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Malignant Pleural Mesothelioma

Clinical Practice Guidelines in Oncology

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Overview

Mesothelioma is a rare cancer that is estimated to occur in approximately 2500 people in the United States every year.[1,2] These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) focus on malignant pleural mesothelioma (MPM), which is the most common type; mesothelioma can also occur in other sites (e.g., peritoneum, pericardium, tunica vaginalis testis). The disease is difficult to treat;

NCCN Clinical Practice Guidelines in Oncology for Malignant Pleural Mesothelioma

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, malignant pleural mesothelioma, asbestos, chemotherapy, surgery, radiation therapy, pleural effusion *(JNCCN* 2012;10:26–41)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

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Disclosures for the NCCN Guidelines Panel for Malignant Pleural Mesothelioma

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Malignant Pleural Mesothelioma panel members can be found on page 41. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

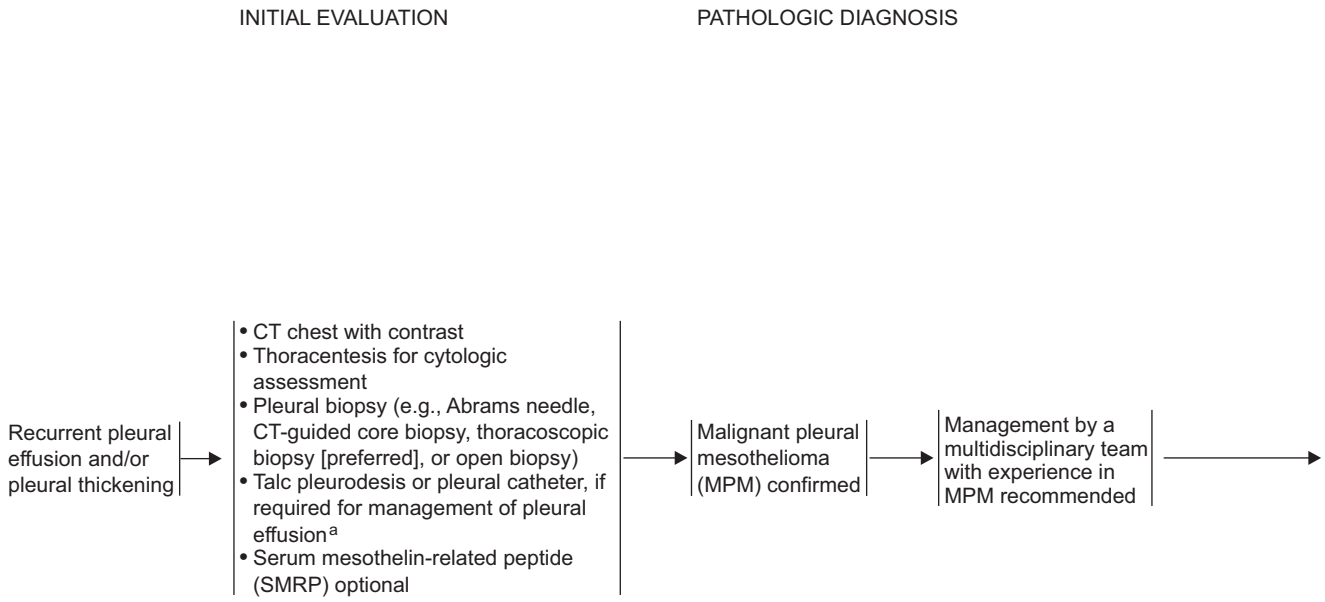
median overall survival is only approximately 1 year. MPM occurs mainly in older men (median age, 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20–40 years later).[3,4]

The incidence of MPM is leveling off in the United States, because asbestos use has decreased since the 1970s; however, the United States still has more cases than anywhere else in the world.[5,6] Although asbestos is no longer mined in the United States, it is still imported.[6] The incidence of MPM is increasing in other countries, such as Russia, Western Europe, China, and India.[1,5,7–11] Mortality rates from MPM are highest in the United Kingdom, Netherlands, and Australia, and are increasing in several other countries, such as Japan, Argentina, and Brazil.[7] Although most mesothelioma is linked to asbestos exposure, reports suggest that it may also be caused by radiotherapy,[12–16] and recent data suggest that erionite (a mineral that may be found in gravel roads) is associated with the disease.[17] Genetic factors may also play a role in MPM.[18]

The histologic subtypes of mesothelioma include epithelioid (most common); biphasic or mixed; and sarcomatoid.[2] Patients with epithelioid histology have better outcomes than those with either mixed (biphasic) or sarcomatoid histologies. Some patients who have been exposed to asbestos only have benign pleural disease, although they may have significant chest pain.[19,20] Although screening for mesothelioma has been studied in high-risk patients (i.e., those with asbestos exposure), these guidelines do not currently recommend screening for MPM.[21–23] Note that the

Text continues on p. 34

NCCN Malignant Pleural Mesothelioma Panel Members



[a]Recommend obtaining PET/CT before pleurodesis.

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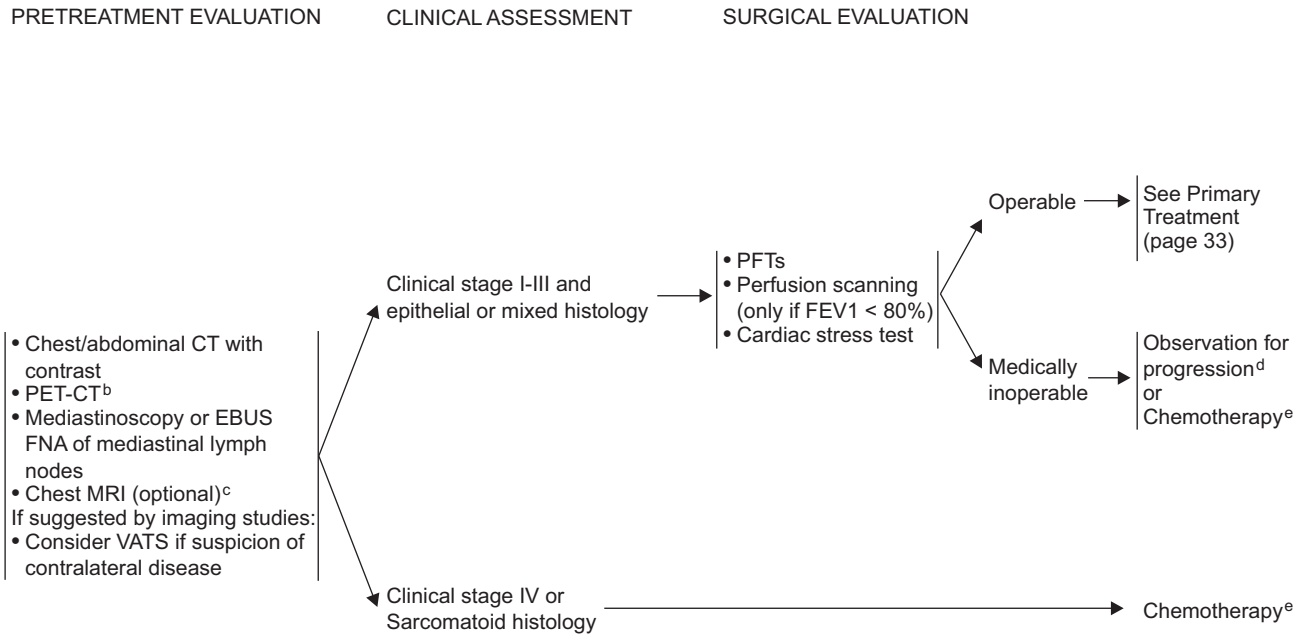
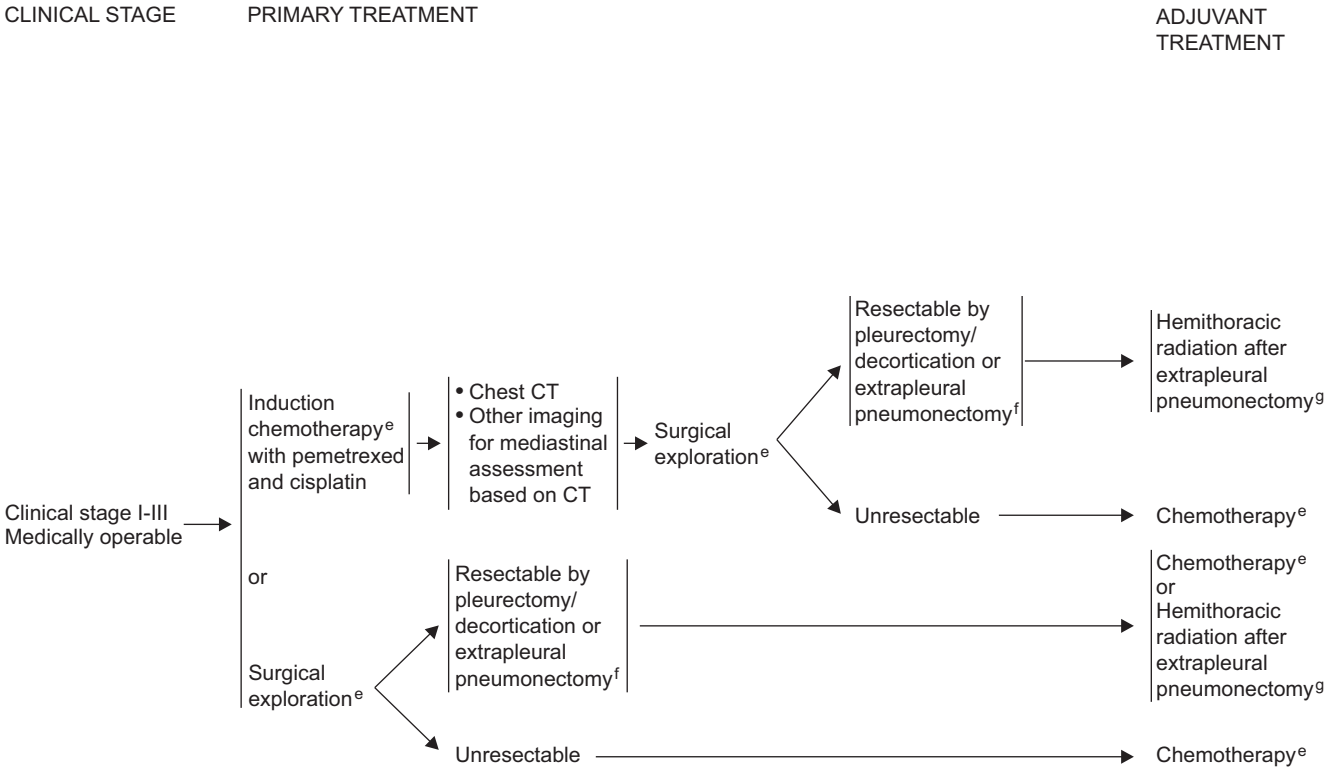


[b]Should be performed before any pleurodesis.
[c]For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[d]Observation for patients who are asymptomatic with minimal burden of disease.
[e]See Principles of Chemotherapy (page 31).



[e]See Principles of Chemotherapy (page 31).
[f]See Principles of Surgical Resection (page 31).
[g]See Principles of Radiation Therapy (pages 32-33).

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PRINCIPLES OF CHEMOTHERAPY

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

Pemetrexed, 500 mg/m^2 day 1
Cisplatin, 75 mg/m^2 day 1
Administered every 3 wk (category 1)[1]

Pemetrexed, 500 mg/m^2 day 1
Carboplatin, AUC 5 day 1
Administered every 3 wk[2,3]

Gemcitabine, 1000-1250 mg/m^2 days 1, 8, and 15
Cisplatin, 80-100 mg/m^2 day 1
Administered in 3- to 4-week cycles[4,5]

Pemetrexed, 500 mg/m^2 every 3 wk[6]

Vinorelbine, 25-30 mg/m^2 weekly[7]

SECOND-LINE CHEMOTHERAPY

Pemetrexed (if not administered as first-line)[8]
Vinorelbine[9]
Gemcitabine[10]

PRINCIPLES OF SURGICAL RESECTION

- Surgical resection should be performed on carefully evaluated patients by board certified thoracic surgeons.
- For patients being considered for surgery, a single-port thoracoscopy on the line of the potential incision is recommended.
- The goal of surgery is complete gross cytoreduction of the tumor. When this is not possible, such as in patients with multiple sites of chest wall invasion, surgery should be aborted.
- The surgical choices are (1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor; and (2) extrapleural pneumonectomy (EPP), which is defined as en-bloc resection of the pleura, lung, ipsilateral diaphragm, and often pericardium. Mediastinal node sampling should be performed.
- For good-risk patients with early disease (confined to the pleural envelope, no N2 lymph node involvement) and favorable histology (epithelioid), EPP may be the best option. For patients with advanced disease (high nodal disease, areas of local invasion), mixed histology, and/or high-risk, pleurectomy/decortication may be a better choice.[11]
- After recovery from surgery, patients should be referred for adjuvant therapy, which may include chemotherapy and radiation therapy, depending on whether any preoperative therapy was used and on the pathologic analysis of the surgical specimen.

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[4] Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 2002;87:491-496.
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PRINCIPLES OF RADIATION THERAPY

General Principles

- Recommendations regarding radiation therapy (RT) should be made by a radiation oncologist.
- The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed within a multidisciplinary team, including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- For patients with resectable MPM who undergo extrapleural pneumonectomy (EPP), adjuvant RT can be recommended for those with good performance status to improve local control.[1-6]
- The goal of adjuvant RT is to improve local control.
- RT can be used to prevent instrument-tract recurrence after pleural intervention.
- RT is an effective palliative treatment for relief of chest pain associated with mesothelioma.
- When there is limited or no resection of disease, delivery of high-dose RT to the entire hemithorax in the setting of an intact lung has not been shown to be associated with significant survival benefit, and the toxicity is significant.[1,5,6] RT under such circumstances or after pleurectomy/decortication is usually not recommended but may be considered with caution under strict dose limits of organs at risk or IRB-approved protocols.
- Acronyms and abbreviations related to RT are the same as listed in the principles of RT for non-small cell lung cancer (see the NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, available at www.NCCN.org).

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment.
  See Recommended Doses for Conventionally Fractionated Radiation Therapy (facing page).
- The dose of radiation for adjuvant therapy after EPP should be 50-60 Gy in 1.8- to 2.0-Gy fractions based on the margin status.A dose of 54 Gy given to the entire hemithorax, the thoracotomy incision, and sites of chest drains was well tolerated.[6,7] When it is challenging to deliver 50 Gy, every effort should be made to deliver a minimum dose of 40 Gy.[1]
- A dose of 60 Gy or greater should be delivered to macroscopic residual tumors, if the doses to adjacent normal structures are limited to their tolerances. In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall.[8-10]
- Daily doses of 4 Gy appear to be more efficacious than fractions of less than 4 Gy in providing relief from chest pain associated with mesothelioma,[9,11] although the optimal daily and total dose of RT for palliative purposes remain unclear.
- For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.[8,12] For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam radiation in combination with surgery.

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS $\leq$ 1, FEV1 > 80%, and good functional pulmonary status; renal scan must confirm good function of contralateral kidney, and restaging PET/CT or CAP CT should confirm absence of disease in contralateral chest, abdomen, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.

Radiation Techniques

- Use of conformal radiation technology is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.
- CT simulation-guided planning with conventional photon/electron RT is recommended.[7] IMRT is a promising treatment technique that allows a more conformal high-dose RT and improved coverage to the hemithorax. IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol. When IMRT is applied, the NCI/ASTRO IMRT guidelines (http://www.astro.org/Research/ResearchHighlights/documents/Imrt.pdf) should be followed strictly. Special attention should be paid to minimize radiation to the contralateral lung,[13] because the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.[14] The mean lung dose should be kept as low as possible, preferably < 8.5 Gy. The low dose volume should be minimized.[15]
- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
- The clinical tumor volume (CTV) for adjuvant RT after EPP should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
- Extensive elective nodal irradiation (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
- The planning target volume (PTV) should consider the target motion and daily setup errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of daily setup of each clinic.

See references on facing page.

Recommended Doses for Conventionally Fractionated Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
Preoperative	45-50 Gy	1.8-2 Gy	4-5 wk
Postoperative • Negative margins • Microscopic-macroscopic positive margins	 50-54 Gy 54-60 Gy	 1.8-2 Gy 1.8-2 Gy	 4-5 wk 5-6 wk
Palliative • Chest wall pain from recurrent nodules • Multiple brain or bone metastasis	 20-40 Gy or 30 Gy 30 Gy	 ≥ 4 Gy 3 Gy 3 Gy	 1-2 wk 2 wk 2 wk
Prophylactic radiation to prevent surgical tract recurrence	21 Gy	7 Gy	1-2 wk

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[5] Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg 1997;63:334-338.
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[15] Krayenbuehl J, Oertel S, Davis JB, Ciernik IF. Combined photon and electron three-dimensional conformal versus intensity-modulated radiotherapy with integrated boost for adjuvant treatment of malignant pleural mesothelioma after pleuropneumonectomy. Int J Radiat Oncol Biol Phys 2007;69:1593-1599.

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recent results about screening for lung cancer with low-dose computed tomography do not apply to malignant mesothelioma.[24] The NCCN Non–Small Cell Lung Cancer panel developed this guideline for MPM in 2010.

Diagnosis

Patients with suspected MPM often have symptoms (e.g., dyspnea and chest pain) and can also have pleural effusion, cough, chest wall mass, weight loss, fever, and sweating.[25] In patients with recurrent pleural effusion and/or pleural thickening, the recommended initial evaluation for suspected MPM includes 1) CT of the chest with contrast, 2) thoracentesis for cytologic assessment, and 3) pleural biopsy (e.g., thoracoscopic biopsy [preferred]; see Initial Evaluation, page 28).[26,27] However, cytologic samples are often negative even when patients have MPM. Talc pleurodesis or pleural catheter may be needed for management of pleural effusion.[28–31] Serum mesothelin–related peptide levels may also be assessed, and these levels may correlate with disease status[32–34]; osteopontin does not seem to be as useful for diagnosis.[35–39]

It can be difficult to distinguish malignant from benign pleural disease and also to distinguish MPM from other malignancies, such as metastatic adenocarcinoma, sarcoma, or other metastases to the pleura.[8,40,41] On CT, thymoma can mimic MPM; however, pleural effusion does not typically occur with thymoma. Diagnosis is difficult, because cytologic samples of pleural fluid are often negative.[42] Calretinin, WT1, D240, and cytokeratin 5/6 are useful immunohistochemical markers for diagnosing MPM, as are markers that typically are positive in pulmonary adenocarcinoma and negative in mesothelioma (e.g., thyroid transcription factor 1, carcinoembryonic antigen; see also the College of American Pathologists' Protocol for the Examination of Specimens from Patients with Malignant Pleural Mesothelioma at http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Mesothelioma_11protocol.pdf).[40]

Management

These guidelines recommend that patients with MPM be managed by a multidisciplinary team with experience in MPM. Treatment options for patients with MPM include surgery, radiotherapy, and/or chemotherapy[2]; select patients (clinical stages I–III, medically operable, good performance status) are candidates for multimodality therapy.[43–47] Definitive radiotherapy alone is not recommended for unresectable MPM (see the algorithm).[48,49] Appropriate patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists to assess whether they are candidates for multimodality treatment.

Pretreatment evaluation for patients diagnosed with MPM is performed to stage patients and assess whether they are candidates for surgery. This evaluation includes chest and abdominal CT with contrast and 18F-fluorodeoxyglucose (FDG)-PET/CT. Video-assisted thoracic surgery can be considered if contralateral disease is suspected. If possible, PET/CT scans should be obtained before pleurodesis, because talc causes pleural inflammation, which can affect the FDG avidity (i.e., false-positive result).[50–52] If surgical resection is being considered, mediastinoscopy or endobronchial ultrasonography fine-needle aspiration of the mediastinal lymph nodes is recommended.[53,54] The following tests may be performed if suggested by imaging: 1) laparoscopy to rule out transdiaphragmatic extension (e.g., extension to the peritoneum indicates stage IV [unresectable] disease) and 2) chest MRI.

Staging is performed using the International Mesothelioma Interest Group TNM staging system, which was approved by the American Joint Committee on Cancer.[55] Most patients have advanced disease at presentation. Accurately staging patients before surgery is difficult, and understaging is common with PET/CT.[52,56] However, PET/CT is useful for determining whether metastatic disease is present.[56,57] Patients with clinical stage I through III MPM can be evaluated for surgery using pulmonary function tests, perfusion scanning (if $FEV_1 < 80\%$), and cardiac stress tests (see Surgical Evaluation, page 29). Surgical resection is recommended for patients with clinical stage I through III MPM who are medically operable and can tolerate the surgery. Trimodality therapy (i.e., chemotherapy, surgery, and radiotherapy) is recommended for patients with clinical stages I through III MPM who are medically operable. Chemotherapy alone is recommended for those who are not operable, those with clinical stage IV MPM, or those with sarcomatoid histology (see Chemotherapy, page 31).

Pleural effusion can be managed using thoracoscopic talc pleurodesis or placement of a drainage catheter.[31,58–60] Therapeutic thoracentesis can also be used to remove pleural fluid and thus decrease dyspnea either before treatment or in patients who are not candidates for more aggressive treatment.

Surgery

Patients must undergo a careful assessment before surgery. Surgical resection for patients with MPM can include either pleurectomy/decortication (P/D; also known as total pleurectomy and lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor; or extrapleural pneumonectomy (EPP), which is enbloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium (see Principles of Surgical Resection, page 31).[61] Radical (or extended) P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[61] Mediastinal nodal dissection is recommended in patients having either P/D or EPP. In medically operable patients, the decision whether to perform a P/D or an EPP may not be made until surgical exploration.

The choice of surgery for MPM is controversial, because data from randomized controlled trials are not available.[2,62–65] EPP often would be required to remove all gross tumor in patients with stages II through III MPM.[25] In addition, neither EPP nor P/D will yield an R0 resection.[2,66] However, EPP is associated with higher morbidity and mortality; therefore, P/D (i.e., lung-preserving surgery) may be a better option for some patients.[67–72] A retrospective analysis (N = 663) found that the type of surgery did not affect survival regardless of whether patients had early-stage or advanced-stage disease.[2,69] In addition, because data from randomized trials are not available, surgery has not been shown to improve survival when compared with systemic therapy.[64]

A recent feasibility trial (Mesothelioma and Radical Surgery [MARS]) in 50 patients assessed whether EPP improves survival when compared with chemotherapy treatment alone.[73,74] Results suggest that EPP is not beneficial and is associated with morbidity when compared with chemotherapy.[73,75] However, a retrospective study (N = 540) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and pemetrexed.[76] The NCCN Guidelines panel and other clinicians recommend EPP for select good-risk patients (i.e., good performance status, absence of comorbidities) but not for those with comorbid conditions.[62,77]

For patients with operable early-stage disease (confined to the pleural envelope [stage I], no N2 lymph node involvement), EPP may be the best option for those with favorable histology (i.e., epithelioid), good performance status, and no comorbidities.[47,69,70,78] PD may be a better choice for those with operable advanced disease (stages II–III), mixed (biphasic) histology, and/or high-risk factors (poor performance status, comorbidities).[79] The NCCN Guidelines panel does not recommend surgery for patients with stage IV MPM or sarcomatoid histology; chemotherapy is recommended for these patients (see next section and Clinical Assessment, page 29).

Chemotherapy

Chemotherapy is recommended either alone for patients with medically inoperable MPM, or as part of a regimen for those with medically operable MPM (see Principles of Chemotherapy, page 31, for specific regimens). Patients with medically operable stage I through III MPM can receive chemotherapy either before or after surgery. Chemotherapy alone is recommended for patients with medically inoperable stages I through IV MPM and those with sarcomatoid histology.[80,81]

A combined first-line regimen using cisplatin and pemetrexed (category 1) is considered the gold standard for MPM, and is currently the only regimen approved by the FDA for malignant mesothelioma.[82,83] A phase III randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; the combined regimen increased survival when compared with cisplatin alone (12.1 vs. 9.3 months; $P = .02$).[82] Other acceptable first-line combination chemotherapy options recommended by NCCN include pemetrexed and carboplatin, which was assessed in 3 large phase II studies (median survival, 12.7, 14, and 14 months, respectively),[84–86] or gemcitabine and cisplatin, which was also assessed in phase II studies (median survival, 9.6–11.2 months).[87,88] Gemcitabine and cisplatin may be useful for patients who cannot take pemetrexed. A comparison of 1704 patients with

medically inoperable MPM treated with cisplatin/pemetrexed or carboplatin/pemetrexed as part of an expanded access trial found that outcomes with the regimens were similar.[89] The carboplatin/pemetrexed regimen is a better choice for patients with poor performance status and/or comorbidities.

Acceptable first-line single-agent options include pemetrexed or vinorelbine.[90–92] Second-line chemotherapy options include pemetrexed (if not administered first-line), vinorelbine, or gemcitabine.[93–95] Limited data are available to guide second-line therapy.[96]

Recently, trimodality therapy using chemotherapy, surgery, and hemithoracic radiotherapy has been used in patients with MPM,[43–46] with a median survival of up to 29 months reported.[44] Nodal status and response to chemotherapy can affect survival.[44,47] A small retrospective series showed that trimodality therapy using EPP did not improve survival over therapy without EPP.[66]

Radiation Therapy

The principles of radiation therapy are described in the algorithm (pages 32 and 33) and are summarized here; the algorithm in the NCCN Guidelines for Non–Small Cell Lung Cancer is also a useful resource (available at www.NCCN.org). In patients with MPM, radiotherapy can be used as part of a multimodality regimen; however, radiotherapy alone is not recommended (see next paragraph). Radiotherapy can also be used as palliative therapy for relief of chest pain or metastases in bone or brain (see also the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[48] The dose of radiation should be based on the purpose of treatment. The most appropriate timing for delivering radiotherapy (i.e., after surgical intervention, with or without chemotherapy) should be discussed by a multidisciplinary team.

After EPP, adjuvant radiotherapy has been shown to significantly reduce the local recurrence rate.[97,98] Patients who are candidates for radiotherapy have good performance status, pulmonary function, and kidney function (see Principles of Radiation Therapy, pages 32 and 33). However, in patients who have limited or no resection of disease (i.e., in the setting of an intact lung), high-dose radiotherapy to the entire hemithorax has not been shown to improve survival, and the toxicity is significant.[48] Radiotherapy can also be used to prevent instrument-tract recurrence after pleural intervention.[45,66,98–101]

CT simulation–guided planning with conventional photon/electron radiotherapy is recommended. The clinical target volumes should be reviewed with the thoracic surgeon to ensure coverage of all volumes at risk. The total doses of radiation are described in the algorithm (see Principles of Radiation Therapy, pages 32 and 33). A dose of 60 Gy or more should be delivered to macroscopic residual tumors, if the doses to normal adjacent structures are limited to their tolerances (see the NCCN Guidelines for Non–Small Cell Lung Cancer). In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall,[102–104] although this is controversial.[105–107]

Intensity-modulated radiotherapy (IMRT) allows a more conformal high-dose radiotherapy and improved coverage to the hemithorax at risk.[48,108] The NCI/ASTRO IMRT guidelines are recommended (http://www.astro.org/Research/ResearchHighlights/documents/Imrt.pdf). The ICRU83 (International Commission on Radiation Units & Measurements Report 83) guidelines are also useful (http://www.icru.org/index.php?option=com_content&task=view&id=171). Radiation to the contralateral lung should be minimized,[48,108,109] because the risk of fatal pneumonitis with IMRT is excessively high if strict limits are not applied.[110–112] The mean lung dose should be kept as low as possible, preferably less than 8.5 Gy. The volume of contralateral lung receiving low-dose radiotherapy (e.g., 5 Gy) should be minimized.[113] For patients with chest pain from mesothelioma, total doses of 20 to 40 Gy seem to be effective in relieving pain[102,103]; however, the optimal dose of radiotherapy for palliative purposes remains unclear.[114]

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Gregory J. Riely, MD, PhD	GlaxoSmithKline plc; Merck & Co., Inc.; Novartis AG; Infinity Pharmaceuticals; and Pfizer Inc.	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Chugai Pharmaceutical Co., Ltd.; and Tragara Pharmaceuticals, Inc.	None	None	9/23/2011
Eric Rohren, MD, PhD	None	None	None	None	9/30/2011
Scott J. Swanson, MD	None	Covidien; and Ethicon, Inc.	None	None	5/19/2011
Douglas E. Wood, MD	None	None	None	None	4/5/2011
Stephen C. Yang, MD	None	None	None	None	5/26/2011