

Current Concepts in the Evaluation and Treatment of Patients With Diffuse Malignant Peritoneal Mesothelioma

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Key Words

Peritoneal mesothelioma, cytoreduction, intraperitoneal chemotherapy

Abstract

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare and ultimately fatal cancer that was first recognized and described a century ago. It is a diffuse primary malignant condition arising from the mesothelial lining of the peritoneum, and its natural history is hallmarked by a propensity to progress almost exclusively within the abdominal cavity throughout the entire course of disease. Patients afflicted with DMPM most commonly present with nonspecific abdominal symptoms that lead to diagnosis when the condition is relatively advanced. Historically, median overall survival for patients with DMPM without treatment is very short, averaging 6 months. Systemic chemotherapy using gemtuzumab and cisplatin has an overall response rate of approximately 25% and a median overall survival of approximately 1 year. Many institutional reports have shown that in selected patients, operative cytoreduction and hyperthermic intraoperative peritoneal chemotherapy using cisplatin or mitomycin C is associated with long-term survival. Recent studies on the molecular biology of DMPM have yielded new insights relating to the potentially important role of the phosphatidylinositol 3-kinase/mammalian target of rapamycin and epidermal growth factor receptor pathways in this disease, which may translate into new therapeutic options for patients with DMPM. (*JNCCN* 2012;10:49–57)

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare cancer that is ultimately fatal in all afflicted individuals. DMPM represents only 15% to 20% of all mesothelioma diagnoses, with most being the pleural variant. Approximately 400 new cases of DMPM are diagnosed annually in the United States, with men and women having an equal incidence of the disease.^{1,2} Several risk factors have been implicated in the development of DMPM. Data indicating a strong association between asbestos exposure and the development of disease have been available for decades.³ Although the risk of peritoneal mesothelioma attributed to asbestos exposure may differ between the sexes, these differences may be from misclassification of exposure in women.⁴ Other factors found to be associated with peritoneal mesothelioma development are previous abdominal radiation and the mineral erionite.^{5,6} Less substantiated and more controversial putative risk factors include a diet low in vegetable consumption, and simian virus 40 infection from contaminated polio vaccines.^{7,8}

The first convincing description of DMPM as a distinct clinical entity representing a diffuse primary malignant process of the peritoneal serosa was provided more than 100 years ago. In 1908, Miller and Wynn⁹ published what is widely believed to be the first documented case of DMPM. In their report, a 32-year-old male miller who presented with abdominal pain and ascites was noted to have an extensive and diffuse intraperitoneal neoplastic process that was not amenable to resection at surgical exploration. He was treated palliatively and succumbed to disease 1 year later. A review of the literature 50 years later found only 13 pathologically confirmed cases of DMPM.¹⁰ However, after that detailed description of the tumor's pathologic features, a marked increase occurred in the number of documented cases in the medical literature, accompanied by an initial

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understanding of the risk factors and clinical features of the condition. From 1960 until the publication of Moertel's widely acclaimed review of the subject in 1972, at least 169 cases were documented in the literature.¹¹ Despite the initial description of DMPM in the early 20th century, results of clinical trials and treatment strategies specifically for patients with DMPM were not reported until the end of the century.

Diagnosis and Extent of Disease Evaluation

Patients with DMPM usually present with nonspecific signs and symptoms that unfortunately lead to a diagnosis of the disease when it is in an advanced stage. The peak age interval for patients at initial presentation is between 40 and 65 years, although it can be diagnosed in teenagers and elderly patients.¹¹ The most common presenting symptoms are abdominal pain and increasing abdominal girth, the latter of which may be caused by ascites.^{12,13} Weight loss and fever are other less-common presenting symptoms.^{12,13} In some series, a palpable abdominal mass has been described on examination.^{12,14,15} Serum laboratory studies may reveal an elevated cancer antigen 125; however, this marker alone is not diagnostic and is typically best used to monitor for disease recurrence or progression.^{11,16} Worsening abdominal symptoms correspond to the natural history of DMPM, because it typically remains confined to the abdominal cavity with spread to the pleura (via direct extension or transdiaphragmatic lymphatics) occurring only at advanced stages in some patients.^{11,15,17} Consequently, morbidity and mortality from DMPM occurs from regional disease progression secondary to progressive intestinal obstruction and cachexia.^{17,18} The median survival in untreated patients is approximately 6 months after diagnosis.¹⁹

The diagnosis of DMPM should be considered in any individual with evidence of a diffuse malignant process in the abdomen on initial clinical evaluation, and can usually be established based on diagnostic imaging with CT scans and tissue biopsy with appropriate immunohistochemical staining. Although CT scan is the diagnostic imaging most commonly used, MRI using specific acquisition protocols may be increasingly used in the future.²⁰ The role of PET or PET/CT is currently unclear.²¹ Findings that are consistent with DMPM on CT scan include pervasive thickening of the peritoneum or mesentery in an irregular or nodular fashion, focal intraperitoneal masses, omental thickening with masses, and ascites.²² Yan et al.²³ described 3 constellations of findings on CT that are associated with an increasing likelihood of encountering disease that is not amenable to complete gross surgical resection. The most favorable findings are when the anatomy of the small bowel and its mesentery are minimally distorted, and the most unfavorable findings are when gross nodular thickening of the peritoneal surfaces is present with marked distortion of the normal architecture of the bowel (Figure 1). Intermediate CT findings include an imageable layer of tumor on the small bowel and its mesentery. CT findings consistent with bowel obstruction are very ominous.²³ CT scan is important not only to assess the extent of disease and assist in treatment planning but also to illustrate findings that distinguish DMPM from other peritoneal malignancies, whether primary or secondary. Two related primary malignancies of the peritoneum with distinctive characteristics on CT are well-differentiated papillary mesothelioma and multicystic mesothelioma.²⁴ These tumors are important to distinguish from DMPM because their treatment strategy is primarily surgical and their clinical course is largely benign.^{25,26}

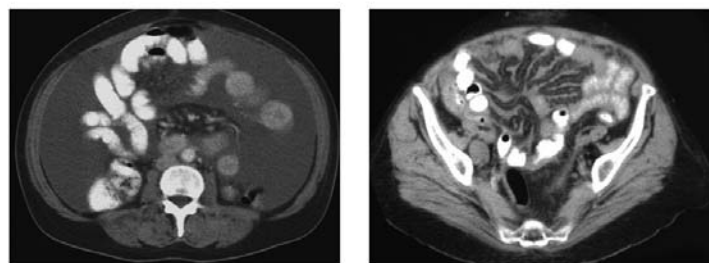


Figure 1 CT scan showing 2 different radiographic findings in patients with diffuse malignant peritoneal mesothelioma. The left panel shows ascites and minimal nodular thickening of the peritoneum, whereas the right panel shows no ascites and irregularity of the small bowel mesentery.

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Peritoneal dissemination from stomach, pancreas, colon, and ovarian neoplasms are secondary peritoneal malignancies that also must be differentiated from DMPM. Upper and lower endoscopy should be performed as clinically indicated.

Tumor immunohistochemistry is critical for the definitive diagnosis of DMPM. Tumor specimens may be obtained through diagnostic laparoscopy or CT-guided biopsy; diagnostic laparoscopy has the added advantage of enabling direct visualization of tumor burden and, consequently, identification of patients whose disease is amenable to operative intervention.²¹ Abdominal paracentesis may be diagnostic; however, usually only scant numbers of malignant cells are present in ascites for diagnosis.¹³ The 3 histologic subtypes of DMPM are epithelioid, sarcomatous, and the mixed/biphasic type. The epithelioid subtype is the most common and associated with the best prognosis (Figure 2).^{27,28}

To establish the diagnosis of DMPM, a panel of immunohistochemical antibodies is used. Antibodies that stain positive in DMPM and are most commonly used are calretinin, cytokeratin 5/6, and vimentin, whereas epithelial membrane antigen and Wilms tumor 1 are antibodies that are less commonly used. Antibodies that stain negative include CEA, B 72.3, MOC-31, and Ber-EP4.^{29,13} These immunohistochemical markers rarely stain consistently as positive or negative; therefore, using at least 2 mesothelioma markers and 2 carcinoma markers is recommended when establishing the diagnosis of DMPM.²⁹ If immunohistochemical staining is equivocal, electron microscopy may then be used to establish the diagnosis. This diagnostic approach is typically available only at centers with expertise in diagnosing DMPM. Electron microscopy is most beneficial for well- to moderately differentiated epithelioid tumors that show features typical of mesothelial cells, such as long, thin microvilli and the presence of a basal lamina.²⁹

Systemic Therapy

Because of the rarity of this disease, a limited number of clinical trials are evaluating systemic chemotherapy specifically for patients with DMPM. Chemotherapeutic regimens were originally derived from those developed for patients with pleural mesothelioma.³⁰ One of the earliest studies evaluating systemic chemotherapy specifically for patients with DMPM was published by Antman et al.¹² in 1983.

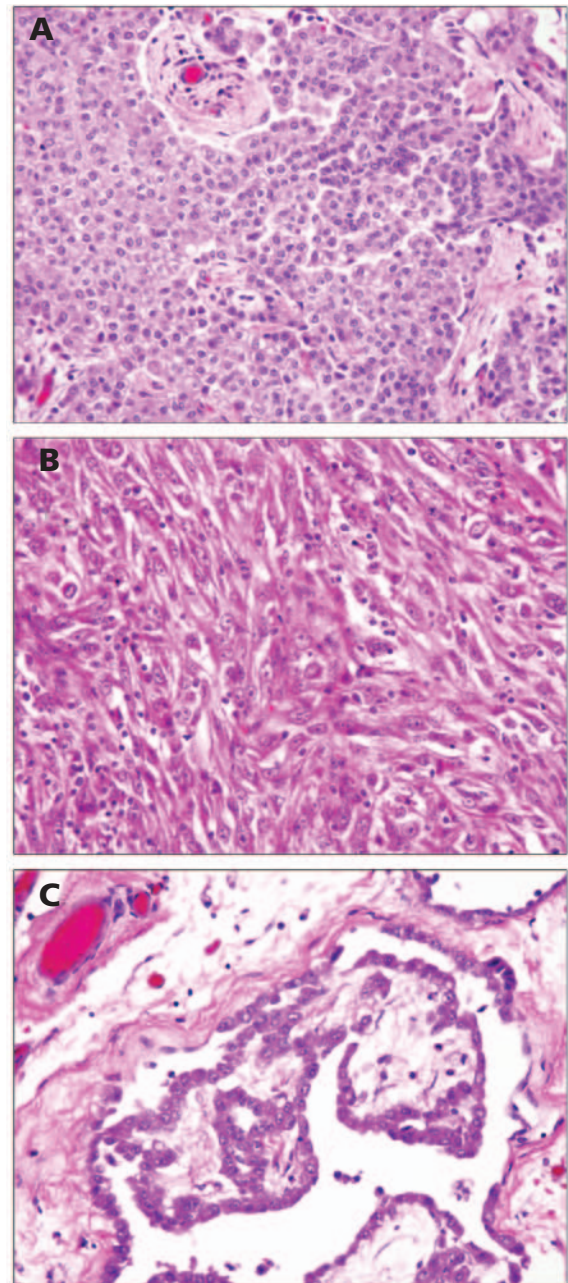


Figure 2 Light micrographs showing examples of the various types of histology that can be observed in diffuse malignant peritoneal mesothelioma, including epithelioid (A), sarcomatoid (B), and tubulopapillary (C) forms of the condition.

In this study, 18 chemotherapy-naïve patients with DMPM were treated with a doxorubicin-containing regimen; 14 had measurable or evaluable disease, 6 of whom (43%) had a measurable response. The median survival in these 6 patients was 22 months, whereas survival for the remaining 8 patients who had stable or progressive disease was 5 months. Un-

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fortunately, despite its clinical benefit, these doxorubicin-containing regimens were associated with significant toxicity.

Over the ensuing 20 years, a paucity of studies evaluated the role of systemic chemotherapy in patients with DMPM; however, in the past decade, 2 phase II studies evaluating the efficacy of pemetrexed-based chemotherapeutic regimens in patients with DMPM were published. After a phase III trial in patients with pleural mesothelioma showed that treatment with pemetrexed and cisplatin improved survival over cisplatin alone, but before the compound received FDA approval, pemetrexed was provided to patients with pleural mesothelioma who were not eligible for the phase III study and to patients with DMPM.³¹ In 2005, Jänne et al.³² reported the tumor response and safety data for 98 patients with surgically unresectable DMPM who received a chemotherapeutic regimen of pemetrexed alone or in combination with cisplatin as part of this expanded access program. The overall disease control rate in 73 patients evaluable for response (complete response + partial response + stable disease) was 71.2%. The median survival for all patients who received pemetrexed alone was 8.7 months, compared with 13.1 months for patients who received the combination regimen (Table 1). Although the disease control rate between the pemetrexed and pemetrexed/cisplatin groups was similar in chemotherapy-naïve patients, the overall response rate for patients who received the combination regimen was 28% versus 0% for 3 patients who received pemetrexed only; all complete responders were in the combination chemotherapy group (Table 1). Because the median survival in chemotherapy-naïve patients given combination pemetrexed and cisplatin had not been reached at the time the study was published and due to the favorable safety profile of the regimen, pemetrexed with cisplatin has been widely adopted as the preferred initial

chemotherapeutic regimen for patients with DMPM with surgically unresectable disease. In previously treated patients, pemetrexed alone or in combination with cisplatin had similar disease control and overall response rates (including no complete responders in both groups), suggesting either regimen may be used beyond first-line chemotherapy.

The results of a second phase II trial that evaluated the efficacy of pemetrexed and gemcitabine in surgically unresectable and chemotherapy-naïve patients with DMPM was published in 2008.³³ Patients received this combination regimen for 6 cycles or until disease progression. The median overall survival of all patients was 26.8 months, with an estimated 1-year survival rate of 67.5%. The median time to disease progression was 10.4 months, and the rate of disease control was 67% in evaluable patients (50% overall). Unfortunately, the toxicity associated with this regimen was significant; 25% of patients did not finish the planned course of therapy and one treatment-related death occurred. Both this study and that by Jänne et al.³² show that pemetrexed, whether in combination with gemcitabine or cisplatin, imparts an improvement in survival over untreated historical controls. [Combination pemetrexed and gemcitabine is a reasonable regimen for patients who cannot tolerate cisplatin (Table 1).³³]

Operative Cytoreduction and Regional Chemotherapy

DMPM typically remains localized to the abdominal cavity, with spread to the pleura (via direct extension or transdiaphragmatic lymphatics) occurring rarely and only at advanced stages of disease.^{11,15,17} Based on this natural history, operative strategies designed to control disease progression within the abdominal cavity have been developed and increasingly used over

Table 1 Pemetrexed Alone Versus With Cisplatin or Gemcitabine

	Group	N	CR	PR	SD
Jänne et al. ³²	All	73	4 (5.5%)	15 (20.5%)	33 (45.2%)
	Previously treated	43	0	10 (23.3%)	21 (48.8%)
	Chemotherapy-naïve	28	3 (10.7%)	4 (14.3%)	12 (42.9%)
	Pemetrexed alone	26	0	5 (19.2%)	14 (53.8%)
	Pemetrexed/cisplatin	47	4 (8.5%)	10 (21.3%)	19 (40.4%)
Simon et al. ³³	Pemetrexed/gemcitabine	15	0	3 (20%)	7 (47%)

Abbreviations: CR, complete response; N, number of patients evaluable for response; PR, partial response; SD, stable disease.

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the past 20 years. Currently, cytoreductive surgery (CRS) together with hyperthermic intraperitoneal chemotherapy (HIPEC), usually with mitomycin C or cisplatin, has been largely established as the best initial therapeutic intervention in selected patients with DMPM.

The intent of operation with CRS and HIPEC is to remove all gross disease and address any remaining microscopic disease through the application of regional chemotherapy. During cytoreduction, large tumors within the abdomen and pelvis are removed via peritonectomy or visceral organ resection if necessary, whereas smaller tumor implants on the mesentery or solid organ surfaces are ablated using argon beam or other types of electrofulguration. Because CT scan usually underestimates the true extent of disease in the abdominal cavity, the extent of disease is assessed at initial exploration using a peritoneal cancer index (PCI), as initially proposed by Sugarbaker et al.¹³ The abdominal cavity is divided into a grid of 9 squares and the small bowel mesentery is separated into 4 quadrants; each grid or quadrant is scored, based on disease burden, on a scale of 0 (no gross disease) to 3 (extensive disease). Therefore, the extent of disease can range from 0 to 39; patients with a PCI of greater than 30 are generally thought to have a low likelihood of having a complete gross cytoreduction. After the cytoreduction, a completeness of cytoreduction score (CCR) is then assigned. A CCR of 0 signifies that no gross disease remains after CRS, whereas a score of 1 indicates that tumor nodules remain but are all 2.5 mm or less in diameter. Residual disease that is greater than 2.5 mm in diameter is assigned a CCR of 3 or 4 depending on the size and extent of the tumor left behind. Cytoreduction is considered to be therapeutic when a CCR of 0 or 1 is obtained, and has been shown to be independently associated with improved survival in several studies.^{34–36}

After a therapeutic CRS is obtained, HIPEC is performed, during which a chemotherapeutic agent, typically mitomycin C or cisplatin, is circulated throughout the abdominal cavity under hyperthermic conditions for 90 to 120 minutes.³⁷ Large catheters and temperature probes are placed within the abdominal cavity, which is then closed temporarily, and the catheters are connected to a closed extracorporeal circuit consisting of a roller pump, heat exchanger, and reservoir bag. Perfusate volumes of 3 to 6 L are used and circulated at a rate of 1 to 1.5 L/min to ensure uniform warming of

the peritoneal cavity. During perfusion the abdomen is gently manipulated to minimize any streaming effect of the perfusate from the inflow to the outflow catheter. At the completion of treatment, the perfusate is drained from the abdominal cavity. Although Chua et al.³⁸ report their institutional experience using cisplatin and doxorubicin during HIPEC in patients with DMPM, conclusions regarding the efficacy of these agents are difficult to draw because of the limited number of patients (n = 20). Recent data from Wake Forest University comparing mitomycin C with cisplatin as the chemotherapeutic agent during HIPEC suggest that patients perfused with cisplatin may have better overall survival compared with those treated with mitomycin C. However, interpretation of these results is limited because of the retrospective nature of the analysis and the small numbers of patients in the study (N = 34).³⁹

Only patients with a good performance status and who have disease that seems amenable to complete gross cytoreduction through radiologic evaluation or intraoperative assessment should be offered this approach. Relative contraindications to CRS and HIPEC are evidence of disease outside the peritoneal cavity, poor performance status, and severe cardiac, pulmonary, hepatic, or renal dysfunction. For patients who are not surgical candidates, systemic chemotherapy should be offered with pemetrexed in combination with cisplatin or gemcitabine. Systemic chemotherapy can be administered either as definitive treatment or in a neoadjuvant context to reduce disease burden to a level that can be treated surgically. The reported complication rates associated with CRS and HIPEC range from 15% to 31%. Common complications include intestinal fistula, postoperative bleeding, pulmonary embolism, wound infection, and catheter-related sepsis.^{27,34,40} Immunosuppression and electrolyte abnormalities are complications related specifically to intraperitoneal chemotherapy administration, but are uncommon.⁴¹ Mortality rates after CRS and HIPEC are between 0% and 7%.^{13,27,36,40,42}

Survival data for patients with DMPM undergoing CRS and HIPEC have largely been from single-institution reviews. The rarity of this disease, and the lack of a standard treatment regimen against which CRS and HIPEC should be compared, make a randomized controlled clinical trial exceedingly difficult to conduct. However, despite the absence of randomized controlled studies showing the benefit of this approach, many in the oncology community have adopted CRS

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and HIPEC as standard care for patients with DMPM based on single-institution studies that consistently show increased survival associated with this approach compared with systemic chemotherapy alone or in conjunction with palliative surgery. The overall median survival for patients treated with CRS and HIPEC ranges from 34.2 to 92 months in these studies (Table 2).^{27,36,42,43}

A multi-institutional registry was published recently combining retrospective data on 405 patients with DMPM treated with CRS and HIPEC at 29 clinical centers worldwide.³⁴ A variety of intraperitoneal chemotherapeutic agents were used during HIPEC, including cisplatin, mitomycin C, and doxorubicin. The median actuarial overall survival was 53 months, with 1-, 3-, and 5-year survival rates of 81%, 60%, and 47%, respectively. Prognostic factors that were shown to be independently associated with improved survival on multivariate analysis were epithelioid subtype, absence of lymph node metastasis, a CCR of 0 or 1, and the use of HIPEC.

In 2003, Feldman et al.²⁷ reported on a single-center study from the NCI on 49 patients with DMPM who underwent CRS and HIPEC with cisplatin. Thirty-five patients were also treated with a single intraperitoneal dose of fluorouracil and paclitaxel on postoperative days 7 to 10. The median progression-free survival was 17 months and the median actuarial overall survival was 92 months (Figure 3). The clinical or treatment parameters that were independent factors associated with prolonged survival were age of 60 years

or younger and complete or near-complete cytoreduction. The pathologic parameters associated with favorable outcome was absence of deep tissue invasion and a history of previous cytoreduction procedure. These factors most likely represent surrogates for favorable tumor biology (Figure 4). The results from both this study and the multi-institutional registry show that the use of CRS and HIPEC is associated with long-term outcome in selected patients with DMPM.

Future Directions

Recent studies have established a possible role of phosphatidylinositol-3 kinase and mammalian target of rapamycin (PI3K/mTOR) signaling pathways and mutations in the epidermal growth factor receptor (EGFR) in the malignant phenotype of DMPM.^{44,45} In the first study, a gene expression analysis on 41 tumor samples was performed to identify potentially important genes and pathways in DMPM. Unsupervised hierarchical clustering of genes revealed 2 distinct gene expression patterns among the tumor samples that corresponded significantly to patient survival. The investigators showed that patients with poor survival had tumors with significantly higher expression of the genes of PI3K/mTOR signaling. The study also showed that epithelioid histology was associated with a better prognosis. When the PI3K/mTOR pathways were inhibited in mesothelioma cell lines in vitro using a dual PI3K/

Table 2 Results of Selected Institutional Series of Cytoreduction and Intraperitoneal Hyperthermic Chemotherapy

Center	N	Optimal Cytoreduction	HIPEC Agents	Overall Survival	Prognostic Factors
Centre Hospitalie Lyon Sud ⁴²	15	11	Cisplatin and MMC	Median, 36 m	Optimal resection, stage at treatment
NCI, Milan ³⁵	49	43	Cisplatin plus MMC or doxorubicin	5-y, 57%	Optimal resection, mitotic count
Columbia-Presbyterian, NY ⁴⁸	27	–	Cisplatin and MMC	Median, 68 m	
Wake Forest, NC ⁴³	12	5	MMC	Median, 34 m	
Washington Hospital Center ¹³	68	41	Cisplatin and doxorubicin	Median, 67 m	Optimal resection, female sex
NCI, Bethesda ²⁷	49	43	Cisplatin	Median, 92 m	Optimal resection, age < 60 y No deep invasion

Abbreviations: HIPEC, intraperitoneal hyperthermic chemotherapy; MMC, mitomycin C.

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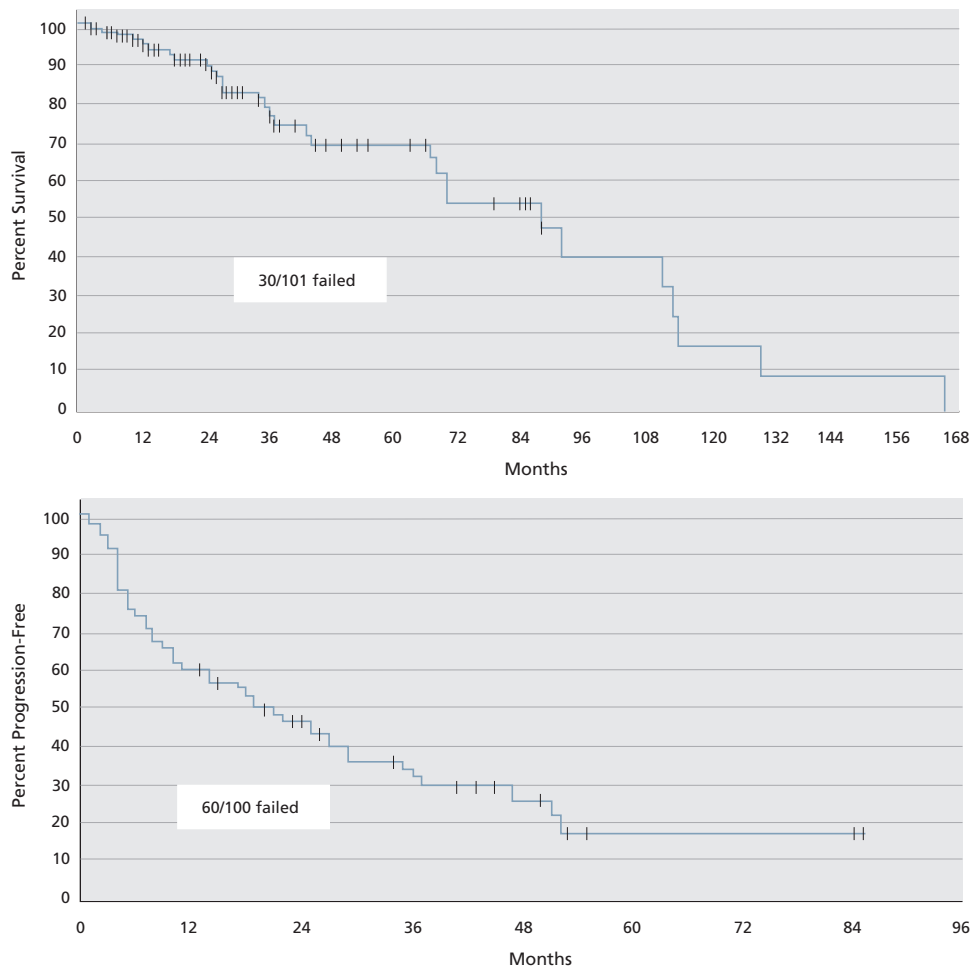


Figure 3 Actuarial survival curves of patients with diffuse malignant peritoneal mesothelioma (DMPM) treated with cytoreductive surgery and hyperthermic intraoperative peritoneal chemotherapy. The top panel shows overall survival in 101 patients with DMPM treated at NCI in Bethesda, Maryland; the bottom panel shows peritoneal progression-free survival in 100 patients for whom outcome data were available.

mTOR inhibitor, a significant inhibition in DMPM cell proliferation was observed in association with decreased PI3K/mTOR protein expression, implicating the role of these pathways in the malignant phenotype of DMPM.⁴⁴ Further study is necessary to determine if inhibition of this pathway may translate to a therapeutic benefit for patients.

The second study evaluated the potential role of EGFR in DMPM and found that 9 different EGFR point mutations with an overall frequency of 34% were identified in 29 DMPM tumor samples.⁴⁵ Of 25 patients who underwent surgical exploration, an optimal cytoreduction (defined by residual tumor nodule size of ≤ 5 mm) was achieved in 100% of the EGFR mutant group (n = 8) versus 50% in the nonmutant group (n = 17), representing a statisti-

cally significant difference. In a subsequent follow-up analysis, the median overall survival and time to disease progression had not been reached for the mutant EGFR group, whereas the median overall survival and time to disease progression in the wild-type group were 44 and 28 months, respectively. Although the number of patients in the study was small, these data suggest that the presence of EGFR mutations may be associated with the ability to perform an optimal cytoreduction and with prolonged survival in patients with DMPM. However, 2 studies of EGFR tyrosine kinase inhibitors in patients with pleural mesothelioma showed only modest median survivals, which were less than the median survival associated with the combination regimen of pemetrexed and cisplatin in this same group.^{46,47}

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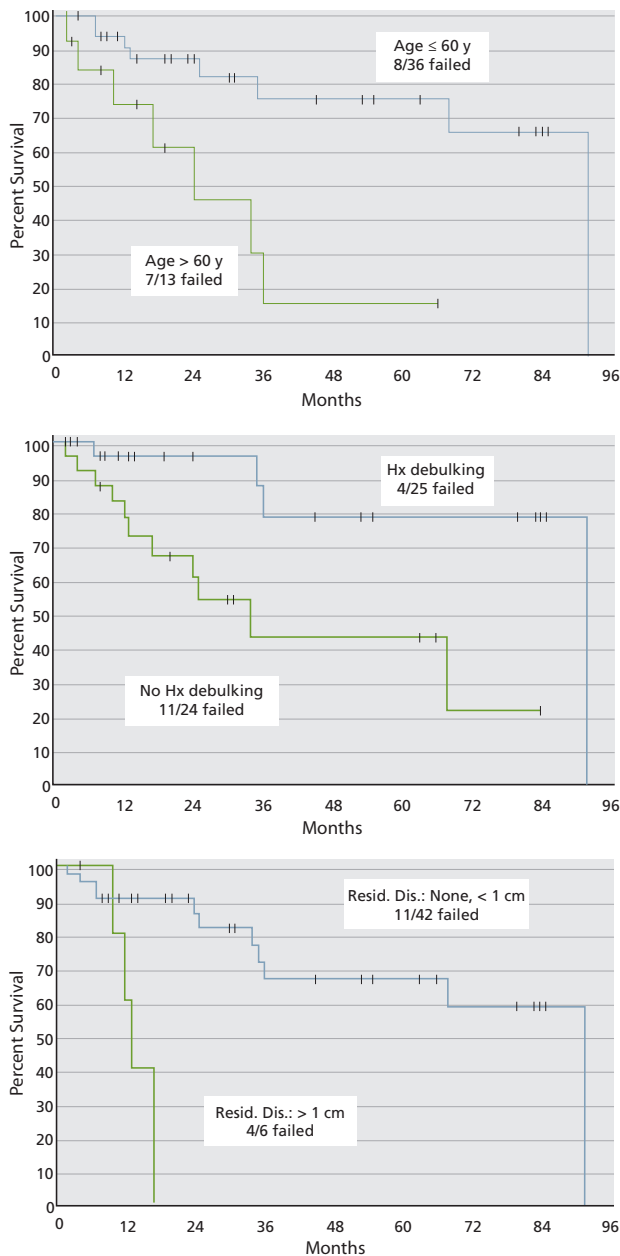


Figure 4 Actuarial overall survival curves showing the effects of age, history (Hx) of previous debulking surgery (middle), and residual disease status in patients with diffuse malignant peritoneal mesothelioma patients after cytoreduction and hyperthermic intraoperative peritoneal chemotherapy.

Conclusions

DMPM is a rare and ultimately fatal disease with a dismal overall survival when left untreated. Systemic chemotherapy using pemetrexed and cisplatin is associated with substantial clinical benefit in some patients. For patients with disease amenable to surgical resection, CRS and HIPEC is an increasingly used

approach, with median overall survivals greater than 4 years reported from many centers. In their review of DMPM in 1960, Winslow and Taylor¹⁰ wrote, “the value of making a diagnosis during life may be questionable, since at the present time there appears to be no cure. As time goes on, however, it may be that a cure will be developed and that such patients will not be considered definitely doomed.” Considerable advances have certainly been made since that prescient statement more than 50 years ago. CRS and HIPEC today represent the standard of care for selected patients with DMPM, and new understanding of the molecular biology of the disease will undoubtedly lead to far more efficacious treatments that will provide long-term control of the condition.

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