National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Malignant Pleural Mesothelioma

Version 3.2016

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Panel Members
Malignant Pleural Mesothelioma

NCCN Guidelines Index
MPM Table of Contents
Discussion

* David S. Ettinger, MD/Chair †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

* Douglas E. Wood, MD/Vice-Chair ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Wallace Akerley, MD †
Huntsman Cancer Institute at the University of Utah

Lyudmila A. Bazhenova, MD † ‡
UC San Diego Moores Cancer Center

Hossein Borghaei, DO, MS † ‡
Fox Chase Cancer Center

David Ross Camidge, MD, PhD †
University of Colorado 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

Thomas Dilling, MD, MS §
Moffitt Cancer Center

Michael Dobelbower, MD, PhD §
University of Alabama at Birmingham Comprehensive Cancer Center

Ramaswamy Govindan, MD †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Mark Hennon, MD ¶
Roswell Park Cancer Institute

Leora Horn, MD, MSc †
Vanderbilt-Ingram Cancer Center

Thierry M. Jahan, MD † ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Ritsuko Komaki, MD §
The University of Texas MD Anderson Cancer Center

Rudy P. Lackner, MD ¶
Fred & Pamela Buffett Cancer Center

Michael Lanuti, MD ¶
Massachusetts General Hospital Cancer Center

Rogerio Lilenbaum, MD †
Yale Cancer Center/Smilow Cancer Hospital

Jules Lin, MD ¶
University of Michigan Comprehensive 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

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

Steven E. Schild, MD §
Mayo Clinic Cancer Center

Theresa A. Shapiro, MD, PhD ¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Neelesh Sharma, MD, PhD † ‡
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Scott J. Swanson, MD ¶
Dana-Farber/Brigham and Women's Cancer Center

James Stevenson, MD †
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Kurt Tauer, MD †
University of Tennessee Health Science Center

Stephen C. Yang, MD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

NCCN
Kristina Gregory, RN, MSN, OCN
Miranda Hughes, PhD

† Medical oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy
≠ Pathology
‡ Hematology/Hematology oncology
ϕ Diagnostic/Interventional radiology
¥ Patient advocate
*Writing committee member

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Table of Contents
Malignant Pleural Mesothelioma

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Updates Malignant Pleural Mesothelioma

NCCN Guidelines Index
MPM Table of Contents
Discussion

Updates in Version 3.2016 of the NCCN Guidelines for Malignant Pleural Mesothelioma from Version 2.2016 include:

MPM-2
- **Imaging clarification: Chest MRI *with contrast* (optional)**

MPM-3
- **Imaging clarification: ~~Other imaging~~ *PET-CT* for mediastinal assessment based on CT.**

Updates in Version 2.2016 of the NCCN Guidelines for Malignant Pleural Mesothelioma from Version 1.2016 include:

MS-1
- **The discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 1.2016 of the NCCN Guidelines for Malignant Pleural Mesothelioma from Version 2.2015 include:

MPM-2
- **Clinical stage IV, Sarcomatoid histology and medically inoperable combined.**
  - **Treatment options differentiated based on performance status.**
  - **PS 0-2: options include chemotherapy or observation until progression, then chemotherapy at progression.**
  - **PS 3-4: best supportive care.**
- **Footnote "g" modified: "Observation *may be considered* for patients who are asymptomatic with minimal burden of disease *if chemotherapy is planned at the time of symptomatic or radiographic progression.***

MPM-C
- **Bullet 3; sentence added: "If it is possible to remove most of the gross disease to help with postoperative management, with a minimal impact on morbidity, then surgery should be continued."**

MPM-D 1 of 3
- **General Principles; Bullet 6 modified: "RT is an effective palliative treatment for relief of chest pain, *bronchial or esophageal obstruction, or other symptomatic sites* associated with mesothelioma."**

MPM-D 2 of 3
- **Radiation Techniques; bullet 2 modified: "CT simulation-guided planning ~~with~~ *using either intensity-modulated radiation therapy (IMRT) or* conventional photon/electron RT is *acceptable*~~recommended~~."**

INITIAL EVALUATION[a]

Recurrent pleural effusion and/or pleural thickening

→

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

→

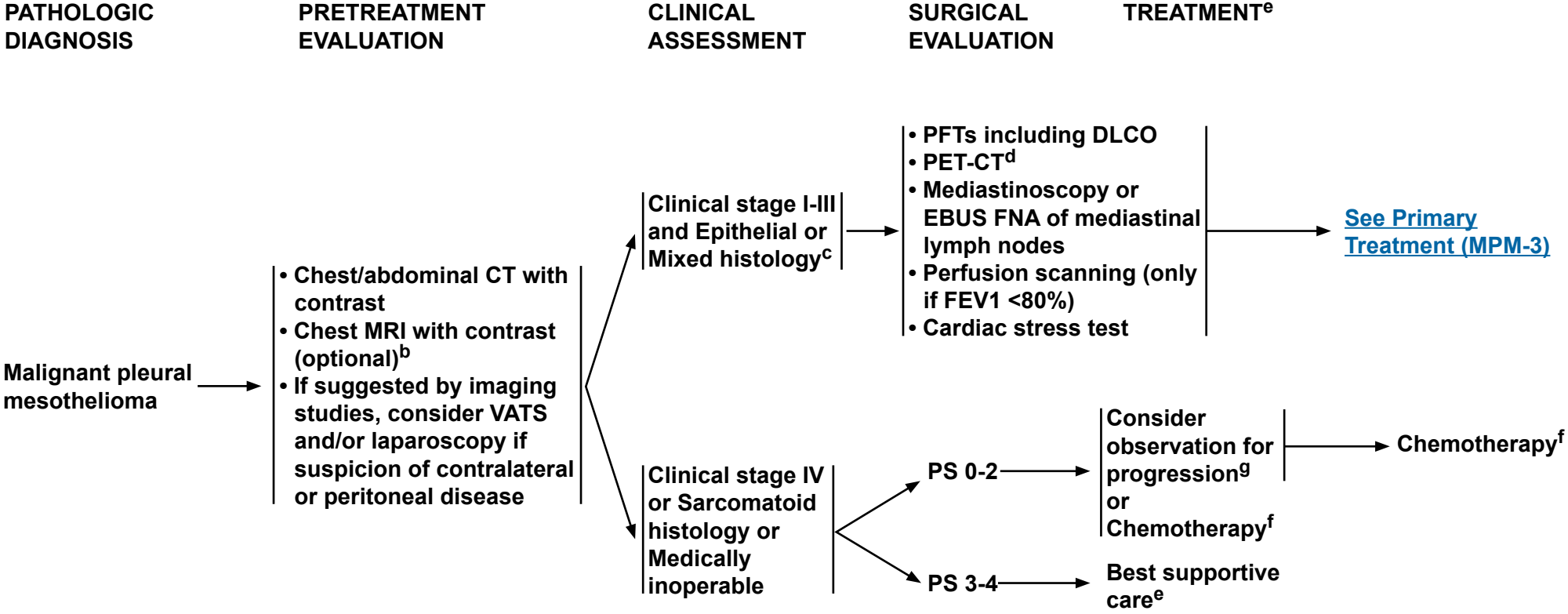
Malignant pleural mesothelioma (MPM) confirmed

→

Management by a multidisciplinary team with experience in MPM recommended
See Pretreatment Evaluation (MPM-2)

[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.

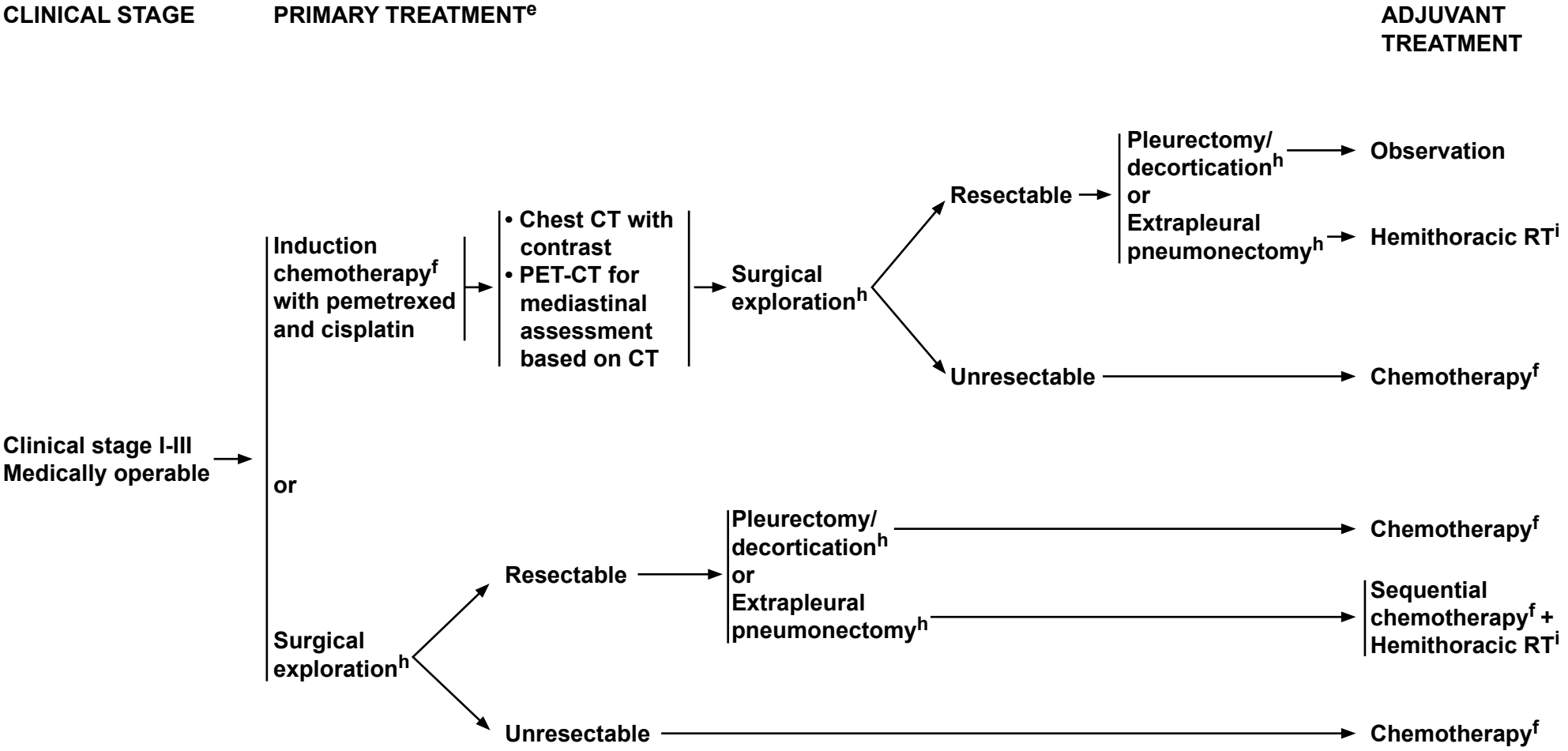


[b]For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[c]Assessment by multidisciplinary team with experience in malignant pleural mesothelioma.
[d]PET-CT should be performed before any pleurodesis.
[e]See Principles of Supportive Care (MPM-A).
[f]See Principles of Chemotherapy (MPM-B).
[g]Observation may be considered for patients who are asymptomatic with minimal burden of disease if chemotherapy is planned at the time of symptomatic or radiographic progression.

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.

NCCN Guidelines Version 3.2016
Malignant Pleural Mesothelioma

NCCN Guidelines Index
MPM Table of Contents
Discussion



[e] See Principles of Supportive Care (MPM-A).
[f] See Principles of Chemotherapy (MPM-B).
[h] See Principles of Surgery (MPM-C).
[i] See Principles of Radiation Therapy (MPM-D)

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.

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/). See the NCCN Guidelines for Lung Cancer Screening.**
- **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.

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.

PRINCIPLES OF CHEMOTHERAPY (1 of 2)

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- **Pemetrexed* 500 mg/m² day 1**
  Cisplatin 75 mg/m² day 1
  Administered every 3 weeks (category 1)[1]
- **Pemetrexed 500 mg/m² day 1**
  Cisplatin 75 mg/m² day 1
  Bevacizumab 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression[2,]**
- **Pemetrexed* 500 mg/m² day 1**
  Carboplatin AUC 5 day 1
  Administered every 3 weeks[3-5]
- **Gemcitabine 1000–1250 mg/m² days 1, 8, and 15**
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[6,7]
- **Pemetrexed* 500 mg/m² every 3 weeks[8]**
- **Vinorelbine 25–30 mg/m² weekly[9]**

SECOND-LINE CHEMOTHERAPY

- **Pemetrexed* (if not administered as first-line) (category 1)[10]**
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[11]
- **Vinorelbine[12,13]**
- **Gemcitabine[13-15]**

***Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma and tunica vaginalis testis mesothelioma.[16]**
****The combination regimen of pemetrexed/cisplatin/bevacizumab is only for unresectable disease.**

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.

PRINCIPLES OF CHEMOTHERAPY (2 of 2)
References

[1]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.
[2]Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2015 Dec 21. [Epub ahead of print]
[3]Castagneto 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.
[4]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.
[5]Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma. J Thorac Oncol 2008;3:756-763.
[6]Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 2002;87:491-496.
[7]Van 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.
[8]Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol 2008;3:764-771.
[9]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.
[10]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.
[11]Zucal PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung Cancer 2012;75:360-367.
[12]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.
[13]Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-274.
[14]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.
[15]van Meerbeeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999;85:2577-2582.
[16]Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agents. Lung Cancer 2009;64:211-218.

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.

PRINCIPLES OF SURGERY[1]

- **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. The goal of cytoreductive surgery is "macroscopic complete resection." In other words, removal of ALL visible or palpable tumors. In cases where this is not possible, such as in multiple sites of chest wall invasion, surgery should be aborted. If it is possible to remove most of the gross disease to help with postoperative management, with a minimal impact on morbidity, then surgery should be continued.**
- **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 with a goal to obtain at least 3 nodal stations.**
- **Numerous studies have defined sarcomatoid as a poor prognostic factor for any surgical or non-surgical treatment of MPM and is a contraindication to EPP.**
- **For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid), PD may be safer than EPP but it is unclear which operation is oncologically better. There is controversy regarding choice of procedure that needs to be weighed, taking into account tumor histology, distribution, patient pulmonary reserve, and availability of adjuvant and intraoperative strategies. P/D and EPP are each reasonable surgical treatment options and should be considered in select patients for complete gross cytoreduction.[2-5]**
- **If N2 disease or a mixed histology tumor is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.**
- **If technically appropriate for even more advanced disease, lung sparing operations like P/D reduces the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection.**
- **Intraoperative adjuvant therapy, such as heated chemotherapy or photodynamic therapy, is still under investigation but may be considered as part of a reasonable multidisciplinary approach to this locally aggressive disease.**
- **After recovery from surgery, patients should be referred for adjuvant therapy, which may include chemotherapy and RT depending on whether any preoperative therapy was used and on the pathologic analysis of the surgical specimen.**

[1]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.
[2]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.
[3]Spaggiari L, Marulli G, Boyolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. Ann Thorac Surg 2014;97:1859-1865.
[4]Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. J Thorac Oncol 2010;5:1649-1654.
[5]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.

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.

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 (PS) to improve local control.[1-6]
- PET scanning for treatment planning can be used as indicated.
- RT can be used to prevent instrument-tract recurrence after pleural intervention.
- RT is an effective palliative treatment for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites 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 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.[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 ≥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.[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 remains 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.

See Radiation Techniques (MPM-D 2 of 3)

See References (MPM-D 3 of 3)

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.

PRINCIPLES OF RADIATION THERAPY (2 of 3)

Recommended Doses for Conventionally Fractionated Radiation Therapy

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

See General Principles and Radiation Dose and Volume (MPM-D 1 of 3)
See References MPM-D (3 of 3)

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 using either intensity-modulated radiation therapy (IMRT) or conventional photon/electron RT is acceptable.[7] 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.[13,14] Special attention should be paid to minimize radiation to the contralateral lung,[15] as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.[16] The mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.[17]
- 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 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 each clinic's daily setup.

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.

PRINCIPLES OF RADIATION THERAPY (3 of 3) - References

[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 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.
[10]de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. Chest 2002;121:480–487.
[11]Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: 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]Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. Med Phys 2011;38:5067–5072.
[14]Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT). Int J Radiat Oncol Biol Phys 2009;73:9–14.
[15]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 1692–1693.
[16]Allen AM, Czerminska M, Jänne PA, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. Int J Radiat Oncol Biol Phys 2006;65:640–645.
[17]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.

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.

Table 1.

International Mesothelioma Interest Group (IMIG) Staging System for Diffuse Malignant Pleural Mesothelioma*

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement
T1a	No involvement of the visceral pleura
T1b	Tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with a least one of the following: -Involvement of the diaphragmatic muscle -Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least one of the following: -Involvement of the endothoracic fascia -Extension into the mediastinal fat -Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall -Nontransmural involvement of the pericardium
T4	Locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: -Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction -Direct transdiaphragmatic extension of the tumor to the peritoneum -Direct extension of tumor to the contralateral pleura -Direct extension of the tumor to mediastinal organs -Direct extension of tumor into the spine -Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor Involving the myocardium

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to the ipsilateral bronchpulmonary or hilar lymph nodes
N2	Metastases in the subcarinal lymph node or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes
N3	Metastasis in contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

*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.

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.

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.

Table of Contents

Overview

Mesothelioma is a rare cancer that is estimated to occur in approximately 2,500 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 the lining of other sites such as the peritoneum, pericardium, and tunica vaginalis testis.[3-5] MPM is difficult to treat, because most patients have advanced disease at presentation. Median overall survival is approximately 1 year; cure is rare.[6-8] MPM occurs mainly in older men (median age at diagnosis, 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20–40 years later).[9-11]

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 and deaths than anywhere else in the world.[12-14] The mortality burden from asbestos-related diseases in the United States did not change from 1999 to 2010.[15] Although asbestos is no longer mined in the United States, it is still imported.[14] The incidence of MPM is increasing in other countries such as Russia, Western Europe, China, and India.[1,13,16-20] Mortality rates from MPM are highest in the United Kingdom, Netherlands, and Australia; mortality rates are increasing in Japan, Argentina, and Brazil.[7,16,21] Russia, China, Brazil, and Canada are the top producers of asbestos.[22] Although most mesothelioma is linked to asbestos exposure, reports suggest that ionizing radiation may also cause mesothelioma, such as in patients previously treated with mantle radiation for Hodgkin lymphoma.[23-32] Recent data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma.[33-35] Genetic factors may also play a role in MPM, with some families carrying a germline mutation in the BRCA1 Associated Protein 1 (*BAP1*) gene.[36-39] Smoking is not a risk factor for mesothelioma.[40] However, patients who smoke and 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 (eg, delays wound healing after surgery) (http://www.smokefree.gov/) (see the NCCN Guidelines® for Smoking Cessation, available at NCCN.org).[41]

The histologic subtypes of mesothelioma include epithelioid (most common), sarcomatoid, and biphasic (mixed) epithelioid and sarcomatoid.[2,42,43] 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.[44,45] Although screening for mesothelioma has been studied in patients at high risk (ie, those with asbestos exposure), these NCCN Guidelines do not recommend screening for MPM because it has not been shown to decrease mortality (see *Initial Evaluation* in the NCCN Guidelines® for Malignant Pleural Mesothelioma).[22,46-48] Note that data and guidelines about screening for lung cancer with low-dose CT do not apply to MPM; there are no data to suggest that screening improves survival for patients with MPM.[22,49]

This Discussion text describes the recommendations in the algorithms in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithms. Additional supplementary material in the NCCN Guidelines includes the *Principles of Supportive Care, Principles of Chemotherapy*, *Principles of Surgery*, and *Principles of Radiation Therapy.* These NCCN Guidelines for Malignant Pleural Mesothelioma were developed and are updated by panel members who are also on the panel for the NCCN Guidelines for Non-Small Cell Lung Cancer. The *Summary of the Guidelines Updates* section in the algorithm briefly

describes the new changes for 2016. The *Principles of Surgery* were extensively revised for the 2015 update. The NCCN Guidelines for Malignant Pleural Mesothelioma are updated at least once a year.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Malignant Pleural Mesothelioma, an electronic search of the PubMed database was performed to obtain key literature on mesothelioma published between September 2014 and September 2015 using the following search term: malignant pleural mesothelioma. The PubMed database was chosen, because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 1; Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 38 citations, and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, then recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Diagnosis

Patients with suspected MPM often have dyspnea and chest pain; they may also have pleural effusion, fatigue, insomnia, cough, chest wall mass, loss of appetite, and weight loss (see the NCCN Guidelines for Adult Cancer Pain, available at NCCN.org).[21,50,51] Patients with MPM often have a high symptom burden when compared with patients who have other types of cancer. 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 of the effusion; and 3) pleural biopsy (eg, thoracoscopic biopsy [preferred]) (see *Initial Evaluation* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[21,22,52-56] However, cytologic samples are often negative even when patients have MPM.[57,58] Fine-needle aspiration (FNA) is not recommended for diagnosis.[21] Talc pleurodesis or pleural catheter may be needed for management of pleural effusion.[59-63] Soluble mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status;[64-67] osteopontin does not appear to be as useful for diagnosis.[68-72] Other potential diagnostic biomarkers are being assessed.[73-77]

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.[17,78-82] On CT, thymoma metastatic to the pleura can mimic MPM; however, pleural effusion does not typically occur with thymoma. Cytologic samples of pleural fluid are often negative or inconclusive, but diagnosis can sometimes be made using cytology.[57,58,83,84] 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 *Protocol for the Examination of Specimens From Patients*

With Malignant Pleural Mesothelioma from the College of American Pathologists [CAP] on the CAP website).[57,79,81,85]

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;[2] select patients (ie, clinical stages I–III, medically operable, good performance status [PS]) are candidates for multimodality therapy.[86-90] Definitive RT alone is not recommended for unresectable MPM; chemotherapy alone is recommended in this setting (see *Treatment* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[91,92] 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 but only for patients being considered for surgery.[52,53,93] Video-assisted thoracic surgery (VATS) or laparoscopy can be considered if contralateral or peritoneal disease is suspected.[94] When indicated, PET-CT scans should be obtained before pleurodesis if possible, because talc produces pleural inflammation, which can affect the FDG avidity (ie, false-positive result).[95-97] If surgical resection is being considered, mediastinoscopy or endobronchial ultrasonography (EBUS) FNA of the mediastinal lymph nodes is recommended.[98,99] 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 to evaluate possible chest, spinal, diaphragmatic, or vascular involvement.

Staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system (see Table 1 in the NCCN Guidelines for Malignant Pleural Mesothelioma), which was approved by the AJCC.[100,101] Note that a new edition (8th) of the AJCC Staging Guidelines is anticipated in mid-2016. Most patients have advanced disease at presentation. However, it is difficult to accurately stage patients before surgery. Understaging is common with PET-CT.[97,102] However, PET-CT is useful for determining whether metastatic disease is present.[102,103] Surgical resection is recommended for patients with clinical stage I to III MPM who are medically operable and can tolerate the surgery. Patients with clinical stage I to III MPM can be evaluated for surgery using pulmonary function tests (PFTs) including diffusing capacity for carbon dioxide (DLCO), perfusion scanning (if forced expiratory volume in 1 second [FEV1] <80%), and cardiac stress tests (see *Surgical Evaluation* in the NCCN Guidelines for Malignant Pleural Mesothelioma). 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 Malignant Pleural Mesothelioma).

Chemotherapy alone is recommended for patients with PS 0 to 2 who are not operable or refuse surgery, those with clinical stage IV MPM, or those with sarcomatoid histology; best supportive care is recommended for patients with PS 3 to 4 (see *Chemotherapy* in this Discussion and *Principles of Chemotherapy* and *Principles of Supportive Care* in the NCCN Guidelines for Malignant Pleural Mesothelioma). Observation may be considered for patients with PS 0 to 2 who are asymptomatic with minimal burden of disease if chemotherapy is planned when progression occurs (either radiologic or symptomatic progression).

Pleural effusion can be managed using thoracoscopic talc pleurodesis or placement of a drainage catheter.[59,63,104-106] 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.[21]

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 Surgery* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[107] Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[107] Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained. The surgical goal for MPM is cytoreductive surgery to achieve macroscopic complete resection by removing all visible or palpable tumors.[108,109] If macroscopic complete resection is not possible—such as patients with multiple sites of chest wall invasion—then surgery should be aborted. However, surgery should be continued if most of the gross disease can be removed to help with postoperative management and if there will be a minimal impact on morbidity.

The choice of surgery for MPM is controversial, because data from randomized controlled trials are not available.[2,21,110-116] Neither EPP nor P/D will yield an R0 resection.[2,117,118] EPP would often be required to remove all gross tumor in patients with stages II to III MPM.[51] However, EPP is associated with higher morbidity and mortality.[111,119] P/D (ie, lung-preserving surgery) is safer than EPP.[119-126] 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.[2,124] A recent meta-analysis suggested a trend in favor of overall survival for extended PD when compared with EPP.[111] Lung-sparing options, such as P/D, reduce the risk for perioperative mortality and yield either equal or better long-term survival than non-surgical therapy in patients with more advanced disease.[117,127]

A feasibility trial (Mesothelioma and Radical Surgery [MARS]) assessed whether patients treated with induction chemotherapy would accept randomization to EPP or no surgery; 112 were patients enrolled in the trial, and 50 patients were randomized.[128] The authors concluded that due to the observed high rate of surgical mortality, EPP was not beneficial when compared with chemotherapy treatment alone. However, these results were controversial because survival was not the primary outcome of the study, the sample size was small, and the surgical mortality was higher than expected.[129] An Australian retrospective study (540 patients) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and treatment with pemetrexed.[130] The NCCN Panel and other clinicians recommend surgery for select patients who require a complete cytoreduction (ie, good PS, no comorbidities, patients with stage II to III disease, favorable histology [ie, epithelioid], no N2 disease), but surgery is not usually recommended for patients at high risk (eg, unfavorable histology [eg, sarcomatoid, mixed tumors]).[6,113,131,132]

The NCCN Panel feels that P/D and EPP are reasonable surgical options that should be considered in select patients to achieve complete gross cytoreduction.[111,124,128,133,134] Although P/D may be safer than EPP, it is not clear which operation is oncologically better. When surgery is

indicated, the choice between P/D and EPP should be made based on several factors including tumor histology and distribution, pulmonary reserve, surgical experience and expertise, and availability of adjuvant and intraoperative strategies.[6,134] For patients with operable early-stage disease (confined to the pleural envelope [stage I], no N2 lymph node involvement), surgery should be considered for select patients.[90,124,125,135,136,137] In patients who are medically operable, the decision about whether to do a P/D or an EPP may not be made until surgical exploration. P/D may be more appropriate for patients with advanced MPM who cannot tolerate an EPP.[120] P/D may also be useful for symptom control (eg, patients with entrapped lung syndrome).[22] The NCCN Panel does not recommend surgery for patients with stage IV MPM or sarcomatoid histology; chemotherapy is recommended for these patients (see *Chemotherapy* in this Discussion and *Treatment* in the NCCN Guidelines for Malignant Pleural Mesothelioma). In addition, surgery is generally not recommended for patients with N2 disease or mixed histology tumor 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 multimodality regimen for patients with medically operable MPM (see *Treatment* and *Principles of Chemotherapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma). Patients with medically operable stage I to III MPM can receive chemotherapy either before or after surgery. Chemotherapy alone is recommended for patients with medically inoperable stages I to IV MPM, those who refuse surgery, and those with sarcomatoid histology.[112,138-140] Pemetrexed-based chemotherapy can also be used for malignant peritoneal mesothelioma and for tunica vaginalis testis mesothelioma.[3]

A combined first-line regimen using cisplatin/pemetrexed (category 1) is considered the gold standard for MPM and is currently the only regimen approved by the FDA.[141-144] A phase 3 randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; the combined regimen increased survival by 2.8 months when compared with cisplatin alone (12.1 vs. 9.3 months, *P*=.02).[143] Based on this trial and the FDA approval, the NCCN Panel recommends cisplatin/pemetrexed (category 1) for patients with MPM. A recent multicenter phase 3 randomized trial (IFCT-GFPC-0701 MAPS) compared adding bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) versus cisplatin/pemetrexed alone for patients with unresectable MPM and PS 0-2 who did not have bleeding or thrombosis.[145] Overall survival was increased in the bevacizumab plus chemotherapy arm by 2.7 months when compared with chemotherapy alone (18.8 vs. 16.1 months; HR = 0.77; *P* = .0167). Grade 3 to 4 adverse events were reported in 71% (158/222) of patients receiving the bevacizumab regimen when compared with 62% (139/224) of those receiving cisplatin/pemetrexed alone. More grade 3 or higher hypertension (23% vs. 0%), grade 3 proteinuria (3.1% vs. 0%), and grade 3-4 thrombotic events (6% vs. 1%) were observed in patients receiving the triplet arm. The NCCN Panel recommends (category 2A) bevacizumab, cisplatin, and pemetrexed for patients with unresectable MPM based on this trial (see *Principles of Chemotherapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma).

Other acceptable first-line combination chemotherapy options recommended by NCCN include: 1) pemetrexed/carboplatin, which was assessed in 3 large phase 2 studies (median survival = 12.7, 14, and 14 months, respectively);[146-148] or 2) gemcitabine/cisplatin, which was also assessed in phase 2 studies (median survival = 9.6–11.2 months).[149-151] Gemcitabine/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.[152] 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.[153-155] Second-line chemotherapy options include pemetrexed (if not administered first line) (category 1), vinorelbine, or gemcitabine.[154,156-162] Data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed.[156,163] Limited data are available to guide second-line therapy, although several agents are in clinical trials.[156,164-167] Preliminary data suggest that immune checkpoint inhibitors may be useful as second-line therapy for MPM.[168-171]

Trimodality therapy using chemotherapy, surgery, and hemithoracic RT has been used in patients with MPM.[86-89,172] Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.[87,172] Nodal status and response to chemotherapy can affect survival.[87,90] In patients who do not receive induction chemotherapy before EPP, postoperative sequential chemotherapy with hemithoracic RT is recommended. Intraoperative adjuvant therapies—such as hyperthermic pleural lavage, photodynamic therapy, or heated chemotherapy—are under investigation.[164,173-180]

Radiation Therapy

The *Principles of Radiation Therapy* are described in the algorithm and are summarized in this Discussion (see the NCCN Guidelines for Malignant Pleural Mesothelioma). 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, bronchial or esophageal obstruction, or other symptomatic sites associated with MPM such as metastases in bone or in the brain (see the NCCN Guidelines for Malignant Pleural Mesothelioma and NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).[21,91,181] The dose of radiation should be based on the purpose of treatment.[182] 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 may reduce the local recurrence rate.[135,183-185] Patients are candidates for RT if they have good PS, pulmonary function, and kidney function (see *Principles of Radiation Therapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma). 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 is associated with significant toxicity.[91] RT can also be used to prevent instrument-tract recurrence after pleural intervention.[88,118,135,186-188]

CT simulation–guided planning using either IMRT or conventional photon/electron RT is acceptable.[172,183,185,189] For treatment planning, PET scans can be used as indicated. 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 Radiation Therapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma). A dose of 60 Gy or more is recommended for 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, available at NCCN.org). 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,[190-192] although this is controversial.[193-195] The optimal dose of RT for palliative purposes remains unclear.[182,196] For patients with chest pain from mesothelioma, total doses of 20 to 40 Gy appear to be effective in providing relief from pain.[21,190,191]

Intensity-modulated RT (IMRT) allows a more conformal high-dose RT and improved coverage to the hemithorax at risk.[91,183,184,197,198] The NCI and ASTRO/ACR IMRT guidelines are recommended (http://rrp.cancer.gov/content/docs/imrt.doc).[199-201] The ICRU-83 (International Commission on Radiation Units & Measurements Report 83) recommendations are also a useful resource.[202,203] RT to the contralateral lung should be minimized,[91,184,204] because fatal pneumonitis may occur with IMRT if strict limits are not applied.[205-207] The mean lung dose should be kept as low as possible, preferably less than 8.5 Gy.[208] The volume of contralateral lung receiving low-dose RT (eg, 5 Gy) should be minimized.[209,210] Hemithoracic IMRT immediately followed by EPP was assessed in 25 patients with stage III or IV MPM on final pathologic review; for patients with epithelial subtypes of MPM, 3-year survival reached 84%.[197] However, 13 patients had grade 3+ surgical complications and one patient died from treatment.

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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19650718.

2. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant pleural mesothelioma. J Clin Oncol 2009;27:2081-2090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255316.

3. Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer 2009;64:211-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19042053.

4. Mirarabshahii P, Pillai K, Chua TC, et al. Diffuse malignant peritoneal mesothelioma--an update on treatment. Cancer Treat Rev 2012;38:605-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22104079.

5. Chekol SS, Sun CC. Malignant mesothelioma of the tunica vaginalis testis: diagnostic studies and differential diagnosis. Arch Pathol Lab Med 2012;136:113-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22208496.

6. Meyerhoff RR, Yang CF, Speicher PJ, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. J Surg Res 2015;196:23-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25791825.

7. Musk AW, Olsen N, Alfonso H, et al. Predicting survival in malignant mesothelioma. Eur Respir J 2011;38:1420-1424. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21737558.

8. Linton A, Pavlakis N, O'Connell R, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. Br J Cancer 2014;111:1860-1869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25188323.

9. Taioli E, Wolf AS, Camacho-Rivera M, et al. Determinants of survival in malignant pleural mesothelioma: a Surveillance, Epidemiology, and End Results (SEER) study of 14,228 patients. PLoS One 2015;10:e0145039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26660351.

10. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. J Occup Med 1992;34:718-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1494965.

11. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 1980;46:2736-2740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7448712.

12. Delgermaa V, Takahashi K, Park EK, et al. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. Bull World Health Organ 2011;89:716-724, 724A-724C. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22084509.

13. Park EK, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. Environ Health Perspect 2011;119:514-518. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21463977.

14. Malignant mesothelioma mortality--United States, 1999-2005. MMWR Morb Mortal Wkly Rep 2009;58:393-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19390506.

15. Bang KM, Mazurek JM, Wood JM, Hendricks SA. Diseases attributable to asbestos exposure: years of potential life lost, United States, 1999-2010. Am J Ind Med 2014;57:38-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24108494.

16. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19079719.

17. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18085053.

18. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14718210.

19. Peto J, Decarli A, La Vecchia C, et al. The European mesothelioma epidemic. Br J Cancer 1999;79:666-672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10027347.

20. Leigh J, Davidson P, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945-2000. Am J Ind Med 2002;41:188-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920963.

21. van Zandwijk N, Clarke C, Henderson D, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis 2013;5:E254-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24416529.

22. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J 2010;35:479-495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19717482.

23. Li X, Brownlee NA, Sporn TA, et al. Malignant (diffuse) mesothelioma in patients with hematologic malignancies: a clinicopathologic study of 45 cases. Arch Pathol Lab Med 2015;139:1129-1136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25844559.

24. Goodman JE, Nascarella MA, Valberg PA. Ionizing radiation: a risk factor for mesothelioma. Cancer Causes Control 2009;20:1237-1254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19444627.

25. Chirieac LR, Barletta JA, Yeap BY, et al. Clinicopathologic characteristics of malignant mesotheliomas arising in patients with a history of radiation for Hodgkin and non-Hodgkin lymphoma. J Clin Oncol 2013;31:4544-4549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24248693.

26. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 2007;25:1489-1497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17372278.

27. Deutsch M, Land SR, Begovic M, et al. An association between postoperative radiotherapy for primary breast cancer in 11 National Surgical Adjuvant Breast and Bowel Project (NSABP) studies and the subsequent appearance of pleural mesothelioma. Am J Clin Oncol 2007;30:294-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17551308.

28. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16174857.

29. Teta MJ, Lau E, Sceurman BK, Wagner ME. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. Cancer 2007;109:1432-1438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17315168.

30. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. Blood 2009;113:3679-3681. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19234144.

31. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. Cancer 1996;77:1379-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8608519.

32. Witherby SM, Butnor KJ, Grunberg SM. Malignant mesothelioma following thoracic radiotherapy for lung cancer. Lung Cancer 2007;57:410-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17475364.

33. Baumann F, Buck BJ, Metcalf RV, et al. The presence of asbestos in the natural environment is likely related to mesothelioma in young individuals and women from Southern Nevada. J Thorac Oncol 2015;10:731-737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25668121.

34. Van Gosen BS, Blitz TA, Plumlee GS, et al. Geologic occurrences of erionite in the United States: an emerging national public health concern for respiratory disease. Environ Geochem Health 2013;35:419-430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23315055.

35. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21788493.

36. Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. Cancer Res 2016;76:206-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26719535.

37. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis 2015;36:76-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25380601.

38. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. J Transl Med 2012;10:179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22935333.

39. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2011;43:1022-1025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21874000.

40. Mossman BT, Lippmann M, Hesterberg TW, et al. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. J Toxicol Environ Health B Crit Rev 2011;14:76-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21534086.

41. Sorensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. Ann Surg 2012;255:1069-1079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22566015.

42. Galateau-Salle F, Churg A, Roggli V, et al. The 2015 World Health Organization Classification of Tumors of the Pleura: advances since the 2004 Classification. J Thorac Oncol 2016;11:142-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26811225.

43. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of malignant mesothelioma: Part 2. Malignant mesothelioma subtypes, pleural synovial sarcoma, molecular and prognostic aspects of mesothelioma, BAP1, aquaporin-1 and microRNA. J Clin Pathol 2013;66:854-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23833051.

44. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21834915.

45. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21742228.

46. van Meerbeeck JP, Hillerdal G. Screening for mesothelioma: more harm than good? Am J Respir Crit Care Med 2008;178:781-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18832552.

47. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19357540.

48. Pass HI, Carbone M. Current status of screening for malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 2009;21:97-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19822280.

49. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21714641.

50. Dyer DS, Mohammed TL, Kirsch J, et al. ACR appropriateness Criteria(R) chronic dyspnea: suspected pulmonary origin. J Thorac Imaging 2013;28:W64-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23846109.

51. Gadgeel S, Pass H. Malignant mesothelioma. Commun Oncol 2006;3:215-224. Available at:

52. Bacchus L, Shah RD, Chung JH, et al. ACR Appropriateness Criteria Review ACR Appropriateness Criteria(R) Occupational Lung Diseases. J Thorac Imaging 2016;31:W1-3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26656194.

53. Armato SG, 3rd, Coolen J, Nowak AK, et al. Imaging in pleural mesothelioma: A review of the 12th International Conference of the International Mesothelioma Interest Group. Lung Cancer 2015;90:148-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26298162.

54. Armato SG, 3rd, Labby ZE, Coolen J, et al. Imaging in pleural mesothelioma: a review of the 11th International Conference of the International Mesothelioma Interest Group. Lung Cancer 2013;82:190-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24018024.

55. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21266919.

56. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17886249.

57. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of mesothelioma: Part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. J Clin Pathol 2013;66:847-853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23814259.

58. Paintal A, Raparia K, Zakowski MF, Nayar R. The diagnosis of malignant mesothelioma in effusion cytology: a reappraisal and results of a multi-institution survey. Cancer Cytopathol 2013;121:703-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24039177.

59. Hunt BM, Farivar AS, Vallieres E, et al. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. Ann Thorac Surg 2012;94:1053-1057; discussion 1057-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22513274.

60. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. Chest 2006;129:362-368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16478853.

61. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19169996.

62. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21325469.

63. Arapis K, Caliandro R, Stern JB, et al. Thoracoscopic palliative treatment of malignant pleural effusions: results in 273 patients. Surg Endosc 2006;20:919-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16738983.

64. Hollevoet K, Reitsma JB, Creaney J, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. J Clin Oncol 2012;30:1541-1549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22412141.

65. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18978568.

66. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19945835.

67. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20075387.

68. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498407.

69. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18670302.

70. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17504993.

71. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med 2005;353:1564-1573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16221779.

72. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17785560.

73. Panou V, Vyberg M, Weinreich UM, et al. The established and future biomarkers of malignant pleural mesothelioma. Cancer Treat Rev 2015;41:486-495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25979846.

74. Creaney J, Dick IM, Robinson BW. Comparison of mesothelin and fibulin-3 in pleural fluid and serum as markers in malignant mesothelioma. Curr Opin Pulm Med 2015;21:352-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26016578.

75. Ostroff RM, Mehan MR, Stewart A, et al. Early detection of malignant pleural mesothelioma in asbestos-exposed individuals with a noninvasive proteomics-based surveillance tool. PLoS One 2012;7:e46091. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23056237.

76. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. N Engl J Med 2012;367:1417-1427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23050525.

77. Brims FJ, Lee YC, Creaney J. The continual search for ideal biomarkers for mesothelioma: the hurdles. J Thorac Dis 2013;5:364-366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23825777.

78. Arif Q, Husain AN. Malignant mesothelioma diagnosis. Arch Pathol Lab Med 2015;139:978-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26230591.

79. Husain AN, Colby T, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2013;137:647-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22929121.

80. Chirieac LR, Pinkus GS, Pinkus JL, et al. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. Am J Cancer Res 2011;1:14-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969119.

81. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19653732.

82. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17056092.

83. Hjerpe A, Ascoli V, Bedrossian CW, et al. Guidelines for the cytopathologic diagnosis of epithelioid and mixed-type malignant mesothelioma. Complementary statement from the International Mesothelioma Interest Group, also endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology. Acta Cytol 2015;59:2-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25824655.

84. Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. Chest 2009;136:888-896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19736192.

85. Butnor KJ, Beasley MB, Cagle PT. Protocol for the Examination of Specimens from Patients With Malignant Pleural Mesothelioma. Based on AJCC/UICC TNM, 7th edition. Protocol web posting date: February 1, 2011.: Collage of American Pathologists; 2011. Available at:

86. de Perrot M, Feld R, Cho BCJ, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Clin Oncol 2009;27:1413-1418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224855.

87. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19364962.

88. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19765853.

89. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17429100.

90. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9869758.

91. Baldini EH. Radiation therapy options for malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 2009;21:159-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19822288.

92. Baldini EH. External beam radiation therapy for the treatment of pleural mesothelioma. Thorac Surg Clin 2004;14:543-548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15559061.

93. De Paoli L, Quaia E, Poillucci G, et al. Imaging characteristics of pleural tumours. Insights Imaging 2015;6:729-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26475741.

94. Grossebner MW, Arifi AA, Goddard M, Ritchie AJ. Mesothelioma--VATS biopsy and lung mobilization improves diagnosis and palliation. Eur J Cardiothorac Surg 1999;16:619-623. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10647830.

95. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17624474.

96. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20139823.

97. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20514576.

98. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19699913.

99. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15037261.

100. Rusch VW, Giroux D. Do we need a revised staging system for malignant pleural mesothelioma? Analysis of the IASLC database. Ann Cardiothorac Surg 2012;1:438-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23977534.

101. Edge SB, Byrd DR, Compton CC, al. e. AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010.

102. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632941.

103. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12878934.

104. Aelony Y, Yao JF. Prolonged survival after talc poudrage for malignant pleural mesothelioma: case series. Respirology 2005;10:649-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16268920.

105. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11426752.

106. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7530167.

107. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21847060.

108. Bolukbas S, Eberlein M, Fisseler-Eckhoff A, Schirren J. Radical pleurectomy and chemoradiation for malignant pleural mesothelioma: the outcome of incomplete resections. Lung Cancer 2013;81:241-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23688589.

109. Sugarbaker DJ, Wolf AS, Chirieac LR, et al. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. Eur J Cardiothorac Surg 2011;40:298-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21310625.

110. Teh E, Fiorentino F, Tan C, Treasure T. A systematic review of lung-sparing extirpative surgery for pleural mesothelioma. J R Soc Med 2011;104:69-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21282797.

111. Cao C, Tian D, Park J, et al. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. Lung Cancer 2014;83:240-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24360321.

112. Bovolato P, Casadio C, Bille A, et al. Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients. J Thorac Oncol 2014;9:390-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24518090.

113. Kaufman AJ, Flores RM. Surgical treatment of malignant pleural mesothelioma. Curr Treat Options Oncol 2011;12:201-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21465419.

114. Kindler HL. Surgery for mesothelioma? The debate continues. Lancet Oncol 2011;12:713-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21723780.

115. Rice D. Surgical therapy of mesothelioma. Recent Results Cancer Res 2011;189:97-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21479898.

116. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15829316.

117. Friedberg JS. The state of the art in the technical performance of lung-sparing operations for malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 2013;25:125-143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24216529.

118. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19546819.

119. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18154820.

120. Nakas A, von Meyenfeldt E, Lau K, et al. Long-term survival after lung-sparing total pleurectomy for locally advanced (International

Mesothelioma Interest Group Stage T3-T4) non-sarcomatoid malignant pleural mesothelioma. Eur J Cardiothorac Surg 2012;41:1031-1036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22219469.

121. Bille A, Belcher E, Raubenheimer H, et al. Induction chemotherapy, extrapleural pneumonectomy, and adjuvant radiotherapy for malignant pleural mesothelioma: experience of Guy's and St Thomas' hospitals. Gen Thorac Cardiovasc Surg 2012;60:289-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22453539.

122. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21345818.

123. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20692844.

124. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18329481.

125. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15224033.

126. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19698846.

127. Halstead JC, Lim E, Venkateswaran RM, et al. Improved survival with VATS pleurectomy-decortication in advanced malignant mesothelioma. Eur J Surg Oncol 2005;31:314-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15780570.

128. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21723781.

129. Weder W, Stahel RA, Baas P, et al. The MARS feasibility trial: conclusions not supported by data. Lancet Oncol 2011;12:1093-1094; author reply 1094-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22041539.

130. Yan TD, Cao CQ, Boyer M, et al. Improving survival results after surgical management of malignant pleural mesothelioma: an Australian institution experience. Ann Thorac Cardiovasc Surg 2011;17:243-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21697784.

131. Baud M, Bobbio A, Lococo F, et al. Should we continue to offer extrapleural pneumonectomy to selected mesothelioma patients? A single center experience comparing surgical and non-surgical management. Jpn J Clin Oncol 2014;44:1127-1129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25187665.

132. Zauderer MG, Krug LM. The evolution of multimodality therapy for malignant pleural mesothelioma. Curr Treat Options Oncol 2011;12:163-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21404104.

133. Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. J Thorac Oncol

2010;5:1649-1654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20871264.

134. Spaggiari L, Marulli G, Bovolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. Ann Thorac Surg 2014;97:1859-1865. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24726598.

135. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11581615.

136. Flores RM. Surgical options in malignant pleural mesothelioma: extrapleural pneumonectomy or pleurectomy/decortication. Semin Thorac Cardiovasc Surg 2009;21:149-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19822286.

137. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19717307.

138. Blomberg C, Nilsson J, Holgersson G, et al. Randomized trials of systemic medically-treated malignant mesothelioma: a systematic review. Anticancer Res 2015;35:2493-2501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25964522.

139. Kelly RJ, Sharon E, Hassan R. Chemotherapy and targeted therapies for unresectable malignant mesothelioma. Lung Cancer 2011;73:256-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21620512.

140. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17409924.

141. Kondola S, Manners D, Nowak AK. Malignant pleural mesothelioma: an update on diagnosis and treatment options. Ther Adv Respir Dis 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26873306.

142. Raynaud C, Greillier L, Mazieres J, et al. Management of malignant pleural mesothelioma: a French multicenter retrospective study (GFPC 0802 study). BMC Cancer 2015;15:857. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26546402.

143. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12860938.

144. Krug LM. An overview of chemotherapy for mesothelioma. Hematol Oncol Clin North Am 2005;19:1117-1136, vii. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16325127.

145. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26719230.

146. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20085865.

147. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16549838.

148. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18156144.

149. Arrieta O, Lopez-Macias D, Mendoza-Garcia VO, et al. A phase II trial of prolonged, continuous infusion of low-dose gemcitabine plus cisplatin in patients with advanced malignant pleural mesothelioma. Cancer Chemother Pharmacol 2014;73:975-982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24687408.

150. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11875695.

151. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12189542.

152. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol 2008;3:756-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18594322.

153. Scagliotti GV, Shin D-M, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12697881.

154. Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol 2008;3:764-771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18594323.

155. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18486741.

156. Abdel-Rahman O, Kelany M. Systemic therapy options for malignant pleural mesothelioma beyond first-line therapy: a systematic review. Expert Rev Respir Med 2015;9:533-549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26366804.

157. Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24690410.

158. Janne PA, Wozniak AJ, Belani CP, et al. Pemetrexed alone or in combination with cisplatin in previously treated malignant pleural mesothelioma: outcomes from a phase IIIB expanded access program. J Thorac Oncol 2006;1:506-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17409909.

159. van Meerbeeck JP, Baas P, Debruyne C, et al. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999;85:2577-2582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10375105.

160. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18375898.

161. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18486273.

162. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15824080.

163. Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung Cancer 2012;75:360-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21937142.

164. Kotova S, Wong RM, Cameron RB. New and emerging therapeutic options for malignant pleural mesothelioma: review of early clinical trials. Cancer Manag Res 2015;7:51-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25670913.

165. Zauderer MG, Krug LM. Novel therapies in phase II and III trials for malignant pleural mesothelioma. J Natl Compr Canc Netw 2012;10:42-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22223868.

166. Thomas A, Hassan R. Immunotherapies for non-small-cell lung cancer and mesothelioma. Lancet Oncol 2012;13:e301-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22748269.

167. Ceresoli GL, Zucali PA, Gianoncelli L, et al. Second-line treatment for malignant pleural mesothelioma. Cancer Treat Rev 2010;36:24-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19879055.

168. Alley EW, Molife LR, Santoro A, et al. Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma: Preliminary results from KEYNOTE-028 [abstract]. Cancer Research 2015;75:Abstract CT103. Available at: http://cancerres.aacrjournals.org/content/75/15_Supplement/CT103.abstract.

169. Alley EW, Schellens JH, Santoro A, et al. Single-agent pembrolizumab for patients with malignant pleural mesothelioma (MPM) [abstract]. World Conference on Lung Cancer. Denver, Colorado: IASCL; 2015:Abstract 3011. Available at: https://cslide.ctimeetingtech.com/library/wclc/browse/search/67d#2yv2J0TV.

170. Marcq E, Pauwels P, van Meerbeeck JP, Smits EL. Targeting immune checkpoints: New opportunity for mesothelioma treatment? Cancer Treat Rev 2015;41:914-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26433514.

171. Calabro L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 2015;3:301-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25819643.

172. Thieke C, Nicolay NH, Sterzing F, et al. Long-term results in malignant pleural mesothelioma treated with neoadjuvant chemotherapy, extrapleural pneumonectomy and intensity-modulated radiotherapy. Radiat Oncol 2015;10:267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26715491.

173. Lang-Lazdunski L, Bille A, Papa S, et al. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy, and systemic chemotherapy in patients with malignant pleural mesothelioma: a 10-year experience. J Thorac Cardiovasc Surg 2015;149:558-565; discussion 565-556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25726878.

174. Lang-Lazdunski L, Bille A, Belcher E, et al. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine followed by adjuvant chemotherapy in patients with malignant pleural mesothelioma. J Thorac Oncol 2011;6:1746-1752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21876457.

175. Friedberg JS, Culligan MJ, Mick R, et al. Radical pleurectomy and intraoperative photodynamic therapy for malignant pleural mesothelioma. Ann Thorac Surg 2012;93:1658-1665; discussion 1665-1657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22541196.

176. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955-963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23434448.

177. Simone CB, 2nd, Cengel KA. Photodynamic therapy for lung cancer and malignant pleural mesothelioma. Semin Oncol 2014;41:820-830. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25499640.

178. Du KL, Both S, Friedberg JS, et al. Extrapleural pneumonectomy, photodynamic therapy and intensity modulated radiation therapy for the treatment of malignant pleural mesothelioma. Cancer Biol Ther 2010;10:425-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20699634.

179. Ried M, Potzger T, Braune N, et al. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience. Eur J Cardiothorac Surg 2013;43:801-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22885228.

180. de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. Chest 2002;121:480-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11834661.

181. Price A. What is the role of radiotherapy in malignant pleural mesothelioma? Oncologist 2011;16:359-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21346022.

182. van Thiel ER, Surmont VF, van Meerbeeck JP. Malignant pleural mesothelioma: when is radiation therapy indicated? Expert Rev Anticancer Ther 2011;11:551-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21504322.

183. Gomez DR, Hong DS, Allen PK, et al. Patterns of failure, toxicity, and survival after extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy for malignant pleural mesothelioma. J Thorac Oncol 2013;8:238-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23247629.

184. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17954086.

185. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12873676.

186. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16054774.

187. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19404212.

188. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9033296.

189. Chance WW, Rice DC, Allen PK, et al. Hemithoracic intensity modulated radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. Int J Radiat Oncol Biol Phys 2015;91:149-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25442335.

190. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7656629.

191. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10078630.

192. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18770063.

193. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18520267.

194. O'Rourke N, Garcia JC, Paul J, et al. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. Radiother Oncol 2007;84:18-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17588698.

195. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15199394.

196. Waite K, Gilligan D. The role of radiotherapy in the treatment of malignant pleural mesothelioma. Clin Oncol (R Coll Radiol) 2007;19:182-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17359904.

197. Cho BC, Feld R, Leighl N, et al. A feasibility study evaluating Surgery for Mesothelioma After Radiation Therapy: the "SMART" approach for resectable malignant pleural mesothelioma. J Thorac Oncol 2014;9:397-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24445595.

198. Rosenzweig KE, Zauderer MG, Laser B, et al. Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2012;83:1278-1283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22607910.

199. Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for intensity-modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys 2009;73:9-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19100920.

200. Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. Med Phys 2011;38:5067-5072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21978051.

201. Holmes T, Das R, Low D, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. Int J Radiat Oncol Biol Phys 2009;74:1311-1318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19616738.

202. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in intensity-modulated radiation therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21802333.

203. ICRU Report 83: Prescribing, recording, and reporting intensity modulated photon beam therapy (IMRT). Journal of the ICRU 2010;10. Available at: http://jicru.oxfordjournals.org/content/10/1.toc.

204. Rice DC, Smythe WR, Liao Z, et al. Dose-dependent pulmonary toxicity after postoperative intensity-modulated radiotherapy for

malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2007;69:350-357. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17467922.

205. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16751058.

206. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19364621.

207. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18262369.

208. Patel PR, Yoo S, Broadwater G, et al. Effect of increasing experience on dosimetric and clinical outcomes in the management of malignant pleural mesothelioma with intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2012;83:362-368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22516382.

209. Stahel RA, Weder W, Lievens Y, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v126-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20555061.

210. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17931793.