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Lung Cancer

Multidisciplinary Treatment of Malignant Pleural Mesothelioma

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Select appropriate treatment strategies for patients with MPM.
2. Discuss the clinical development of new agents and therapeutic strategies, and how they could be integrated into the current armamentarium.
3. Summarize the current understandings and pitfalls in staging MPM patients.

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ABSTRACT

The incidence of malignant pleural mesothelioma (MPM) is increasing worldwide, and is predicted to peak in the next 10–20 years. Difficulties in MPM diagnosis and staging, especially of early disease, have thwarted the development of a universally accepted therapeutic approach. Single modality therapies (surgery, radiotherapy, chemotherapy) have generally failed to significantly prolong patient survival. As a result, multimodality treatment regimens have been developed. Radical surgery with extrapleural pneumonectomy and adjuvant treatments has become the preferred option in early disease, but the benefits of such an aggressive approach have been questioned because of significant treatment-related morbidity and mortality. In the past few years, there have been several major advances in the management of patients with MPM, including more accurate staging and patient selection, improvements in surgical techniques and postoperative care, novel chemotherapy regimens with definite activity such as antifolate (pemetrexed or raltitrexed)–platinum combinations, and new radiotherapy techniques such as intensity-modulated radiation therapy. Induction chemotherapy followed by surgery and adjuvant radiotherapy has shown promising results. A number of molecular alterations occurring in MPM have been reported, providing broader insights into its biology and leading to the identification of new targets for therapy. However, currently available treatments still appear to have modest results. Further studies are needed to provide evidence-based recommendations for the treatment of early and advanced stages of this disease. ***The Oncologist*** 2007;12:850–863

Disclosure of potential conflicts of interest is found at the end of this article.

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor, usually associated with a poor prognosis. The incidence of MPM is increasing throughout most of the world, and it is expected to rise in the next 10–20 years as a result of widespread exposure to asbestos in the past decades [1]. The management of patients with MPM is controversial. Difficulties in diagnosing and staging, especially in early disease, have thwarted the development of a generally accepted stage-related approach. MPM is a heterogeneous disease often associated with different clinical courses; a number of prognostic factors have been described, and two major prognostic scoring systems have been published [2, 3]. There is no definite standard of care, and only a minority of patients are eligible for any potentially curative therapy. Until recently each single modality treatment, that is, surgery, radiotherapy (RT), and chemotherapy, has failed to prolong patient survival. The results of each individual treatment are difficult to interpret because of the varying patient selection, the relatively small number of patients prospectively followed up in single studies, and often the combination with another treatment modality for each of them. No randomized data exist to support one or the other treatment modality as a better treatment option for these patients. Because of the relatively low incidence of the disease, such randomized controlled studies with an adequate number of cases are difficult to perform. Therefore, for many years a nihilistic attitude has existed about MPM treatment [4, 5], with several retrospective studies reporting a median survival duration of <1 year and 5-year survival rates of $\leq 1\%$ [6]. As a result, trials comparing chemotherapy with best supportive care (BSC) are still ongoing [7], while, on the other hand, several aggressive multimodality approaches have been proposed in selected patients [8].

In the past few years there have been several major advances in the management of patients with MPM [9]. A number of molecular alterations occurring in this disease have been reported, providing broader insights into its biology and leading to the identification of new targets for therapy [10]. Two phase III randomized trials have set the cisplatin–antifolate combination as the reference regimen for first-line chemotherapy [11, 12], and several biological agents have been explored or are currently under evaluation [13]. More accurate staging and patient selection and improvements in surgical techniques and postoperative care have contributed to lower morbidity and mortality rates after radical surgery [14]. Finally, new RT techniques, such as intensity-modulated radiation therapy (IMRT), have provided the potential to conform radiation doses tightly to target volumes, thereby reducing normal tissue toxicity [15].

In our review, we have analyzed the current literature data critically in terms of management of patients with MPM, focusing on the most recent advances as well as on combined-modality approaches.

Staging

Correct clinical staging is mandatory in the approach to treat MPM. Early staging systems have reflected mainly the experiences of individual institutions on their respective patient populations; considerable discrepancies among the various systems have resulted in nonuniformity of reporting. At present, the recommended classification for clinical use is the International Mesothelioma Interest Group (IMIG) staging system (Table 1) [16], which is based mainly on surgical and pathological variables, and may not be completely applicable to cross-sectional imaging; moreover, the lymphatic drainage of the pleura is quite complex and is not fully reflected in the IMIG system, in which the lymph node (N) classification mirrors that of lung cancer [17, 18]. Contrast-enhanced computed tomography (CT) is the primary imaging technique for the evaluation of MPM; rind-like extension of the tumor on the pleural surfaces is the most common CT feature, which is seen in up to 70% of cases [19]. For patients being assessed for surgery, magnetic resonance imaging (MRI) can provide additional staging information. MRI is used typically to assess equivocal findings on CT concerning the local extent of the tumor, particularly to detect chest wall and diaphragmatic involvement [20, 21]. Because of the suboptimal accuracy of radiological staging in MPM, some authors have advocated the need for extended surgical staging with mediastinoscopy, laparoscopy, and peritoneal lavage [22–24]. The use of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for the diagnosis of MPM has recently been described. FDG-PET has been proven to be useful in the detection of malignant pleural lesions [25] and in the assessment of the extent of tumor involvement. In one study on 65 MPM patients, this imaging technique correctly detected extrathoracic metastases, but failed to reliably identify the locoregional (tumor and mediastinal nodal) status of MPM [26]; sensitivity was 19% for locally advanced disease (T4) and 11% for nodal metastases. Integrated CT-PET with coregistration of anatomic and functional imaging data increases the accuracy of MPM staging for T4 disease, while it remains inaccurate in the evaluation of nodal metastases [27, 28]. As a result of difficulties in monitoring radiological treatment response by CT criteria [29], the use of PET also appears promising in the assessment of response to chemotherapy [30].

Table 1. IMIG staging system

T, N, M	Region involved	Characteristics
T1a	Limited to the ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae.	No involvement of the visceral pleura.
T1b	Ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae.	Scattered tumor foci that also involve the visceral pleura.
T2	Each ipsilateral pleural surface.	At least one of the following: (i) involvement of the diaphragmatic muscle, or (ii) a confluent visceral pleural tumor (including fissures) or tumor extension from the visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumor (each ipsilateral pleural surface)	At least one of the following: (i) involvement of the endothoracic fascia, (ii) extension into mediastinal fat, (iii) a solitary, completely resectable focus of tumor that extends into the soft tissues of the chest wall, or (iv) nontransmural involvement of the pericardium
T4	Locally advanced, technically unresectable tumor (each ipsilateral pleural surface)	At least one of the following: (i) diffuse tumor extension or multiple tumor foci in the chest wall with or without associated rib destruction, (ii) direct transdiaphragmatic extension to the peritoneum, (iii) direct extension to the contralateral pleura, (iv) direct extension to the mediastinal organs, (v) direct extension to the spine, or (vi) extension to the internal surface of the pericardium with or without pericardial effusion or involvement of the myocardium
NX		Presence of regional lymph nodes not assessable
N0		No regional lymph node metastases
N1		Metastases in ipsilateral bronchopulmonary or hilar lymph nodes
N2		Metastases in subcarinal or ipsilateral mediastinal lymph nodes, including ipsilateral internal mammary lymph nodes
N3		Metastases in contralateral mediastinal, contralateral internal mammary, and ipsilateral or contralateral supraclavicular lymph nodes
MX		Presence of distant metastases not assessable
M0		No distant metastases
M1		Distant metastases present

Stage	Tumor	Lymph nodes	Metastases
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	T2	N0	M0
III	Any T3	Any N1 or N2	M0
IV	Any T4	Any N3	Any M1

Abbreviations: IMIG, International Mesothelioma Interest Group; M, metastases; N, lymph nodes; T, tumor.

Chemotherapy

Most patients with MPM are potential candidates for chemotherapy at some point in their treatment. For many years a nihilistic attitude has existed about medical treatment of MPM. Most chemotherapy studies have used either single agents or combination regimens in the setting of small phase II trials; the rates of objective tumor regression have been generally <20%, with no significant impact on median survival [31]. In a meta-analysis of early trials published between 1965 and 2001, cisplatin was found to be the

most active single drug [32]. Combination chemotherapy has been associated with higher response rates, but not with longer survival. In a small randomized study on 43 patients, the early (versus delayed) use of chemotherapy (mitomycin, vinblastine, and cisplatin; the MVP schedule) in the management of patients with stable symptoms after control of any pleural effusion has been shown to provide a longer period of symptom control and a trend toward a survival advantage [33]. However, trials comparing chemotherapy with BSC are still ongoing [7, 34].

Several new cytotoxic agents with definite activity in mesothelioma have recently been evaluated, including gemcitabine, vinorelbine, and the antifolates pemetrexed and raltitrexed. A single study has reported a response rate of 48% with the cisplatin–gemcitabine combination [35], but additional phase II studies have documented a lower level of efficacy [36, 37]. Vinorelbine has been shown to have activity in a small phase II study [38]; similar results have been achieved with vinflunine, a new semisynthetic fluorinated vinca alkaloid [39]. In contrast, taxanes, such as paclitaxel and docetaxel, showed very low or no activity [40, 41]. Recently, two randomized controlled trials comparing single-agent cisplatin with its combination with an antifolate agent have been reported (Table 2) [11, 12]. A large phase III trial comparing pemetrexed and cisplatin with cisplatin alone in 448 chemotherapy-naïve patients with MPM has demonstrated that the combined regimen is associated with significantly better survival, time to progression, and response rates (41.3%, versus 16.7% in the control arm) [11]. Supplementation with folic acid and vitamin B_{12} has reduced toxicity significantly. Furthermore, the raltitrexed–cisplatin combined regimen as first-line treatment has been reported to produce a longer overall survival duration than with cisplatin in a population of 250 patients [12], confirming that cisplatin with an antifolate should be the reference regimen in patients with MPM. The magnitude of the survival benefit is similar in both studies: a 2.8-month longer median survival time in the pemetrexed study (12.1 versus 9.3 months) and a 2.6-month longer median survival time in the raltitrexed study (11.4 versus 8.8 months). However, in the former trial this difference is statistically significant, whereas in the latter it has borderline significance, probably because of the limited sample size. In both trials the combination arm was significantly superior in terms of lung function improvement and symptom control [42, 43]. Considering that many MPM patients are unfit to receive cisplatin-based chemotherapy, schedules with carboplatin have been explored in an attempt to reduce toxicity, while maintaining the same survival benefit [44–47]. Recently, the results of a phase II trial of the pemetrexed–carboplatin combination as front-line treatment in 102 patients with MPM have been published [46]. Despite the apparently lower radiological response rate, the time to disease progression and overall survival time were similar (6.5 months and 12.7 months, respectively) to the results achieved with the standard pemetrexed–cisplatin regimen. These results were confirmed independently by another trial using the same treatment schedule on a large number of patients [47]. MPM is often diagnosed late in the course of life, and an increasing rate of diagnosis in elderly patients is reported by several mesothelioma registers and epidemiological studies [48]. The carboplatin-based schedules seem attractive for this growing subset of patients. In a retrospective analysis on the outcome of elderly patients (≥70 years) with MPM included in two large trials of the pemetrexed–carboplatin combination as first-line therapy, this regimen was proven to be active and well tolerated [49], although these data should be considered with caution because of the bias risk related to subgroup retrospective analyses.

There is no consensus about the optimal duration of first-line chemotherapy in MPM. Maintenance chemotherapy with pemetrexed after six courses of pemetrexed-containing induction therapy has been studied only in a small series of MPM patients: although tolerance was fairly good, results were inconclusive because of the small number of patients and the nonrandomized trial design [50].

Patients benefiting from first-line treatment are still relatively healthy when progression occurs and thus are potential candidates for second-line therapy. Until recently, most MPM chemotherapy trials have focused on chemotherapy-naïve patients, with few providing results to guide decisions regarding second-line therapy. Therefore, the role of second-line chemotherapy in MPM has yet to be proven. Some case study reports and phase II studies including pretreated patients [51, 52] and a few small trials dedicated to second-line chemotherapy [53, 54] have provided evidence of efficacy in this patient setting (Table 3). Recently, noteworthy activity of pemetrexed, both alone and combined with carboplatin, as second-line treatment following prior platinum-based chemotherapy has been reported [55]. More importantly, in a randomized, multicenter phase III study examining pemetrexed as second-line chemotherapy versus BSC alone, a statistically significant longer time to disease progression was demonstrated in the chemotherapy-receiving arm (3.8 versus 1.5 months); no difference in overall survival was seen, possibly as a result of the influence of poststudy therapy in the BSC arm [56]. However, because the phase III trial evaluating the pemetrexed–cisplatin combination as first-line therapy [11] has resulted in this regimen becoming a frequent choice for first-line standard of care, second-line chemotherapy should focus on other compounds [57–59] (Table 3).

Table 2. Randomized trials with cisplatin and antifolates in MPM

Study	Regimen	*n*	RR (%)	mTTP (months)	mSv (months)	1-Yr Sv (%)
Vogelzang et al. [11]	Cisplatin + pemetrexed	226	41.3	5.7	12.1	50.3
	Cisplatin	222	16.7	3.9	9.3	38.0
			$p < .0001$	$p = .001$	$p = .02$	$p = .012$
van Meerbeeck et al. [12]	Cisplatin + raltitrexed	126	23.6	5.3	11.4	46.2
	Cisplatin	124	13.6	4.0	8.8	39.6
			$p = .056$	$p = .058$	$p = .0483$	$p = .0483$

Abbreviations: MPM, malignant pleural mesothelioma; mTTP, median time to progression; mSv, median survival; RR, response rate; Sv, survival rate.

Table 3. Studies of second-line chemotherapy in MPM

Study	Regimen	*n*	RR (%)	mTTP (months)	mSv (months)
Pemetrexed-naïve patients					
Giaccone et al. [53]	ZD0437 (platinum analogue)	47	12[a]	2.5	6.7
Porta et al. [54]	Raltitrexed + oxaliplatin	14	0	1.9	3.2
Sorensen et al. [55]	Pemetrexed with or without carboplatin	39	23	4.9	6.5
Jassem et al. [56][b]	Pemetrexed	123	19.2	3.8	8.6
Pemetrexed-pretreated patients					
Zucali et al. [58]	Gemcitabine + vinorelbine	28	7.4	2.8	NR
Serke et al. [59]	Oxaliplatin with or without gemcitabine	18	22[a]	NR	NR

[a]Responses reported as "minor responses."
[b]Randomized trial of pemetrexed versus best supportive care (data reported for the pemetrexed arm only).
Abbreviations: MPM, malignant pleural mesothelioma; mSv, median survival; mTTP, median time to progression; NR, not reported; RR, response rate.

Targeted Therapies

Several biological agents have been explored or are currently under evaluation in MPM patients [10]. The epidermal growth factor receptor (EGFR) is highly expressed in the majority of MPMs [60, 61]; vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are important autocrine growth factors in this disease [10, 62]. Studies testing EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) have shown limited or no activity [63, 64], and so have trials with imatinib mesylate [65]. The lack of EGFR mutations that confer sensitivity to gefitinib and erlotinib in non-small cell lung cancer could explain resistance to EGFR tyrosine kinase inhibitors in MPM [60, 66]. The use of a number of angiogenesis inhibitors has been or is being investigated within clinical trials on MPM. Pivotal trials with PTK787 and thalidomide have demonstrated no activity [67, 68], whereas a certain activity has been reported with SU5416, an inhibitor of the VEGF receptor (VEGFR) Flk-1, hampered by an excessive risk for thrombosis [69]. Bevacizumab, a recombinant human anti-VEGF monoclonal antibody that blocks the binding of VEGF to its receptors, is under evaluation in a double-blind, placebo-controlled, randomized phase II trial in combination with cisplatin and gemcitabine. The accrual of that study has concluded, but data are still blinded; pooled data showed a median progression-free survival time of 6.4 months, a median overall survival time of 15.7 months, and a 1-year survival rate of 60.1%. Baseline serum VEGF levels predicted progression-free and overall survival times, but not response [70]. Other novel agents under investigation include sorafenib, an inhibitor of VEGFR-2, PDGFR-b, and B-Raf tyrosine kinase; in a single-arm phase II study on 51 patients with MPM who were either chemotherapy-naïve or had already received pemetrexed, a partial response was observed in 4.7% of cases, with a median time to treatment failure of 4.1 months and an overall survival time of 6.3 months [71]. In a phase I trial, vorinostat, a histone deacetylase inhibitor, has produced objective responses in 20% of MPM patients, and a phase III double-blind, placebo-controlled trial is under way [72]. Bortezomib, a proteasome

inhibitor, has shown activity in preclinical models of MPM via various pathways including the inhibition of angiogenesis and nuclear transcription factor kappa B, which has been reported as a crucial cellular effector for chemoresistance in MPM [73, 74]. An international multicenter phase II clinical trial of this agent in MPM patients is ongoing [75].

Surgery

The role of surgery in the management of MPM is still debated [76, 77]. The results of each trial are difficult to interpret because of the varying patient selection, the different staging systems, and often the addition of other treatment modalities [78]. The three most used surgical procedures are pleurodesis, pleurectomy/decortication (P/D), and extrapleural pneumonectomy (EPP). No randomized controlled studies comparing these techniques or comparing surgery with an alternative treatment are available. Recently a feasibility pilot study has been started in the United Kingdom, in which MPM patients are randomized after three cycles of induction chemotherapy to have or not have EPP followed by radical RT. If the feasibility study, which aims to recruit 50 patients, is positive, the trial (denoted the Mesothelioma and Radical Surgery [MARS] trial) will continue as a full trial whose main objectives will be to determine whether EPP is better than no surgery in terms of survival and quality of life [79].

Pleural effusion is a common and debilitating complication of MPM; evacuation of the pleural fluid and prevention of its reaccumulation, with complete lung expansion, are important goals in the management of these patients. Different techniques and sclerosing agents have been used [80], but thoracoscopy and talc insufflation seem to give the best results with low morbidity. In large series of patients with malignant pleural effusion, this procedure has been reported to prevent further fluid accumulation in nearly 80% of cases, although survival prolongation has not been observed [81, 82].

P/D and EPP are cytoreductive procedures whose aim is the local control of MPM, a locally aggressive disease with propensity to recur locoregionally. P/D allows the removal of the visceral, parietal, and pericardial pleura; it is less technically demanding than EPP, and therefore it can be performed in most centers. Morbidity is limited, and the procedure can be tolerated by patients whose functional status precludes EPP; mortality rates are in the range of 1.5%–5% [83, 84]. However, P/D has several limitations: complete resection is impossible in most cases, and postoperative RT fields and doses are limited because of the presence of the lung. As a result, local recurrence occurs in the vast majority of patients [84]. EPP is a more aggressive procedure entailing en bloc resection of the parietal and visceral pleura with the enclosed lung, pericardium, ipsilateral diaphragm, and mediastinal nodes. The pericardial and diaphragmatic defects are reconstructed with patches to prevent cardiac or abdominal organ herniation. With EPP, cytoreduction is more effective than with P/D [77], and a higher amount of RT can be delivered [85]. On the other hand, EPP is a complex operation, which should be performed in selected centers and by skilled surgeons only. Postoperative morbidity is frequent, occurring in up to 60% of patients [14]. Major complications include atrial fibrillation, prolonged intubation, vocal cord paralysis, deep vein thrombosis, technical complications (patch dehiscence, intrathoracic hemorrhage), tamponade, acute respiratory distress syndrome, cardiac arrest, and empyema. However, as more experience has been gained with the procedure, the mortality rate has declined from 30% in the early series [86] to $<$10% in modern series [14, 87–89]. In the largest published series, Sugarbaker et al. [14] reported a 3.4% mortality rate in 328 patients, suggesting that in expert hands EPP can now be considered a relatively safe procedure for selected patients with MPM.

Because evidence-based recommendations derived from randomized clinical trials do not exist, there has been a long debate regarding which technique is more appropriate. Interpretation and comparison of data in surgical series are very difficult because they are based on retrospective case series and noncomparative phase II studies only, and because in most studies RT and chemotherapy were added [78]. Moreover, some authors have incorporated data from earlier years, or updated old series in new papers, or extracted subsets of patients from previous studies, which makes result interpretation even more difficult. In a large retrospective series with long follow-up, no survival difference was observed between EPP and P/D patients [90].

Surgery alone has not been tested extensively in MPM; therefore, the results of the main trials on P/D and EPP are discussed in the present review within the section on multimodality treatment.

RT

The role of RT in the treatment of MPM is not well defined yet [91]. There is no evidence that RT alone affects survival, although several studies have demonstrated that it can indeed improve symptoms like dyspnea, dysphagia, vena cava obstruction, and, mainly, pain [92, 93]. Three small randomized controlled trials have evaluated the role of prophylactic external beam RT in reducing the frequency of thoracic procedure tract metastases [94–96]. The results of these trials are conflicting: in one only a significant reduction in tract malignant seeding was reported [94], and

when the data were pooled, there was not sufficient evidence to definitively recommend prophylactic radiation on thoracic diagnostic tracts; that must be decided on an individualized case assessment [91]. Although tolerance to RT improves with dose fractionation, curative RT is difficult to deliver to patients with MPM because of the large volumes of the lungs, liver, heart, spinal cord, and even kidneys that would receive potentially toxic doses. Therefore, few trials considering definitive radical irradiation in these patients are available. In a review of MPM patients treated with different doses of RT using palliation as the endpoint, only one of 23 patients who had received <40 Gy achieved symptom improvement, while four of six patients who had been given >40 Gy had satisfactory symptom palliation [97]. In a phase II study on 47 patients, Linden et al. [98] delivered hemithoracic RT at a dose of 40 Gy in 20 fractions, alone or in combination with doxorubicin and cyclophosphamide. Symptom control was poor, and 100% of patients experienced radiation-induced pulmonary fibrosis, 23% radiation pneumonitis, and 4% bronchopleural fistula. A prospective nonrandomized study from Finland has evaluated different multimodality treatment programs, using various hemithoracic irradiation schedules in combination with chemotherapy. Regimens included conventionally fractionated RT, split-course therapy with an additional boost to the major tumor areas, hypofractionation, hyperfractionation, or a combination of hypo- and hyperfractionation. The authors treated >100 patients in different, consecutive time periods [99, 100] and concluded that the results achieved by the altered fractionation regimens do not differ from those obtained with conventional fractionation; moreover, toxicities, namely, radiation pneumonitis and fibrosis, were severe. More recently, Zierhut et al. [101] reported the Heidelberg group experience over a 12-year time span on three-dimensionally planned RT delivered to 42 MPM patients, mostly with palliative intent. The median delivered dose was 40 Gy, with a range of 7.5–60 Gy and various fractionation schedules; the median overall survival duration was 5.4 months after RT and the median progression-free survival time was 2 months [101]. None of the above-mentioned studies included formal measures of quality of life or a symptom control analysis. Based on the results of these early studies, radical RT alone or combined with chemotherapy should not be offered as a curative treatment option to patients with MPM.

RT has more often been added to surgery in an attempt to improve local control and reduce local failure [102]. Studies of adjuvant RT are analyzed in the Multimodality Treatment section below.

Following the limitations of RT in MPM, because of the diffuse nature of the disease, several new treatment techniques have been implemented [103]. Recently, a novel modality of irradiation, known as intensity-modulated radiation therapy (IMRT), has been developed for the treatment of several tumors. IMRT is used to deliver dose distributions that conform to complicated convex and concave target volumes. This is potentially advantageous for large, irregular targets with critical structures in close proximity [104], such as in the case of MPM [105–107].

Multimodality Treatment

Failure of single-modality treatments to increase survival in MPM patients has led to a variety of multimodality approaches [8, 108]. Cytoreductive surgery (P/D or EPP) has been added to systemic and/or intrapleural chemotherapy, and to external-beam or intraoperative RT, with the main aim of improving local control. Other procedures, such as hyperthermia and photodynamic therapy, have been used in small noncontrolled trials [108]. Early studies of neoadjuvant chemotherapy followed by EPP and hemithoracic RT have been published, and confirmatory trials on larger series of patients are ongoing [109].

Surgery and Postoperative RT

P/D Plus RT

Gupta et al. [84] have recently reported a retrospective review including 123 patients treated with P/D and adjuvant RT at Memorial Sloan-Kettering Cancer Center from 1974 to 2003. Intraoperative brachytherapy was added in nearly half of the cases. The 1-year actuarial local control rate for all patients was 42%; the median overall survival duration was 13.5 months. Radiation dose <40 Gy, nonepithelial histology, and left-sided disease were negative prognostic factors. The authors concluded that P/D with adjuvant RT is not an effective treatment option for patients with MPM [84].

EPP Plus RT

In a phase II trial published by Rusch et al. [110], 88 patients were resected (70% with EPP) and 57 received adjuvant hemithoracic radiation at a dose of 54 Gy. Treatment proved to be feasible and generally well tolerated. The median survival time was 33.8 months for stage I–II and 10 months for stage III–IV tumors. Patients with advanced disease at presentation had a high risk for distant relapse, suggesting the need for systemic therapy to be added to this regimen. Acceptable RT dose distributions were obtained using a combined photon and electron technique with blockade of critical normal structures [85].

Intraoperative RT

Two small series of MPM patients treated with intraoperative RT (IORT) have been reported. Rosenzweig et al. [111] observed 13 patients (7 EPP, 6 P/D) treated with IORT and postoperative external-beam RT. Treatment turned out to be prohibitively toxic, with serious complications mainly in the EPP group. Lee et al. [112] have carried out a retrospective review of 24 patients treated with IORT and external beam RT; the median overall survival time was 18.1 months. In spite of this aggressive RT treatment, the most frequent type of failure was locoregional.

Clinical Implementations of IMRT

A few centers have implemented IMRT clinically in small patient series [106, 113, 114]. Münter et al. [113] reported on the use of a standard fractionation schedule of a total dose of 40–50 Gy in a small series of 11 patients with unresectable MPM who had experienced failure of surgery or first-line chemotherapy. The 1-year overall survival rate after RT was 18%. No severe acute or late side effects, especially no severe lung toxicity, were reported. The authors concluded that for palliative situations IMRT might be suitable only for patients with a small tumor burden, but its use should be better applied to patients resected with EPP [113]. Forster et al. [106] have described the pilot MD Anderson Cancer Center experience with IMRT in seven MPM patients treated after EPP. Acute toxicity was mild; the most severe side effects were nausea or vomiting. After a minimum follow-up of 13 months, no disease recurrence within the ipsilateral hemithorax was observed [106]. These results were updated by the same group in a series of 57 sequential MPM patients, in which an excellent local control rate was reported (93%), with a 3-year disease-free survival rate of 55% in patients without nodal metastases at surgery, and with distant metastases as the leading cause of death [115]. In a recent paper on the initial experience with IMRT as adjuvant therapy after EPP conducted at Dana-Farber Cancer Institute in Boston, a high rate of fatal pneumonitis (6 of 13 patients) was reported [114]. Therefore, great caution in the use of IMRT in MPM patients is recommended until a clearer understanding of the dose-volume effects of this technique for this patient population is gained.

EPP and Adjuvant Chemoradiation

The largest series evaluating multimodality treatment in MPM has been reported by the Brigham and Women's Hospital group in Boston. An early report on 120 patients [87] was subsequently updated in a paper reporting the results of EPP followed by adjuvant chemotherapy and RT in a total of 183 patients [88]. In that study, careful patient selection was applied based on a standardized preoperative assessment including radiological evaluation (CT and MRI scans and echocardiograms) and accurate pulmonary and cardiac function tests. From 1980 to 1997, 140 men and 43 women of 31–76 years of age were enrolled. Seven perioperative deaths occurred, which is equal to a mortality rate of 3.8%. Perioperative morbidity occurred in 50% of patients. The 176 survivors were given adjuvant treatment after a recovery period of 4–6 weeks. Chemotherapy was administered first; several different regimens were evaluated over time; platinum-based schedules were used since 1985. Hemithoracic RT was delivered at a dose of 30 Gy, and the mediastinum received 40 Gy. A boost dose was given to areas of gross residual disease, positive resection margins, or positive lymph nodes, for a total cumulative dose to the boost region of 54 Gy. The median survival duration was 19 months, with 2- and 5-year survival rates of 38% and 15%, respectively. The subset analysis identified three prognostic variables significantly associated with longer survival: epithelial cell type, negative resection margins, and extrapleural nodes without metastases (Table 4) [88]. A subset of these 183 patients was reviewed to assess the pattern of failure. Forty-six patients with a median follow-up of 18 months were analyzed [116]. Disease recurrence was observed in 25 patients (54%); locoregional relapse was seen in 35% of cases, abdominal recurrence in 26%, and contralateral chest recurrence in 17%. Hence, despite this aggressive protocol, locoregional recurrence was still the predominant mode of failure. However, the high rate of systemic failure suggests that a multimodality approach might have an impact in the natural history of the disease.

Based on the results of the Boston group, other authors have reported on small series of patients treated with the same trimodality treatment, confirming that this approach is feasible [89, 117]. However, it remains challenging mainly because of its high perioperative morbidity rate. Safe outcomes require a multidisciplinary team approach, and mortality can be minimized by early detection and aggressive treatment of complications [14, 118].

Surgery and Intrapleural Chemotherapy/Photodynamic Therapy

Intrapleural chemotherapy has the theoretical advantage of achieving high local drug concentrations and prolonged drug exposure with less systemic toxicity; on the other hand, activity is limited by tissue penetration of the drug. In a Memorial Sloan-Kettering study, P/D with intrapleural cisplatin and mitomycin was used to treat 28 patients, most of whom also received systemic chemotherapy. The median survival duration was 17 months; 80% of patients had locoregional recurrence; one perioperative death and two

Table 4. Trimodality therapy in MPM: Brigham's study [ref 88]

Prognostic variable	*n*	mSv (months)	2-Yr Sv (%)	5-Yr Sv (%)	Odds ratio (CI)
Histology					
Epithelial	103	NR	52	21	
Mixed/sarcomatous	73		16	0	3.0 (2.0–4.5)
Resection margins					
Negative	66	NR	44	25	
Positive	110		33	9	1.7 (1.2–2.6)
Extrapleural nodes					
Negative	136	NR	42	17	
Positive	40		23	0	2.0 (1.3–3.2)
Three positive prognostic factors	31	51	68	46	-
All patients	176	19	38	15	-

Abbreviations: CI, 95% confidence interval; MPM, malignant pleural mesothelioma; mSv, median survival; NR, not reported; Sv, survival rate.

cases of grade 4 nephrotoxicity occurred [119]. Other authors have used hyperthermic cisplatin lavage after P/D based on the rationale that hyperthermia has been shown to induce cell death and also seems to improve the efficacy of chemotherapeutic agents [120]. Richards et al. [121] recently reported the results of a phase I–II study of P/D and intraoperative intracavitary hyperthermic cisplatin lavage in MPM patients not candidates for EPP. Cisplatin was administered at a sequentially escalated dose, from 50 to 250 mg/m^2. An apparent dose-related survival benefit was observed; patients with epithelial tumors treated with high-dose cisplatin lavage had a 26-month median survival time.

Photodynamic therapy combines light with a photosensitizer having selective uptake in cancer cells. In two small trials [122, 123] this technique did not seem to add a survival benefit to resected MPM patients.

Neoadjuvant Chemotherapy

The difficulty in providing adjuvant chemotherapy in EPP patients and the introduction into clinical practice of apparently effective chemotherapy regimens in recent years have spurred investigations on a neoadjuvant treatment approach to MPM (Table 5) [109, 124]. In a pilot study, Weder et al. [125] treated 19 MPM patients with clinical stage T1–3, N0–2, M0 disease—the most frequent being T2N0—with three cycles of neoadjuvant cisplatin and gemcitabine. The response rate to chemotherapy was 32%; EPP was performed in 16 patients with no perioperative mortality; major surgical complications occurred in six patients. Postoperative RT was delivered to 13 patients. The median survival time was 23 months; 1-year and 2-year survival rates were 79% and 37%, respectively [125]. The results of this single-center study were recently confirmed by a multicenter phase II trial (SAKK 17/00) [126], in which the same inclusion criteria as the pilot trial allowed the enrollment of 61 patients. The resectability rate was 61%; the median survival duration of the whole population was 19.8 months; in the 45 patients undergoing EPP, the median survival time was 23 months. This approach was not associated with more psychological distress. In these studies, complications after neoadjuvant chemotherapy and EPP are a major concern. However, in a pooled analysis of the two trials, postoperative morbidity and mortality rates (62% and 3.2%, respectively) were comparable with those observed after EPP alone in the Brigham series [127]. Recently, Flores et al. [128] reported on a phase II trial of induction chemotherapy, EPP, and postoperative high-dose RT in 21 patients with locally advanced (stage III–IV) MPM. Patients received four cycles of cisplatin and gemcitabine and, in the absence of disease progression, underwent EPP and adjuvant hemithoracic RT (54 Gy). The partial response rate to chemotherapy was 26%; eight of nine patients undergoing surgical exploration received EPP. The overall median survival duration was 19 months; the median survival time for EPP patients was 33.5 months. Finally, Rea et al. [129] reported on a single-center experience of induction chemotherapy with carboplatin and gemcitabine, EPP, and postoperative RT (45 Gy) in 21 patients. The resectability rate was 81%, the perioperative morbidity rate was 52%, and no mortality was observed. The median survival duration of the whole series was 25.5 months; patients who received EPP had a 5-year survival of rate of 24%.

Overall, preliminary data on multimodality treatment with induction chemotherapy seem promising (Table 5), but need to be confirmed in larger series. Trials are ongoing with the new cisplatin–pemetrexed chemotherapy combination in Eu-

Table 5. Studies of neoadjuvant chemotherapy in MPM

Study	*n*	Stage	Chemotherapy regimen	Postoperative RT	mSv (months)	Perioperative morbidity
Weder et al. [125][a]	19	T1–3 N0–2	Cisplatin + gemcitabine	High-risk areas (45–60 Gy)	23 months	37.5%
Weder et al. [126][b]	61	T1–3 N0–2	Cisplatin + gemcitabine	High-risk areas (45–60 Gy)	19.8	NR
Opitz et al. [132][c]	72	T1–3 N0–2	Cisplatin + gemcitabine or cisplatin + pemetrexed	Optional (75% treated)	23	62% (mortality 3.2%)[d]
Flores et al. [128]	21	T3–4 N0–2	Cisplatin + gemcitabine	Hemithoracic (54 Gy)	19	No grade 4 toxicity
Rea et al. [129]	21	I-III	Carboplatin + gemcitabine	Hemithoracic (45 Gy)	25.5	52.4%

[a]Single-center pilot trial.
[b]Multicenter trial (SAKK 17/00).
[c]Single-center retrospective analysis including patients from previous studies.
[d]Data reported in an analysis on 63 patients published separately [127].
Abbreviations: MPM, malignant pleural mesothelioma; mSv, median survival; NR, not reported; RT, radiotherapy.

rope and in the U.S. [130, 131]. Very preliminary data suggest that this regimen may produce treatment outcomes that are superior to those seen with cisplatin plus gemcitabine [132].

Conclusions

MPM remains a difficult disease to treat. No standard therapy exists, and randomized studies are lacking [133]. However, in the last few years, much progress has been made in this field.

The combination of pemetrexed with a platinum derivative can now be considered as standard in unresectable disease. Schedules with carboplatin should be considered, particularly in elderly and unfit patients. Although there is no consensus about the optimal duration of first-line chemotherapy, no evidence of a benefit with prolonged administration exists, and the use of six courses seems a reasonable option. Pemetrexed or a pemetrexed-containing regimen should be administered as second-line therapy in patients who have not received it as first-line treatment. Pemetrexed-pretreated patients should be enrolled ideally in dedicated prospective trials.

Radical surgery (EPP) and multimodality treatments are increasingly used, but the role of this aggressive approach should be further confirmed. Induction chemotherapy followed by surgery and adjuvant RT is promising. Clear, reproducible, and safe RT protocols are needed. Outside of clinical trials, multimodality treatments should be limited to patients with early (T1–T2) disease with no evidence of nodal involvement at the preoperative assessment. Careful patient staging and stratification based on the use of validated prognostic indexes [2, 3], and of new prognosticators such as FDG-PET [134], are essential to refer patients to the proper treatment and to avoid unnecessary and distressing treatments when they are not indicated.

Functional imaging, mainly with FDG-PET, is providing new insights into staging and response evaluation to chemotherapy and targeted agents in MPM.

Finally, advances in the knowledge of MPM molecular mechanisms hopefully will lead to the development of novel targeted agents for the treatment of advanced and early-stage disease.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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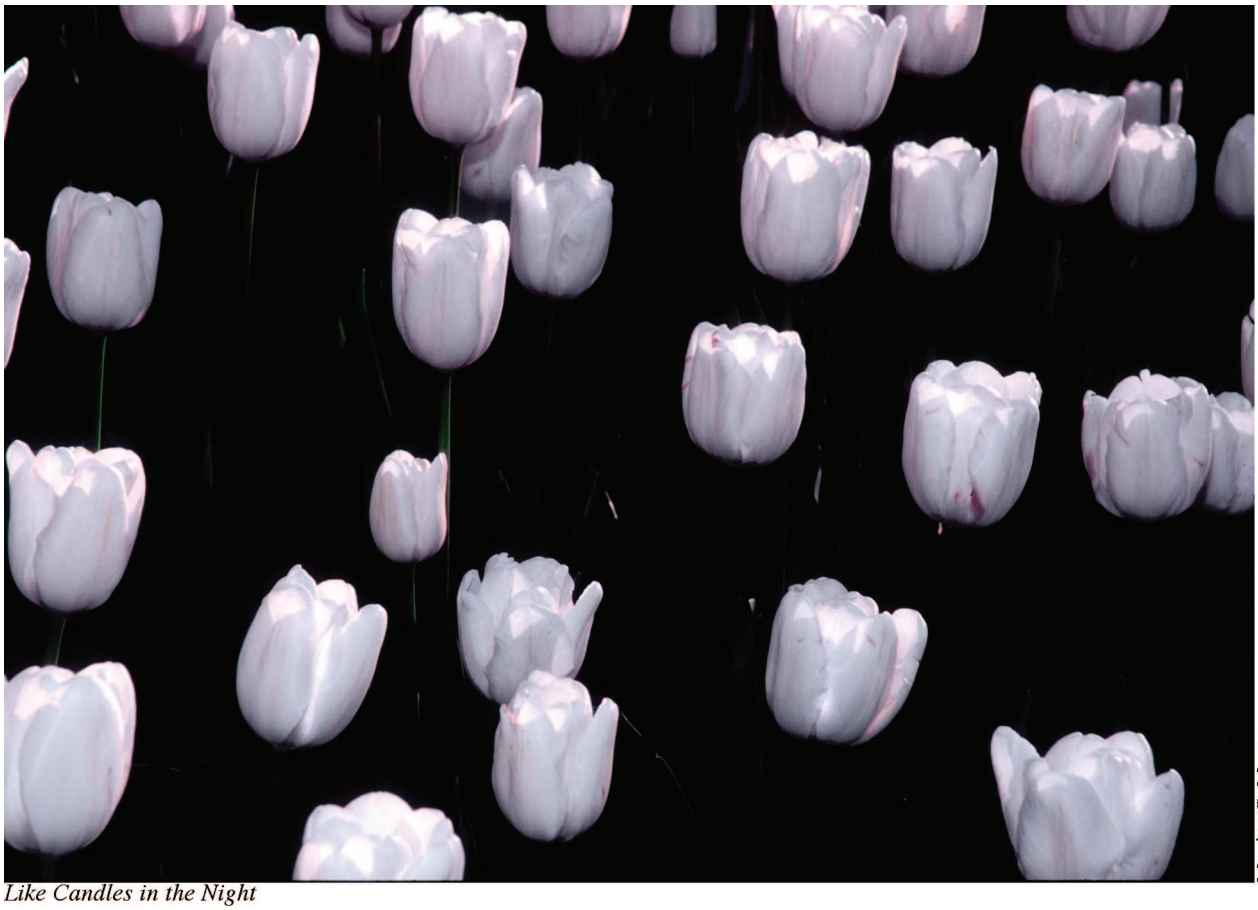

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Like Candles in the Night