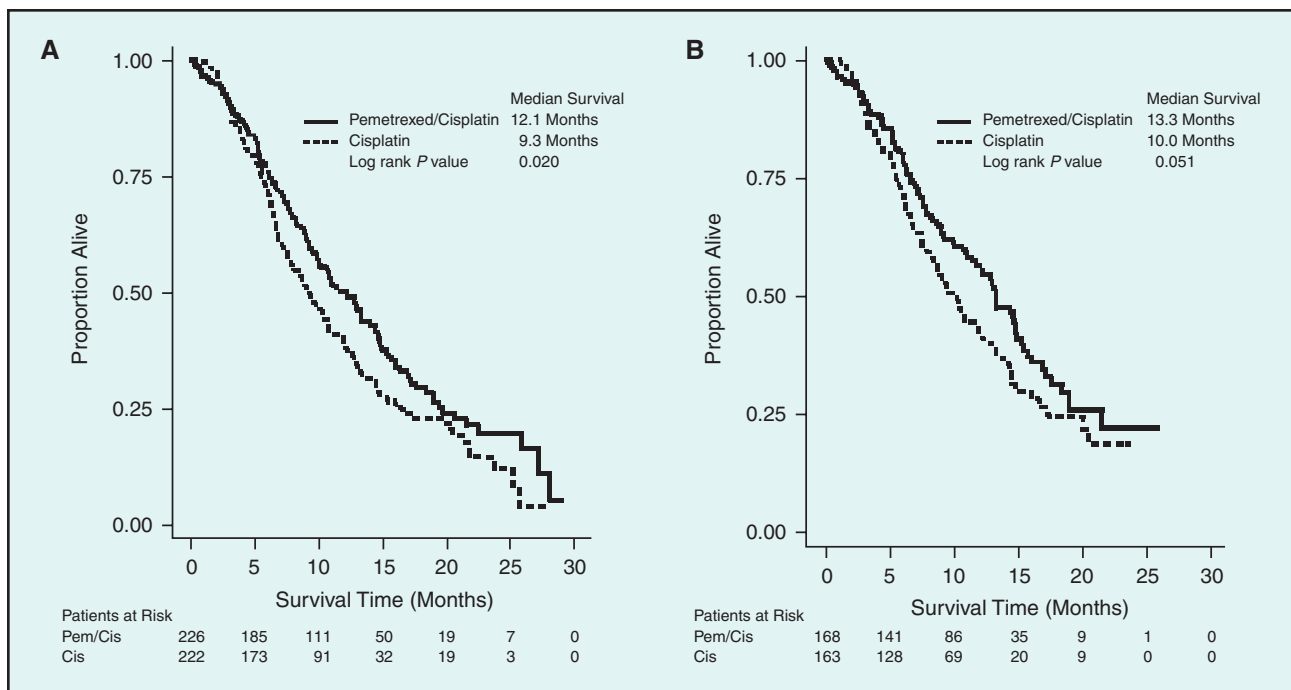


Fig 2. — Kaplan-Meier estimates of overall survival time for all patients (A) and for fully supplemented patients (B). From Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003;21:2636-2644. Reprinted with permission from the American Society of Clinical Oncology.

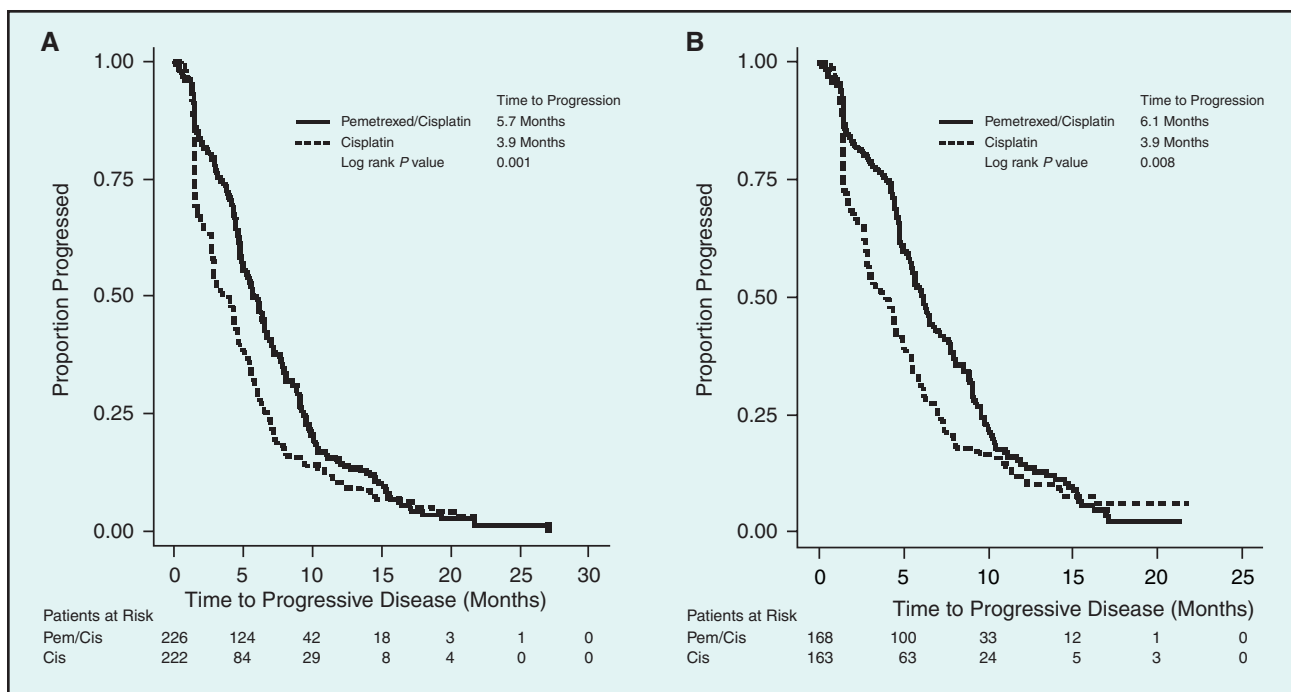


Fig 3. — Kaplan-Meier estimates of time to progressive disease for all patients (A) and for fully supplemented patients (B). From Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003;21:2636-2644. Reprinted with permission from the American Society of Clinical Oncology.

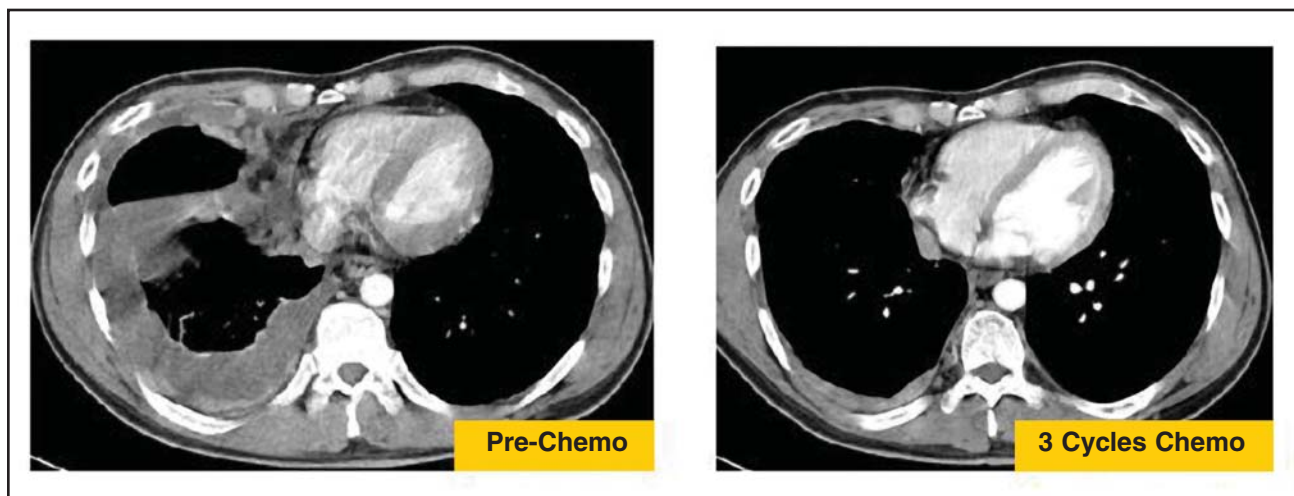


Fig 4. — Effect of chemotherapy (3 cycles of cisplatin/pemetrexed) on T2N2 epithelial pleural mesothelioma. Chest CT at level of cardiac ventricles. Images provided courtesy of *OncoView: Current Opinions in Thoracic Oncology*, a publication of the Moffitt Cancer Center's Thoracic Oncology Program. February 2005;2(1). www.MoffittCancerCenter.org.

seen occasionally in a chest tube tract or surgical wound tumor implantation. Some groups employ hemithoracic adjuvant radiotherapy, after EPP, for treatment of the entire resected hemithorax or for treatment of known residual localized unresected tumor. Although adjuvant radiotherapy along with chemotherapy is used by some groups after radical EPP, there are no randomized studies that show that radiotherapy adds any value to just adjuvant chemotherapy alone in the setting of a fully resected tumor.

Chemotherapy

The role of chemotherapy in MPM is now established beyond any ambiguity. The recently reported phase III trial of cisplatin plus pemetrexed¹⁷ demonstrated a statistically significant survival advantage (12.1 months) for the combination vs cisplatin alone (9.3 months) in all eligible patients. The study was initially started without vitamin supplementation. Vitamin supplementation was initiated after chemotherapy-related deaths occurred in the pemetrexed arm. Fig 2 shows the overall survival curves of all patients and for those patients in whom full vitamin supplementation was instituted. Fig 3 shows the Kaplan-Meier estimates of time to progressive disease for all patients and for fully supplemented patients.

Additionally, there was statistically significant improvement in response rate for the doublet (41% vs 17%; $P < .0001$), improvement in lung function by the sixth cycle ($P = .006$), improvement in dyspnea by the sixth cycle ($P = .004$), and improvement in pain by the fourth cycle ($P = .017$). Based on these data, cisplatin in combination with pemetrexed is the currently accepted first-line treatment for MPM.¹⁷ Fig 4 depicts a chest CT of a patient treated with cisplatin and pemetrexed at our institution who continues to be progression-free 3 years after the initial diagnosis.

Other drugs have also shown activity in MPM. Table 2 outlines the single-agent efficacy of agents active in MPM, and Table 3 outlines studies using the most popular cisplatin combinations. Data from studies using some of the newer agents are presented in Table 4, showing that response rates with some of these targeted agents have been singularly disappointing.

Patients with MPM have some of the highest vascular endothelial growth factor (VEGF) levels compared to most solid tumors. Bevacizumab is a recombinant humanized monoclonal antibody to VEGF. Compounds targeting VEGF have demonstrated promise in MPM and therefore are being evaluated in several clinical trials.⁹

Currently, a multicenter, double-blind, placebo-controlled, randomized trial¹⁸ is looking at bevacizumab in

Table 2. — Response Rate of Mesothelioma to Available Chemotherapeutic Agents

Drug	Total No. of Patients	No. of Studies	Response Rate
Doxorubicin	69	2	12%
Liposomal doxorubicin	109	3	5%
Epirubicin	69	2	12%
Gemcitabine	60	3	12%
Cisplatin	73	3	18%
Carboplatin	88	3	11%
Vinorelbine	29	1	24%
Paclitaxel	60	2	5%
Ifosfamide	83	3	8%
Docetaxel	41	2	15%
Methotrexate	78	3	41%
Trimetrexate	52	1	12%
Edatrexate	20	1	25%
Edatrexate/leucovorin	40	1	16%
Pemetrexed	64	1	14%

Table 3. — Malignant Pleural Mesothelioma Treated With Combination Chemotherapy

Regimen	No. of Studies	% Responders (Range)	Survival Range (Mos)
Doxorubicin + cisplatin	5	14–46	8.8–2.3
Cisplatin + gemcitabine	4	9–48	10–10.3 40%–53% (1-yr)

combination with gemcitabine and cisplatin. The safety analysis done so far does not show any significant increase in toxicities in the bevacizumab arm. Response and survival data are anxiously awaited. As pemetrexed and cisplatin demonstrated a survival advantage over cisplatin alone, we are currently conducting a phase II trial where bevacizumab is being added to cisplatin and pemetrexed.

There are no standard second-line treatment options for the treatment of advanced MPM. Typically, one of the agents listed in Table 1 is used as a second-line treatment. The most commonly used second-line treatments are gemcitabine, vinorelbine, doxorubicin, and irinotecan (CPT-11). Ranpirnase (Onconase), an antitumor ribonuclease, is a novel agent under active investigation in the second-line treatment of MPM. Used as a single agent at 480 µg/m² intravenously weekly, ranpirnase demonstrated prolonged periods of stable disease in phase II trials and a potential survival benefit, compared with doxorubicin, in a small unpublished phase III trial.^{19,20} In all clinical studies, it has generally demonstrated a favorable safety profile except for easily controlled allergic reactions and dose modifications for renal impairment. At present, a phase III trial of doxorubicin with or without ranpirnase is nearing completion in patients with MPM without prior chemotherapy or one prior chemotherapy regimen. Results of this trial are anxiously awaited.

Multimodality Therapy

Due to the failure of any single modality of treatment to significantly affect long-term survival, a variety of combinations of therapy, usually involving cytoreduc-

tive surgery (P/D or EPP), have been used to treat MPM. Unfortunately, most reports are retrospective case series so results are difficult to compare objectively.

The most well-known and largest series comes from the Brigham and Women's Hospital, involving EPP followed by chemoradiation.¹⁵ In 137 patients treated in a 17-year period beginning in 1980, the mortality rate of EPP was 3.8% (morbidity 50%), with adjuvant chemotherapy using varying regimens given beginning 4 to 6 weeks after surgery, then followed by hemithoracic radiation (30 to 40 Gy). The median survival was 19 months, and 2-year and 5-year survival rates were 38% and 15%, respectively. In the subset with epithelial histology and negative nodes with complete resection, the 5-year survival rate was 46%. Locoregional recurrence was the predominant mode of failure in most patients despite intensive local treatment with surgery and radiotherapy.

Nevertheless, other series with EPP and systemic chemotherapy or EPP and adjuvant radiotherapy have shown median survivals similar to the Brigham series, also with better results occurring in the subset of node-negative epithelial tumors. With complete macroscopic tumor resection, there are no convincing data to suggest that employing two adjuvant modalities (with the increased toxicity) improves results more than using one.¹²

Phase I reports of other multimodality approaches include radical P/D with intraoperative radiotherapy and conformal radiotherapy and, in some patients, adjuvant chemotherapy. In a small, highly selected series of 32 patients, there was a 6.3% mortality rate and an 18-month median survival; most treatment failures were locoregional.^{21,22}

Cytoreductive surgery with intraoperative photodynamic therapy (PDT) has been studied in several centers. The use of intraoperative intrapleural chemotherapy has been reported in several small series including hyperthermic (40–41°C) perfusion, most with cisplatin. This modality appears feasible, albeit with significantly increased morbidity, but currently there is no documented survival benefit of this technique.^{12,15,22}

Table 4. — Recent Phase II Trials of New Agents in Mesothelioma

Chemotherapy/Group	No. Patients (Yr Published)	Response Rate (%)	Survival (mos)
Imatinib/Chicago	17 (2004)	0	12+ (all with prior chemotherapy)
Erlotinib/SWOG	64 (2004)	0	7.0
Gefitinib/CALGB	43 (2003)	2	5.0
Capecitabine/CALGB	26 (2004)	4	4.9
Thalidomide/Amsterdam	31 (2001)	0	N/A
Vatalanib(PTK 787)/CALGB	40 (ongoing)	N/A	N/A

Conclusions

Malignant mesothelioma continues to be a difficult disease to treat. Maintaining a high index of suspicion may result in an earlier diagnosis and a more successful treatment outcome. The overall outlook for the treatment of this disease has improved with the emergence of newer therapies. Several new agents are currently under active investigation and hold promise to further improve treatment outcomes. Results of currently ongoing clinical trials are anxiously awaited. In fact, survival for patients with MPM is now generally greater than for patients with advanced non-small cell lung cancer.

As with any rare disease, referral of the patient to a center with extensive experience and expertise in this disease is recommended to enhance the probability of accruing such patients to clinical trials.

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