Malignant Pleural Mesothelioma

Version 1.2013

NCCN.org
## NCCN Guidelines Version 1.2013 Panel Members

### Malignant Pleural Mesothelioma

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>David S. Ettinger, MD/Chair</td>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
</tr>
<tr>
<td>Lee M. Krug, MD/Lead</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Wallace Akerley, MD</td>
<td>Huntsman Cancer Institute at the University of Utah</td>
</tr>
<tr>
<td>Hossein Borghaei, DO, MS</td>
<td>Fox Chase Cancer Center</td>
</tr>
<tr>
<td>Andrew C. Chang, MD</td>
<td>University of Michigan Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Richard T. Cheney, MD</td>
<td>Roswell Park Cancer Institute</td>
</tr>
<tr>
<td>Lucian R. Chirieac, MD</td>
<td>Dana-Farber/Brigham and Women's Cancer Center</td>
</tr>
<tr>
<td>Thomas A. D'Amico, MD</td>
<td>Duke Cancer Institute</td>
</tr>
<tr>
<td>Todd L. Demmy, MD</td>
<td>Roswell Park Cancer Institute</td>
</tr>
<tr>
<td>Ramaswamy Govindan, MD</td>
<td>Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine</td>
</tr>
<tr>
<td>Frederic W. Grannis, Jr., MD</td>
<td>City of Hope Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Stefan C. Grant, MD, JD</td>
<td>University of Alabama at Birmingham Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Leora Horn, MD, MSc</td>
<td>Vanderbilt-Ingram Cancer Center</td>
</tr>
</tbody>
</table>

### Writing Committee Members

- Thierry M. Jahan, MD
  - UCSF Helen Diller Family Comprehensive Cancer Center
- Melissa Johnson, MD
  - Robert H. Lurie Comprehensive Cancer Center of Northwestern University
- Ritsuko Komaki, MD
  - The University of Texas MD Anderson Cancer Center
- Feng-Ming (Spring) Kong, MD, PhD
  - University of Michigan Comprehensive Cancer Center
- Mark G. Kris, MD
  - Memorial Sloan-Kettering Cancer Center
- Rudy P. Lackner, MD
  - UNMC Eppley Cancer Center at The Nebraska Medical Center
- Inga T. Lennes, MD
  - Massachusetts General Hospital Cancer Center
- Billy W. Loo, Jr., MD, PhD
  - Stanford Cancer Institute
- Renato Martins, MD, MPH
  - Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
- Gregory A. Otterson, MD
  - The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
- Jyoti D. Patel, MD
  - Robert H. Lurie Comprehensive Cancer Center of Northwestern University
- Mary C. Pinder-Schenck, MD
  - Moffitt Cancer Center
- Katherine M. Pisters, MD
  - The University of Texas MD Anderson Cancer Center
- Karen Reckamp, MD, MS
  - City of Hope Comprehensive Cancer Center
- Gregory J. Riely, MD, PhD
  - Memorial Sloan-Kettering Cancer Center
- Eric Rohren, MD, PhD
  - The University of Texas MD Anderson Cancer Center
- Theresa A. Shapiro, MD
  - The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
- Scott J. Swanson, MD
  - Dana-Farber/Brigham and Women’s Cancer Center
- Kurt Tauer, MD
  - University of Tennessee Cancer Institute
- Douglas E. Wood, MD
  - Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
- Stephen C. Yang, MD
  - The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
- Kristina Gregory, RN, MSN, OCN
- Miranda Hughes, PhD

### Disclosures

- Medical oncology
- Surgery/Surgical oncology
- Radiation oncology/Radiotherapy
- Pathology
- Hematology/Hematology oncology
- Diagnostic/Interventional radiology
- Patient advocate
- Writing Committee Member
# Malignant Pleural Mesothelioma

## Summary of Guidelines Updates

### Initial Evaluation (MPM-1)

### Pretreatment Evaluation (MPM-2)

### Clinical Stage I-III, Treatment for Medically Inoperable (MPM-2)

### Clinical Stage I-III, Treatment for Medically Operable (MPM-3)

### Principles of Supportive Care (MPM-A)

### Principles of Chemotherapy (MPM-B)

### Principles of Surgical Resection (MPM-C)

### Principles of Radiation Therapy (MPM-D)

### Staging (ST-1)

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Summary of changes in the 1.2013 version of the Guidelines for Malignant Pleural Mesothelioma from the 2.2012 version include:

MPM-1
- Footnote “a” added: “There are no data to suggest that screening improves survival.”
- The following moved to “Principles of Supportive Care”
  - “Talc pleurodesis or pleural catheter, if required for management of pleural effusion” and associated footnote “Recommend obtaining PET-CT before pleurodesis.”

MPM-2
- Pretreatment Evaluation, last bullet modified: Consider VATS and/or laparoscopy if suspicion of contralateral or peritoneal disease.
- Footnote “d” added: “Assessment by multidisciplinary team with experience in malignant pleural mesothelioma.”
- Footnote “e” added: “See Principles of Supportive Care (MPM-A).” (also applies to MPM-3)

MPM-3
- Surgical exploration; Extrapleural pneumonectomy, “chemotherapy or hemithoracic RT” changed to “chemotherapy + hemithoracic RT.”

MPM-A
- “Principles of Supportive Care” is a new section for the Guidelines.

MPM-B
- References 4, 10, 13 and 14 added.
- Second-line chemotherapy: category 1 added to pemetrexed.
- Second-line chemotherapy, pemetrexed: The following sentence was added, “Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted.”
- Footnote “**” added: “Pemetrexed-based chemotherapy may also be used for peritoneal mesothelioma and tunica vaginalis testis mesothelioma.”

MPM-C
- Bullet 1 modified: Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons with experience in managing MPM.

- Bullet 4 modified: 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. The goal is to obtain 3 nodal stations, if technically feasible.
- Bullet 5 is new to the page: “Numerous studies have defined sarcomatoid and mixed tumors as poor prognostic factors after EPP.”
- Bullet 6 modified: For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid) in good-risk patients, P/D should be the first option. EPP may be considered in select patients for complete gross cytoreduction (the best option. For advanced disease (high nodal disease, areas of local invasion), mixed histology, and/or high-risk patients, pleurectomy/decortication may be a better choice.
- Bullet 7 is new to the page: “If N2 disease is identified, surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.”

MPM-D (2 of 3)
- Table for “Recommended Doses for Conventionally Fractionated Radiation Therapy,” preoperative doses deleted.
- First statement modified: After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤1, FEV1 > 80%, and good functional pulmonary status; renal scan must confirm good function of contralateral kidney, restaging PET/CT or CAP CT should confirmed by renal scan; and absence of disease in abdomen, contralateral chest, or elsewhere.
- References 13 and 14 added.
INITIAL EVALUATION\textsuperscript{a}

- CT chest with contrast
- Thoracentesis for cytologic assessment
- Pleural biopsy (eg, Abrams needle, CT-guided core biopsy, thoracoscopic biopsy [preferred], or open biopsy)
- Soluble mesothelin-related peptide (optional)

\textsuperscript{a}There are no data to suggest that screening improves survival.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Malignant pleural mesothelioma →
- Chest/abdominal CT with contrast
- PET-CT
- Mediastinoscopy or EBUS
- FNA of mediastinal lymph nodes
- Chest MRI (optional)
  If suggested by imaging studies:
- Consider VATS and/or laparoscopy if suspicion of contralateral or peritoneal disease

Clinical stage I-III and Epithelial or Mixed histology
- Clinical stage IV or Sarcomatoid histology

Operable → See Primary Treatment (MPM-3)

Medically inoperable → Observation for progression or Chemotherapy

Chemotherapy

PRETREATMENT EVALUATION

CLINICAL ASSESSMENT

SURGICAL EVALUATION

TREATMENT

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Principles of Supportive Care (MPM-A).

See Principles of Chemotherapy (MPM-B).

b Should be performed before any pleurodesis.

c For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.

d Assessment by multidisciplinary team with experience in malignant pleural mesothelioma.

e See Principles of Supportive Care (MPM-A).

f Observation for patients who are asymptomatic with minimal burden of disease.

g See Principles of Chemotherapy (MPM-B).
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Malignant Pleural Mesothelioma

**CLINICAL STAGE**

**PRIMARY TREATMENT**

- Induction chemotherapy with pemetrexed and cisplatin
- Surgical exploration

**ADJUVANT TREATMENT**

- Resectable
  - Pleurectomy/decortication
  - Extrapleural pneumonectomy
  - Hemithoracic RT
- Unresectable
  - Chemotherapy

**Clinical stage I-III**

- Medically operable
  - Surgery

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See Principles of Supportive Care (MPM-A).
See Principles of Chemotherapy (MPM-B).
See Principles of Surgery (MPM-C).
See Principles of Radiation Therapy (MPM-D).

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PRINCIPLES OF SUPPORTIVE CARE

- Pleural effusions: Talc pleurodesis or pleural catheter, if required for management of pleural effusion\(^a\)
- Smoking cessation counseling and intervention (http://www.smokefree.gov/)
- Pain management: See NCCN Guidelines for Adult Cancer Pain
- Nausea/vomiting: See NCCN Guidelines for Antiemesis
- Psychosocial distress: See NCCN Guidelines for Distress Management
- See NCCN Guidelines for Palliative Care as indicated

\(^a\)Recommend obtaining PET/CT before pleurodesis. Confirm diagnosis of malignant pleural mesothelioma (MPM) prior to pleurodesis. If MPM is suspected, consider evaluation by a multidisciplinary team with expertise in MPM.
## PRINCIPLES OF CHEMOTHERAPY

### FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

<table>
<thead>
<tr>
<th><em>Pemetrexed</em> 500 mg/m² day 1</th>
<th><em>Cisplatin</em> 75 mg/m² day 1</th>
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</thead>
<tbody>
<tr>
<td>Administered every 3 weeks (category 1)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

- **Pemetrexed*** 500 mg/m² day 1
- **Carboplatin AUC 5 day 1**
- **Gemcitabine 1000-1250 mg/m² days 1, 8, and 15**
- **Cisplatin 80-100 mg/m² day 1**
- **Vinorelbine 25-30 mg/m² weekly**<sup>8</sup>

*Pemetrexed-based chemotherapy may also be used for peritoneal mesothelioma and tunica vaginalis testis mesothelioma.<sup>14</sup>*

### SECOND-LINE CHEMOTHERAPY

- **Pemetrexed*** (if not administered as first-line) (category 1)<sup>9</sup>
- **Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted**<sup>10</sup>
- **Vinorelbine**<sup>11</sup>
- **Gemcitabine**<sup>12,13</sup>

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PRINCIPLES OF SURGERY

- Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons with experience in managing MPM.
- 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. In cases where this is not possible, such as in 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. The goal is to obtain 3 nodal stations, if technically feasible.
- Numerous studies have defined sarcomatoid and mixed tumors as poor prognostic factors after EPP.
- For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid) in good-risk patients, P/D should be the first option. EPP may be considered in select patients for complete gross cytoreduction.
- If N2 disease is identified, surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.
- After recovery from surgery, patients should be referred for adjuvant therapy, which may include chemotherapy and radiation therapy (RT) depending on whether any preoperative therapy was used and on the pathologic analysis of the surgical specimen.

PRINCIPLES OF RADIATION THERAPY (1 of 3)

General Principles

- Recommendations regarding 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 in a multidisciplinary team, including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- For patients with resectable MPM, who undergo EPP, adjuvant RT can be recommended for patients with good performance status to improve local control.\textsuperscript{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.\textsuperscript{1,5,6} RT under such circumstances or after P/D 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 NCCN Guidelines for Non-Small Cell Lung Cancer.

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 (MPM-D 2 of 3).

  - The dose of radiation for adjuvant therapy following EPP should be 50-60 Gy in 1.8-2.0 Gy 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.\textsuperscript{5,7} When it is challenging to deliver 50 Gy, every effort should be made to deliver a minimum dose of 40 Gy.\textsuperscript{1}

  - A dose ≥60 Gy 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.\textsuperscript{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,\textsuperscript{9,11} although the optimal daily and total dose of RT for palliative purposes remains unclear.

  - For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.\textsuperscript{8,12} For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam radiation in combination with surgery.
### PRINCIPLES OF RADIATION THERAPY (2 of 3)

#### Recommended Doses for Conventionally Fractionated Radiation Therapy

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Total dose</th>
<th>Fraction size</th>
<th>Treatment duration</th>
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</thead>
<tbody>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative margins</td>
<td>50-54 Gy</td>
<td>1.8-2 Gy</td>
<td>4-5 weeks</td>
</tr>
<tr>
<td>Microscopic-macroscopic positive margins</td>
<td>54-60 Gy</td>
<td>1.8-2 Gy</td>
<td>5-6 weeks</td>
</tr>
<tr>
<td>Palliative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest wall pain from recurrent nodules</td>
<td>20-40 Gy</td>
<td>≥4 Gy</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Multiple brain or bone metastasis</td>
<td>or 30 Gy</td>
<td>3 Gy</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Prophylactic radiation to prevent surgical tract recurrence</td>
<td>21 Gy</td>
<td>7 Gy</td>
<td>1-2 weeks</td>
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</table>

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤1, good functional pulmonary status; good function of contralateral kidney confirmed by renal scan; and absence of disease in abdomen, contralateral chest, 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. IMRT is a promising treatment technique that allows for 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 and ASTRO/ACR IMRT guidelines should be strictly followed. Special attention should be paid to minimize radiation to the contralateral lung, as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied. The mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.
- 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 target 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 set-up errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

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PRINCIPLES OF RADIATION THERAPY (3 of 3) - References


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### Table 1.
**International Mesothelioma Interest Group (IMIG) Staging System for Diffuse Malignant Pleural Mesothelioma**

<table>
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<th>Stage Grouping</th>
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<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
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<td>Any T</td>
<td>Any N</td>
<td>Any N</td>
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*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.*

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Discussion

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.

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Overview

Mesothelioma is a rare cancer that is estimated to occur in approximately 2,500 people in the United States every year. This NCCN Guideline focuses on malignant pleural mesothelioma (MPM), which is the most common type; mesothelioma can also occur in lining of other sites (e.g., peritoneum, pericardium, tunica vaginalis testis). The disease is difficult to treat, because most patients have advanced disease at presentation. Median overall survival is approximately 1 year; cure is rare. MPM occurs mainly in older men (median age of 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20–40 years later).

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 reported cases than anywhere else in the world. Although asbestos is no longer mined in the United States, it is still imported. The incidence of MPM is increasing in other countries (such as Russia, Western Europe, China, and India). Mortality rates from MPM are highest in the United Kingdom, Netherlands, and Australia; mortality rates are increasing in several countries (such as Japan, Argentina, and Brazil). Russia, China, Brazil, and Canada are the top producers of asbestos. Although most mesothelioma is linked to asbestos exposure, reports suggest that radiotherapy may also cause mesothelioma. Recent data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma. Genetic factors may also play a role in MPM. Smoking is not a risk factor for mesothelioma. However, patients who smoke have been exposed to asbestos are at increased risk for lung cancer. In addition, patients who smoke should be encouraged to quit because smoking impedes treatment (e.g., delays wound healing after surgery).

Diagnosis

Patients with suspected MPM often have symptoms (such as dyspnea and chest pain) and can also have pleural effusion, cough, chest wall mass, weight loss, fever, and sweating. 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., thorascopic biopsy [preferred]) (see “Initial Evaluation” in the NCCN Guidelines for MPM). Note that the recent data about screening for lung cancer with low-dose CT do not apply to MPM. The NCCN Non-Small Cell Lung Cancer Panel developed this guideline for MPM in 2010.

The histologic subtypes of mesothelioma include epithelioid (most common), biphasic or mixed, and sarcomatoid. 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. Although screening for mesothelioma has been studied in high-risk patients (i.e., those with asbestos exposure), the NCCN Guidelines do not recommend screening for MPM because it has not been shown to decrease mortality. Note that the recent data about screening for lung cancer with low-dose CT do not apply to MPM.

Serum mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status; osteopontin does not appear to be as useful for diagnosis.
metastatic adenocarcinoma, sarcoma, or other metastases to the pleura. On CT, thymoma can mimic MPM; however, pleural effusion does not typically occur with thymoma. Cytologic samples of pleural fluid are often negative. Calretinin, WT-1, D2-40, and cytokeratin (CK) 5/6 are useful immunohistochemical markers for the diagnosis of MPM, as are markers that typically are positive in pulmonary adenocarcinoma and negative in mesothelioma (eg, thyroid transcription factor 1 [TTF-1], carcinoembryonic antigen [CEA]) (see also the College of American Pathologists [CAP] protocol http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Mesothelioma_12protocol.pdf).

Management

The NCCN Guidelines recommend that patients with MPM be managed by a multidisciplinary team with experience in MPM. Treatment options for patients with MPM include surgery, radiation therapy (RT), and/or chemotherapy; select patients (ie, clinical stages I–III, medically operable, good performance status [PS]) are candidates for multimodality therapy. Definitive RT alone is not recommended for unresectable MPM (see “Treatment” in the NCCN Guidelines for MPM). Appropriate patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists to assess if they are candidates for multimodality treatment.

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

Staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system (see Table 1), which was approved by the American Joint Committee on Cancer (AJCC). Most patients have advanced disease at presentation. However, it is difficult to accurately stage patients before surgery. Understaging is common with PET-CT. However, PET-CT is useful for determining whether metastatic disease is present. Patients with clinical stage I to III MPM can be evaluated for surgery using pulmonary function tests (PFTs), perfusion scanning (if FEV1 < 80%), and cardiac stress tests (see “Surgical Evaluation” in the NCCN Guidelines for MPM). Surgical resection is recommended for patients with clinical stage I to III MPM who are medically operable and can tolerate the surgery. multimodality therapy (ie, chemotherapy, surgery, RT) is recommended for patients with clinical stages I to III MPM who are medically operable (see “Treatment” in the NCCN Guidelines for MPM). Chemotherapy alone is recommended for those who are not operable, those with clinical stage IV MPM, or those with sarcomatoid histology (see the section on “Chemotherapy” in this Discussion and “Principles of Chemotherapy” in the NCCN Guidelines for MPM).

Pleural effusion can be managed using thoracoscopic talc pleurodesis or placement of a drainage catheter. Therapeutic/palliative thoracentesis can also be used to remove pleural fluid and thus...
decrease dyspnea either before treatment or for patients who are not candidates for more aggressive treatment.

**Surgery**

It is essential that patients receive a careful assessment before surgery is performed. Surgical resection for patients with MPM can include either 1) pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor; or 2) extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium (see “Principles of Surgical Resection” in the NCCN Guidelines for MPM). Radical (or extended) P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy. Mediastinal nodal dissection is recommended in patients having either P/D or EPP. In medically operable patients, the decision about whether to do 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. EPP would often be required to remove all gross tumor in patients with stages II to III MPM. Neither EPP nor P/D will yield an R0 resection. However, EPP is associated with higher morbidity and mortality. Therefore, P/D (ie, lung-preserving surgery) may be a better option for many patients with stage I to III disease. A retrospective analysis (n=663) suggested that survival was greater after P/D than after EPP, but this may have been confounded by patient selection.

A recent feasibility trial (Mesothelioma and Radical Surgery [MARS]) in 50 patients assessed whether EPP improves survival when compared with chemotherapy treatment alone. Results suggest that EPP is not beneficial and is associated with morbidity when compared with chemotherapy, but these results were controversial due to the small sample size and the higher than expected surgical mortality. A retrospective study (540 patients) reported that several factors yielded increased survival for select patients including EPP, surgeon experience, and pemetrexed. The NCCN Panel and other clinicians recommend EPP for select good-risk patients who require a complete cytoreduction (ie, good PS, no comorbidities, stage II-III patients, favorable histology [ie, epithelioid], no N2 disease), but EPP is not recommended for high-risk patients (eg, unfavorable histology [eg, sarcomatoid, mixed tumors]). A retrospective study (540 patients) reported that several factors yielded increased survival for select patients including EPP, surgeon experience, and pemetrexed. The NCCN Panel and other clinicians recommend EPP for select good-risk patients who require a complete cytoreduction (ie, good PS, no comorbidities, stage II-III patients, favorable histology [ie, epithelioid], no N2 disease), but EPP is not recommended for high-risk patients (eg, unfavorable histology [eg, sarcomatoid, mixed tumors]).

For patients with operable early-stage disease (confined to the pleural envelope [stage I], no N2 lymph node involvement), P/D should be the first option. P/D may be more appropriate for patients with advanced MPM who cannot tolerate an EPP. P/D may also be useful for symptom control (eg, patients with entrapped lung syndrome). The NCCN Panel does not recommend surgery for patients with stage IV MPM or sarcomatoid histology; chemotherapy is recommended for these patients (see the section on “Chemotherapy” in this Discussion and “Treatment” in the NCCN Guidelines for MPM). In addition, surgery is not generally recommended for patients with N2 disease unless performed at a center of expertise or in a clinical trial.

**Chemotherapy**

Chemotherapy is recommended either alone for medically inoperable patients with MPM or as part of a regimen for patients with medically operable MPM (see “Treatment” in the NCCN Guidelines for MPM). Patients with medically operable stage I to III MPM can receive chemotherapy either before or after surgery (see “Treatment” in the NCCN Guidelines for MPM). Chemotherapy alone is recommended for...
patients with medically inoperable stages I to IV MPM and those with sarcomatoid histology.\textsuperscript{93,94}

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 U.S. Food and Drug Administration for MPM.\textsuperscript{95,96} 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, \(P = .02\)).\textsuperscript{95} Other acceptable first-line combination chemotherapy options recommended by NCCN include: 1) pemetrexed and carboplatin, which was assessed in 3 large phase II studies (median survival = 12.7, 14, and 14 months, respectively),\textsuperscript{97-99} or 2) gemcitabine and cisplatin, which was also assessed in phase II studies (median survival = 9.6 to 11.2 months).\textsuperscript{100,101} Gemcitabine and cisplatin may be useful for patients who cannot take pemetrexed. A comparison of 1,704 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.\textsuperscript{102} The carboplatin/pemetrexed regimen is a better choice for patients with poor PS and/or comorbidities.

Acceptable first-line single-agent options include pemetrexed or vinorelbine.\textsuperscript{103-105} Second-line chemotherapy options include pemetrexed (if not administered first line) (category 1), vinorelbine, or gemcitabine.\textsuperscript{104,106-110} Data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed.\textsuperscript{111} Limited data are available to guide second-line therapy, although several agents are in clinical trials.\textsuperscript{112-114}

Trimodality therapy using chemotherapy, surgery, and hemithoracic RT has been used in patients with MPM.\textsuperscript{54-57,115} Median survival of up to 29 months has been reported for patients who complete trimodality therapy.\textsuperscript{55} Nodal status and response to chemotherapy can affect survival.\textsuperscript{55,58} In a small retrospective series, trimodality therapy using EPP did not improve survival when compared with patients who did not receive EPP.\textsuperscript{77}

**Radiation Therapy**

The Principles of Radiation Therapy are described in the NCCN Mesothelioma algorithm and are summarized in this Discussion; the NCCN Guidelines for Non-Small Cell Lung Cancer are also a useful resource. In patients with MPM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended (see next paragraph). RT can also be used as palliative therapy for relief of chest pain or metastases in bone or in the brain (see the NCCN Guidelines for Central Nervous System Cancers).\textsuperscript{59,116} The dose of radiation should be based on the purpose of treatment.\textsuperscript{117} The most appropriate timing of delivering RT (ie, after surgical intervention, with or without chemotherapy) should be discussed with a multidisciplinary team.

After EPP, adjuvant RT has been shown to significantly reduce the local recurrence rate.\textsuperscript{118,119} Patients are candidates for RT if they have good PS, pulmonary function, and kidney function (see “Principles of RT” in the NCCN Guidelines for MPM). However, in patients with limited or no resection of disease (ie, in the setting of an intact lung), high-dose RT to the entire hemithorax has not been shown to improve survival and the toxicity is significant.\textsuperscript{59} RT can also be used to prevent instrument-tract recurrence after pleural intervention.\textsuperscript{56,77,119-122}

CT simulation–guided planning with conventional photon/electron RT is recommended. The clinical target volumes should be reviewed with the thoracic surgeon to ensure coverage of all the volumes at risk. The total
doses of radiation are described in the algorithm (see “Principles of RT” in the NCCN Guidelines for MPM). 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, although this is controversial.

Intensity-modulated RT (IMRT) allows a more conformal high-dose RT and improved coverage to the hemithorax at risk. The NCI and ASTRO/ACR IMRT guidelines are recommended (http://rrp.cancer.gov/content/docs/imrt.doc). The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) guidelines are also useful http://www.icru.org/index.php?option=com_content&task=view&id=171.

RT to the contralateral lung should be minimized, because fatal pneumonitis may occur with IMRT if strict limits are not applied. 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 RT (eg, 5 Gy) should be minimized. For patients with chest pain from mesothelioma, total doses of 20 to 40 Gy appear to be effective in providing relief from pain; however, the optimal dose of RT for palliative purposes remains unclear.
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