

NCCN

Malignant Pleural Mesothelioma

Clinical Practice Guidelines in Oncology

David S. Ettinger, MD; Wallace Akerley, MD;
Hossein Borghaei, DO, MS; Andrew Chang, MD;
Richard T. Cheney, MD; Lucian R. Chirieac, MD;
Thomas A. D'Amico, MD; Todd L. Demmy, MD;
Apar Kishor P. Ganti, MD; Ramaswamy Govindan, MD;
Frederic W. Grannis, Jr., MD; Leora Horn, MD, MSc;
Thierry M. Jahan, MD; Mohammad Jahanzeb, MD;
Anne Kessinger, MD; Ritsuko Komaki, MD;
Feng-Ming (Spring) Kong, MD, PhD, MPH; Mark G. Kris, MD;
Lee M. Krug, MD; Inga T. Lennes, MD;

Billy W. Loo, Jr., MD, PhD; Renato Martins, MD;
Janis O'Malley, MD; Raymond U. Osarogiagbon, MD;
Gregory A. Otterson, MD; Jyoti D. Patel, MD;
Mary Pinder-Schenck, MD; Katherine M. Pisters, MD;
Karen Reckamp, MD, MS; Gregory J. Riely, MD, PhD;
Eric Rohren, MD, PhD; Scott J. Swanson, MD;
Douglas E. Wood, MD; and Stephen C. Yang, MD

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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

© National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.

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.

Journal of the National Comprehensive Cancer Network

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

*David S. Ettinger, MD/Chair†

The Sidney Kimmel Comprehensive Cancer Center at
Johns Hopkins

Wallace Akerley, MD†

Huntsman Cancer Institute at the University of Utah

Hossein Borghaei, DO, MS†‡

Fox Chase Cancer Center

Andrew Chang, MD¶

University of Michigan Comprehensive Cancer Center

Richard T. Cheney, MD‡

Roswell Park Cancer Institute

Lucian R. Chirieac, MD‡

Dana-Farber/Brigham and Women's Cancer Center

Thomas A. D'Amico, MD¶

Duke Cancer Institute

Todd L. Demmy, MD¶

Roswell Park Cancer Institute

Ramaswamy Govindan, MD†

Siteman Cancer Center at Barnes-Jewish Hospital and
Washington University School of Medicine

Frederic W. Grannis, Jr., MD¶

City of Hope Comprehensive Cancer Center

Leora Horn, MD, MSc, FRCPC†

Vanderbilt-Ingram Cancer Center

Thierry M. Jahan, MD†‡

UCSF Helen Diller Family Comprehensive Cancer Center

Mohammad Jahanzeb, MD†

St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

Anne Kessinger, MD†

UNMC Eppley Cancer Center at
The Nebraska Medical Center

Ritsuko Komaki, MD§

The University of Texas MD Anderson Cancer Center

Feng-Ming (Spring) Kong, MD, PhD, MPH§

University of Michigan Comprehensive Cancer Center

Mark G. Kris, MD†

Memorial Sloan-Kettering Cancer Center

*Lee M. Krug, MD†

Memorial Sloan-Kettering Cancer 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

Janis O'Malley, MD¶

University of Alabama at Birmingham
Comprehensive Cancer Center

Raymond U. Osarogbiagbon, MD†

St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

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 Pinder-Schenck, MD†

H. Lee Moffitt Cancer Center & Research Institute

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

Scott J. Swanson, MD¶

Dana-Farber/Brigham and Women's Cancer Center

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

NCCN Staff: Kristina Gregory, RN, MSN, and Miranda Hughes, PhD

KEY:

*Writing Committee Member

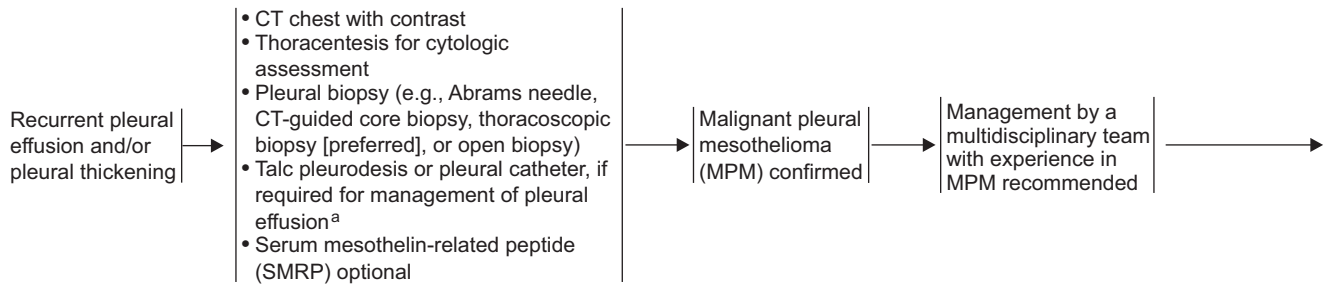
Specialties: †Medical Oncology; ‡Hematology/Hematology Oncology;

¶Surgery/Surgical Oncology; ‡Pathology; §Radiation Oncology/

Radiotherapy; ¶Diagnostic/Interventional Radiology

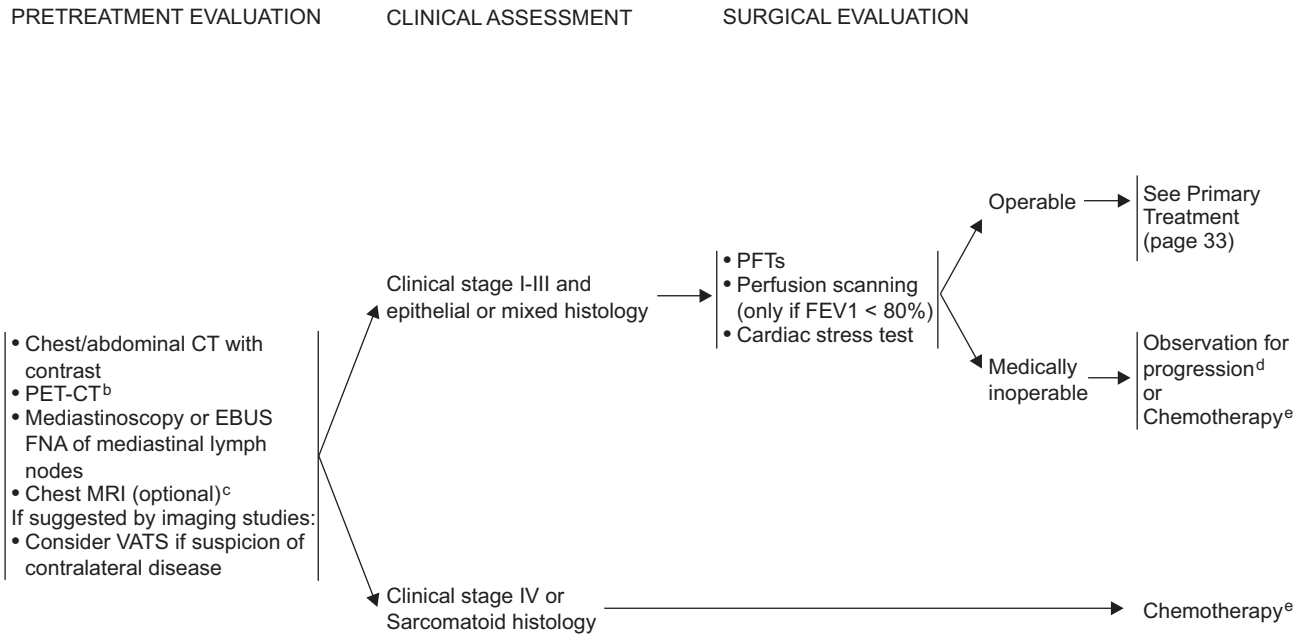
INITIAL EVALUATION

PATHOLOGIC DIAGNOSIS

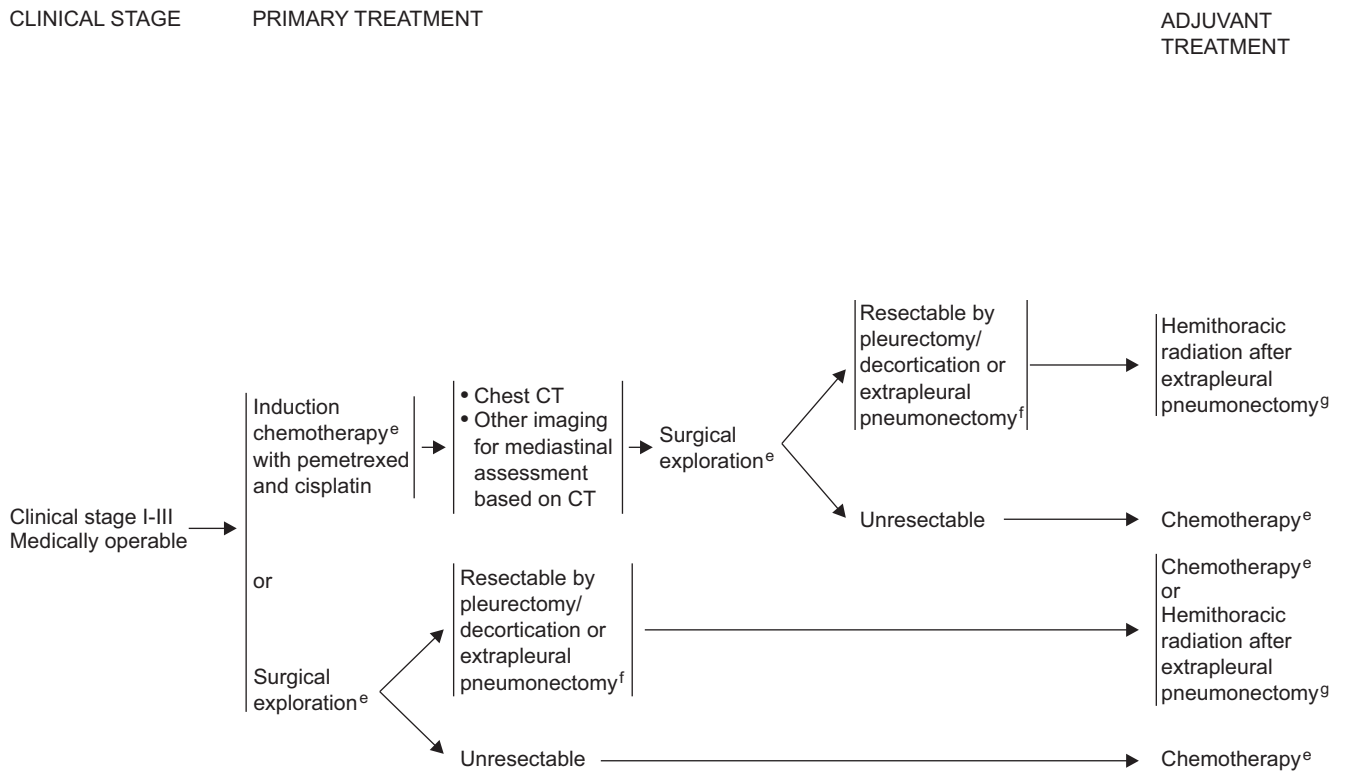


^aRecommend obtaining PET/CT before pleurodesis.

Malignant Pleural Mesothelioma Version 2:2012



^bShould be performed before any pleurodesis.
^cFor further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
^dObservation for patients who are asymptomatic with minimal burden of disease.
^eSee Principles of Chemotherapy (page 31).



^eSee Principles of Chemotherapy (page 31).

^fSee Principles of Surgical Resection (page 31).

^gSee Principles of Radiation Therapy (pages 32-33).

Malignant Pleural Mesothelioma Version 2:2012

PRINCIPLES OF CHEMOTHERAPY

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

Pemetrexed, 500 mg/m² day 1
Cisplatin, 75 mg/m² day 1
Administered every 3 wk (category 1)¹

Pemetrexed, 500 mg/m² day 1
Carboplatin, AUC 5 day 1
Administered every 3 wk^{2,3}

Gemcitabine, 1000-1250 mg/m² days 1, 8, and 15
Cisplatin, 80-100 mg/m² day 1
Administered in 3- to 4-week cycles^{4,5}

Pemetrexed, 500 mg/m² every 3 wk⁶

Vinorelbine, 25-30 mg/m² weekly⁷

SECOND-LINE CHEMOTHERAPY

Pemetrexed (if not administered as first-line)⁸
Vinorelbine⁹
Gemcitabine¹⁰

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.

¹Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636-2644.

²Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma. *Ann Oncol* 2008;19:370-373.

³Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol* 2006;24:1443-1448.

⁴Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491-496.

⁵Van Haarst JM, Baas J, Manegold CH, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002;86:342-345.

⁶Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol* 2008;3:764-771.

⁷Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685-1694.

⁸Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008;26:1698-1704.

⁹Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009;63:94-97.

¹⁰Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005;16:923-927.

¹¹Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008;135:620-626.

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.

Malignant Pleural Mesothelioma Version 2:2012

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 <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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

- ¹ Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2005;63:1045-1052.
- ² Gupta V, Krug LM, Laser B, et al. Patterns of local and nodal failure in malignant pleural mesothelioma after extrapleural pneumonectomy and photon-electron radiotherapy. *J Thorac Oncol* 2009;4:746-750.
- ³ Bölükbas S, Manegold C, Eberlein M, et al. Survival after trimodality therapy for malignant pleural mesothelioma: radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. *Lung Cancer* 2011;71:75-81.
- ⁴ Hasani A, Alvarez JM, Wyatt JM, et al. Outcome for patients with malignant pleural mesothelioma referred for trimodality therapy in western Australia. *J Thorac Oncol* 2009;4:1010-1016.
- 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.
- ⁶ Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 2001;122:788-795.
- ⁷ Yajnik S, Rosenzweig KE, Mychalczak B, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2003;56:1319-1326.
- ⁸ Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma: a randomized trial of local radiotherapy. *Chest* 1995;108:754-758.
- ⁹ de Graff-Strukowska L, van der Zee J, van Putten, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura—a single institution experience with 189 patients. *Int J Radiat Oncol Biol Phys* 1999;43:511-516.
- ¹⁰ de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma. *Chest* 2002;121:480-487.
- ¹¹ Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: a review of a 5-year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990;13:4-9.
- ¹² Di Salvo M, Gambaro G, Pagella S, et al. Prevention of malignant seeding at drain sites after invasive procedures (surgery and/or thoracoscopy) by hypofractionated radiotherapy in patients with pleural mesothelioma. *Acta Oncol* 2008;47:1094-1098.
- ¹³ Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2007;84:1685-1692.
- ¹⁴ Allen AM, Czerminska M, Janne PA, et al. Fatal pneumonitis associated with intensity modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640-645.
- ¹⁵ Kraysenbuehl 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.

Malignant Pleural Mesothelioma

Text continued from p. 27

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 chemotherapy²; 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).

Malignant Pleural Mesothelioma

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 en bloc 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

Malignant Pleural Mesothelioma

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

References

1. Price B, Ware A. Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005. *Crit Rev Toxicol* 2009;39:576–588.
2. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant pleural mesothelioma. *J Clin Oncol* 2009;27:2081–2090.
3. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. *J Occup Med* 1992;34:718–721.

Malignant Pleural Mesothelioma

4. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canada. *Cancer* 1980;46:2736–2740.
5. Park EK, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect* 2011;119:514–518.
6. Malignant mesothelioma mortality—United States, 1999–2005. *MMWR Morb Mortal Wkly Rep* 2009;58:393–396.
7. Nishikawa K, Takahashi K, Karjalainen A, et al. Recent mortality from pleural mesothelioma, historical patterns of asbestos use, and adoption of bans: a global assessment. *Environ Health Perspect* 2008;116:1675–1680.
8. Larson T, Melnikova N, Davis SI, Jamison P. Incidence and descriptive epidemiology of mesothelioma in the United States, 1999–2002. *Int J Occup Environ Health* 2007;13:398–403.
9. Price B, Ware A. Mesothelioma trends in the United States: an update based on Surveillance, Epidemiology, and End Results Program data for 1973 through 2003. *Am J Epidemiol* 2004;159:107–112.
10. Peto J, Decarli A, La Vecchia C, et al. The European mesothelioma epidemic. *Br J Cancer* 1999;79:666–672.
11. Leigh J, Davidson P, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945–2000. *Am J Ind Med* 2002;41:188–201.
12. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005;97:1354–1365.
13. Teta MJ, Lau E, Scurman BK, Wagner ME. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. *Cancer* 2007;109:1432–1438.
14. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. *Blood* 2009;113:3679–3681.
15. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. *Cancer* 1996;77:1379–1385.
16. Witherby SM, Butnor KJ, Grunberg SM. Malignant mesothelioma following thoracic radiotherapy for lung cancer. *Lung Cancer* 2007;57:410–413.
17. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A* 2011;108:13618–13623.
18. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet* 2011;43:1022–1025.
19. Allen RK, Cramond T, Lennon D, Waterhouse M. A retrospective study of chest pain in benign asbestos pleural disease. *Pain Med* 2011;12:1303–1308.
20. Ameille J, Brochard P, Letourneux M, et al. Asbestos-related cancer risk in patients with asbestosis or pleural plaques. *Rev Mal Respir* 2011;28:e11–17.
21. van Meerbeeck JP, Hillerdal G. Screening for mesothelioma: more harm than good? *Am J Respir Crit Care Med* 2008;178:781–782.
22. Roberts HC, Patsios DA, Paul NS, et al. Screening for malignant pleural mesothelioma and lung cancer in individuals with a history of asbestos exposure. *J Thorac Oncol* 2009;4:620–628.
23. Pass HI, Carbone M. Current status of screening for malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 2009;21:97–104.
24. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
25. Gadgeel S, Pass H. Malignant mesothelioma. *Commun Oncol* 2006;3:215–224.
26. Kao SC, Yan TD, Lee K, et al. Accuracy of diagnostic biopsy for the histological subtype of malignant pleural mesothelioma. *J Thorac Oncol* 2011;6:602–605.
27. Greillier L, Cavailles A, Fraticelli A, et al. Accuracy of pleural biopsy using thoracoscopy for the diagnosis of histologic subtype in patients with malignant pleural mesothelioma. *Cancer* 2007;110:2248–2252.
28. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. *Chest* 2006;129:362–368.
29. Schneider T, Reimer P, Storz K, et al. Recurrent pleural effusion: who benefits from a tunneled pleural catheter? *Thorac Cardiovasc Surg* 2009;57:42–46.
30. Zahid I, Routledge T, Bille A, Scarci M. What is the best treatment for malignant pleural effusions? *Interact Cardiovasc Thorac Surg* 2011;12:818–823.
31. Arapis K, Caliendo R, Stern JB, et al. Thoracoscopic palliative treatment of malignant pleural effusions: results in 273 patients. *Surg Endosc* 2006;20:919–923.
32. Schneider J, Hoffmann H, Dienemann H, et al. Diagnostic and prognostic value of soluble mesothelin-related proteins in patients with malignant pleural mesothelioma in comparison with benign asbestosis and lung cancer. *J Thorac Oncol* 2008;3:1317–1324.
33. Luo L, Shi HZ, Liang QL, et al. Diagnostic value of soluble mesothelin-related peptides for malignant mesothelioma: a meta-analysis. *Respir Med* 2010;104:149–156.
34. Hollevoet K, Nackaerts K, Thimpont J, et al. Diagnostic performance of soluble mesothelin and megakaryocyte potentiating factor in mesothelioma. *Am J Respir Crit Care Med* 2010;181:620–625.
35. Wheatley-Price P, Yang B, Patsios D, et al. Soluble mesothelin-related peptide and osteopontin as markers of response in malignant mesothelioma. *J Clin Oncol* 2010;28:3316–3322.
36. Creaney J, Yeoman D, Demelker Y, et al. Comparison of osteopontin, megakaryocyte potentiating factor, and mesothelin proteins as markers in the serum of patients with malignant mesothelioma. *J Thorac Oncol* 2008;3:851–857.
37. Grigoriu BD, Scherpereel A, Devos P, et al. Utility of osteopontin and serum mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment. *Clin Cancer Res* 2007;13:2928–2935.
38. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. *N Engl J Med* 2005;353:1564–1573.
39. Cristaudo A, Foddis R, Vivaldi A, et al. Clinical significance of serum mesothelin in patients with mesothelioma and lung cancer. *Clin Cancer Res* 2007;13:5076–5081.
40. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2009;133:1317–1331.
41. Ordonez NG. What are the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma? A review and update. *Hum Pathol* 2007;38:1–16.
42. Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. *Chest* 2009;136:888–896.
43. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy

Malignant Pleural Mesothelioma

- and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009;27:1413–1418.
44. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009;27:3007–3013.
 45. Bolukbas S, Manegold C, Eberlein M, et al. Survival after trimodality therapy for malignant pleural mesothelioma: radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. *Lung Cancer* 2011;71:75–81.
 46. Weder W, Stahel RA, Bernhard J, et al. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. *Ann Oncol* 2007;18:1196–1202.
 47. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg* 1999;117:54–63.
 48. Baldini EH. Radiation therapy options for malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 2009;21:159–163.
 49. Baldini EH. External beam radiation therapy for the treatment of pleural mesothelioma. *Thorac Surg Clin* 2004;14:543–548.
 50. Ahmadzadehfar H, Palmedo H, Strunk H, et al. False positive 18F-FDG-PET/CT in a patient after talc pleurodesis. *Lung Cancer* 2007;58:418–421.
 51. Nguyen NC, Tran I, Hueser CN, et al. F-18 FDG PET/CT characterization of talc pleurodesis-induced pleural changes over time: a retrospective study. *Clin Nucl Med* 2009;34:886–890.
 52. Pilling J, Dartnell JA, Lang-Lazdunski L. Integrated positron emission tomography-computed tomography does not accurately stage intrathoracic disease of patients undergoing trimodality therapy for malignant pleural mesothelioma. *Thorac Cardiovasc Surg* 2010;58:215–219.
 53. Rice DC, Steliga MA, Stewart J, et al. Endoscopic ultrasound-guided fine needle aspiration for staging of malignant pleural mesothelioma. *Ann Thorac Surg* 2009;88:862–868; discussion 868–869.
 54. Pilling JE, Stewart DJ, Martin-Ucar AE, et al. The case for routine cervical mediastinoscopy prior to radical surgery for malignant pleural mesothelioma. *Eur J Cardiothorac Surg* 2004;25:497–501.
 55. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*, 7th edition. New York: Springer; 2010.
 56. Wilcox BE, Subramaniam RM, Peller PJ, et al. Utility of integrated computed tomography-positron emission tomography for selection of operable malignant pleural mesothelioma. *Clin Lung Cancer* 2009;10:244–248.
 57. Flores RM, Akhurst T, Gonen M, et al. Positron emission tomography defines metastatic disease but not locoregional disease in patients with malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 2003;126:11–16.
 58. Aelony Y, Yao JF. Prolonged survival after talc poudrage for malignant pleural mesothelioma: case series. *Respirology* 2005;10:649–655.
 59. Schulze M, Boehle AS, Kurdow R, et al. Effective treatment of malignant pleural effusion by minimal invasive thoracic surgery: thoracoscopic talc pleurodesis and pleuroperitoneal shunts in 101 patients. *Ann Thorac Surg* 2001;71:1809–1812.
 60. Petrou M, Kaplan D, Goldstraw P. Management of recurrent malignant pleural effusions. The complementary role talc pleurodesis and pleuroperitoneal shunting. *Cancer* 1995;75:801–805.
 61. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol* 2011;6:1304–1312.
 62. Kaufman AJ, Flores RM. Surgical treatment of malignant pleural mesothelioma. *Curr Treat Options Oncol* 2011;12:201–216.
 63. Kindler HL. Surgery for mesothelioma? The debate continues. *Lancet Oncol* 2011;12:713–714.
 64. Rice D. Surgical therapy of mesothelioma. *Recent Results Cancer Res* 2011;189:97–125.
 65. Maziak DE, Gagliardi A, Haynes AE, et al. Surgical management of malignant pleural mesothelioma: a systematic review and evidence summary. *Lung Cancer* 2005;48:157–169.
 66. Hasani A, Alvarez JM, Wyatt JM, et al. Outcome for patients with malignant pleural mesothelioma referred for trimodality therapy in Western Australia. *J Thorac Oncol* 2009;4:1010–1016.
 67. Zahid I, Sharif S, Routledge T, Scarci M. Is pleurectomy and decortication superior to palliative care in the treatment of malignant pleural mesothelioma? *Interact Cardiovasc Thorac Surg* 2011;12:812–817.
 68. Shahin Y, Wellham J, Jappie R, et al. How successful is lung-preserving radical surgery in the mesothelioma and radical surgery-trial environment? A case-controlled analysis. *Eur J Cardiothorac Surg* 2011;39:360–363.
 69. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008;135:620–626.
 70. Sugarbaker DJ, Jaklitsch MT, Bueno R, et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. *J Thorac Cardiovasc Surg* 2004;128:138–146.
 71. Yan TD, Boyer M, Tin MM, et al. Extrapleural pneumonectomy for malignant pleural mesothelioma: outcomes of treatment and prognostic factors. *J Thorac Cardiovasc Surg* 2009;138:619–624.
 72. Schipper PH, Nichols FC, Thomse KM, et al. Malignant pleural mesothelioma: surgical management in 285 patients. *Ann Thorac Surg* 2008;85:257–264; discussion 264.
 73. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011;12:763–772.
 74. Treasure T, Waller D, Tan C, et al. The Mesothelioma and Radical Surgery randomized controlled trial: the MARS feasibility study. *J Thorac Oncol* 2009;4:1254–1258.
 75. Sharif S, Zahid I, Routledge T, Scarci M. Extrapleural pneumonectomy or supportive care: treatment of malignant pleural mesothelioma? *Interact Cardiovasc Thorac Surg* 2011;12:1040–1045.
 76. Yan TD, Cao CQ, Boyer M, et al. Improving survival results after surgical management of malignant pleural mesothelioma:

Malignant Pleural Mesothelioma

- an Australian institution experience. *Ann Thorac Cardiovasc Surg* 2011;17:243–249.
77. Zauderer MG, Krug LM. The evolution of multimodality therapy for malignant pleural mesothelioma. *Curr Treat Options Oncol* 2011;12:163–172.
 78. Flores RM. Surgical options in malignant pleural mesothelioma: extrapleural pneumonectomy or pleurectomy/decortication. *Semin Thorac Cardiovasc Surg* 2009;21:149–153.
 79. Luckraz H, Rahman M, Patel N, et al. Three decades of experience in the surgical multi-modality management of pleural mesothelioma. *Eur J Cardiothorac Surg* 2010;37:552–556.
 80. Kelly RJ, Sharon E, Hassan R. Chemotherapy and targeted therapies for unresectable malignant mesothelioma. *Lung Cancer* 2011;73:256–263.
 81. Ellis P, Davies AM, Evans WK, et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. *J Thorac Oncol* 2006;1:591–601.
 82. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636–2644.
 83. Krug LM. An overview of chemotherapy for mesothelioma. *Hematol Oncol Clin North Am* 2005;19:1117–1136, vii.
 84. Katirtzoglou N, Gkiozos I, Makrilia N, et al. Carboplatin plus pemetrexed as first-line treatment of patients with malignant pleural mesothelioma: a phase II study. *Clin Lung Cancer* 2010;11:30–35.
 85. Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol* 2006;24:1443–1448.
 86. Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). *Ann Oncol* 2008;19:370–373.
 87. van Haarst JMW, Baas P, Manegold C, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002;86:342–345.
 88. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491–496.
 89. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol* 2008;3:756–763.
 90. Scagliotti GV, Shin DM, Kindler HL, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. *J Clin Oncol* 2003;21:1556–1561.
 91. Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol* 2008;3:764–771.
 92. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685–1694.
 93. Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008;26:1698–1704.
 94. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009;63:94–97.
 95. Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005;16:923–927.
 96. Ceresoli GL, Zucali PA, Gianoncelli L, et al. Second-line treatment for malignant pleural mesothelioma. *Cancer Treat Rev* 2010;36:2–32.
 97. Yajnik S, Rosenzweig KE, Mychalczak B, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2003;56:1319–1326.
 98. Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 2001;122:788–795.
 99. Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2005;63:1045–1052.
 100. Gupta V, Krug LM, Laser B, et al. Patterns of local and nodal failure in malignant pleural mesothelioma after extrapleural pneumonectomy and photon-electron radiotherapy. *J Thorac Oncol* 2009;4:746–750.
 101. 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.
 102. Boutin C, Rey F, Vierrat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. *Chest* 1995;108:754–758.
 103. de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura—a single-institution experience with 189 patients. *Int J Radiat Oncol Biol Phys* 1999;43:511–516.
 104. Di Salvo M, Gambaro G, Pagella S, et al. Prevention of malignant seeding at drain sites after invasive procedures (surgery and/or thoracoscopy) by hypofractionated radiotherapy in patients with pleural mesothelioma. *Acta Oncol* 2008;47:1094–1098.
 105. Davies HE, Musk AW, Lee YC. Prophylactic radiotherapy for pleural puncture sites in mesothelioma: the controversy continues. *Curr Opin Pulm Med* 2008;14:326–330.
 106. O'Rourke N, Garcia JC, Paul J, et al. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. *Radiation Oncol* 2007;84:18–22.
 107. Bydder S, Phillips M, Joseph DJ, et al. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. *Br J Cancer* 2004;91:9–10.
 108. Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2007;84:1685–1692; discussion 1692–1683.
 109. Rice DC, Smythe WR, Liao Z, et al. Dose-dependent pulmonary

Malignant Pleural Mesothelioma

- toxicity after postoperative intensity-modulated radiotherapy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2007;69:350–357.
- 110.** Allen AM, Czerminska M, Janne PA, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640–645.
- 111.** Kristensen CA, Nottrup TJ, Berthelsen AK, et al. Pulmonary toxicity following IMRT after extrapleural pneumonectomy for malignant pleural mesothelioma. *Radiother Oncol* 2009;92:96–99.
- 112.** Miles EF, Larrier NA, Kelsey CR, et al. Intensity-modulated radiotherapy for resected mesothelioma: the Duke experience. *Int J Radiat Oncol Biol Phys* 2008;71:1143–1150.
- 113.** 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.
- 114.** Waite K, Gilligan D. The role of radiotherapy in the treatment of malignant pleural mesothelioma. *Clin Oncol (R Coll Radiol)* 2007;19:182–187.

Malignant Pleural Mesothelioma

Individual Disclosures of the NCCN Malignant Pleural Mesothelioma Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Wallace Akerley, MD	Genentech, Inc.; and OSI Pharmaceuticals, Inc.	Genentech, Inc.	None	None	11/10/10
Hossein Borghaei, DO, MS	Genentech, Inc.; and Spectrum Pharmaceuticals, Inc.	Amgen Inc.; Eli Lilly and Company; and Genentech, Inc.	None	None	4/5/11
Andrew Chang, MD	None	None	None	None	5/25/11
Richard T. Cheney, MD	None	None	None	None	5/23/11
Lucian R. Chirieac, MD	None	None	None	None	5/3/11
Thomas A. D'Amico, MD	None	Scanlan International	None	None	9/27/11
Todd L. Demmy, MD	None	None	None	None	9/30/10
David S. Ettinger, MD	None	Boehringer Ingelheim GmbH; Eli Lilly and Company; Genentech, Inc.; and Biodesix	None	None	6/13/11
Ramaswamy Govindan, MD	None	AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Eli Lilly and Company; and GlaxoSmithKline plc	None	None	3/16/11
Frederic W. Grannis, Jr., MD	None	Steven Phillips (Levy Phillips & Konigsberg, LLP)	None	None	5/24/11
Leora Horn, MD, MSc, FRCP	None	None	None	None	7/14/11
Thierry M. Jahan, MD	Eli Lilly and Company; Genentech, Inc.; ImClone LLC; Morphotek Inc.; and Novartis AG	Poniard Pharmaceuticals	None	None	4/22/11
Mohammad Jahanzeb, MD	OXIGENE, Inc.	Genentech, Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S. LLC	None	None	10/27/10
Anne Kessinger, MD	Pharmacyclics, Inc.; and sanofi-aventis U.S. LLC	None	None	None	5/4/11
Ritsuko Komaki, MD	Pfizer Inc.	None	None	None	5/4/11
Feng-Ming (Spring) Kong, MD, PhD, MPH	None	None	None	None	9/23/10
Mark G. Kris, MD	None	Boehringer Ingelheim GmbH; Covidien; National Cancer Institute; Chugai Pharmaceutical Co., Ltd.; Clovis Oncology; and Pfizer Inc.	None	None	5/6/11
Lee M. Krug, MD	Eli Lilly and Company; Merck & Co., Inc.; Novartis AG; and CanBas Co., Ltd.	Genentech, Inc.; and Morphotek Inc.	None	None	6/2/11
Inga T. Lennes, MD	None	None	None	None	5/19/11
Billy W. Loo, Jr., MD, PhD	None	General Electric Company; and Varian Medical Systems, Inc.	None	None	5/25/11
Renato Martins, MD, MPH	Amgen Inc.; Bayer AG; Eisai Co., Ltd.; Eli Lilly and Company; Exelixis, Inc.; Genentech, Inc.; Novartis AG; Infinity Pharmaceuticals; and Pfizer Inc.	Eli Lilly and Company; and Genentech, Inc.	None	None	3/21/11
Janis O'Malley, MD	None	None	None	None	4/13/11
Raymond U. Osarogjagbon, MD	Bristol-Myers Squibb Company; and Eli Lilly and Company	Genentech, Inc.; and OSI Pharmaceuticals, Inc.	None	None	6/15/11
Gregory A. Otterson, MD	Abraxis Oncology; Boehringer Ingelheim GmbH; Celgene Corporation; Eli Lilly and Company; Genentech, Inc.; Pfizer Inc.; and Pharmacyclics, Inc.	Abraxis BioScience, Inc.; and Genentech, Inc.	None	None	6/21/11
Jyoti D. Patel, MD	Eli Lilly and Company	Genentech, Inc.	None	None	4/7/11
Mary Pinder-Schenck, MD	None	None	None	None	5/9/11
Katherine M Pisters, MD	None	None	None	None	4/28/11
Karen Reckamp, MD, MS	Amgen Inc.; GlaxoSmithKline plc; Astellas Pharma Inc.; and Pfizer Inc.	Amgen Inc.; Eli Lilly and Company; Genentech, Inc.; and Response Genetics, Inc.	None	None	9/23/11
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