National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Malignant Pleural Mesothelioma

Version 2.2018 — February 26, 2018

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Malignant Pleural Mesothelioma

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NCCN Guidelines Version 2.2018
Malignant Pleural Mesothelioma

NCCN Malignant Pleural Mesothelioma Panel Members
Summary of Guidelines Updates

Initial Evaluation (MPM-1)
Pretreatment Evaluation (MPM-2)
Clinical Stage I-III and Epithelial Histology; Evaluation (MPM-2)
Clinical Stage IV or Sarcomatoid Histology or
Mixed Histology or Medically Inoperable; Treatment (MPM-2)
Clinical Stage I-III, Treatment for Medically Operable or Epithelial Histology (MPM-3)

Principles of Systemic Therapy (MPM-A)
Principles of Supportive Care (MPM-B)
Principles of Surgery (MPM-C)
Principles of Radiation Therapy (MPM-D)

Staging (ST-1)

Clinical Trials: NCCN believes that the best management for any patient with cancer 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/clinicians.html.

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 2.2018 of the NCCN Guidelines for Malignant Pleural Mesothelioma from Version 1.2018 include:

MPM-D 1 of 3

- **General Principles**
  Bullet 5 has been modified: *Prophylactic* RT may prevent instrument-tract recurrence after pleural intervention.

MS-1

- **The Discussion section has been updated to reflect the changes in the algorithm.**

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Updates in Version 1.2018 of the NCCN Guidelines for Malignant Pleural Mesothelioma from Version 2.2017 include:

MPM-1
- **Initial Evaluation, bullet 3: "thoracoscopic biopsy [preferred]" moved to be first option within parentheses following "Pleural biopsy"**

MPM-2
- **Footnote e modified: PET/CT should be performed before any pleurodesis*, if practical*.**

MPM-3
- **Clinical Stage: "and Epithelial histology" added after "Clinical stage I-III Medically operable"**
- **Primary Treatment, top branch: "or carboplatin" added after "Induction chemotherapy with pemetrexed and cisplatin"**

MPM-A 1 of 2
- **First-line Combination Chemotherapy Regimens**
  - **Pemetrexed/carboplatin regimen modified with this addition**
    - **± bevacizumab 15 mg/kg day 1**
    - **± maintenance bevacizumab 15 mg/kg (if bevacizumab given in combination with pemetrexed and carboplatin) every 3 weeks until disease progression.**
    - **Footnote ** modified: The combination regimen of pemetrexed/cisplatin/bevacizumab or *pemetrexed/carboplatin/bevacizumab* is only for unresectable disease.**
    - **Footnote removed: The carboplatin/pemetrexed regimen is recommended for patients with poor PS and/or comorbidities.**
- **Subsequent Systemic Therapy**
  - **Nivolumab ± ipilimumab: category changed from a category 2A to a category 2B.**

MPM-A 2 of 2
- **References 6, 18 added.**

MPM-C
- **Bullet 8; the following has been added as the last sentence: P/D can provide excellent symptomatic control of recurrent pleural effusions.**

MPM-D 1 of 3
- **General Principles**

  Bullet 1 has been modified: Recommendations regarding RT should be made by a *board-certified* radiation oncologist.

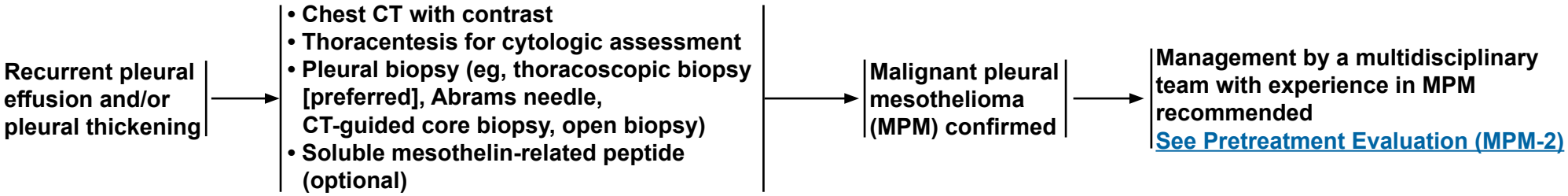
  Bullet 5 has been modified: RT ~~can be used to~~ *may* prevent instrument-tract recurrence after pleural intervention.

  Bullet 9 has been added: Advanced technologies may be used, such as image-guided RT (IGRT) for treatment involving IMRT/SRS/SBRT.
- **Radiation Dose and Volume, bullet 5; last sentence has been removed: For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.**

MPM-D 3 of 3
- **A new reference 7 has been added: Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. Lancet Oncol 2016;17:1094-1104.**

ST-1
- **Staging has been updated to reflect the changes in the AJCC Staging Manual, Eighth Edition (2017).**

INITIAL EVALUATION[a]



[a]There are no data to suggest that screening improves survival.

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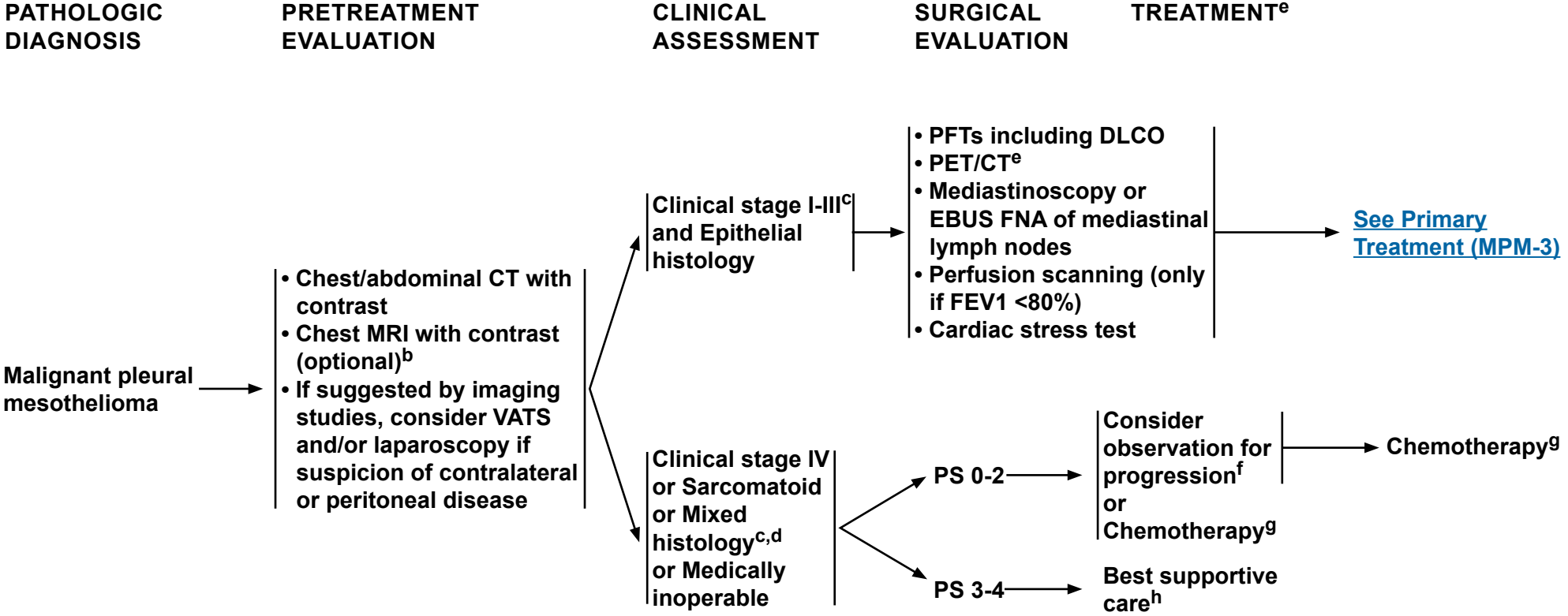

[b]For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[c]If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.
[d]Assessment by multidisciplinary team with experience in malignant pleural mesothelioma.
[e]PET/CT should be performed before any pleurodesis, if practical.
[f]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.
[g]See Principles of Systemic Therapy (MPM-A).
[h]See Principles of Supportive Care (MPM-B).

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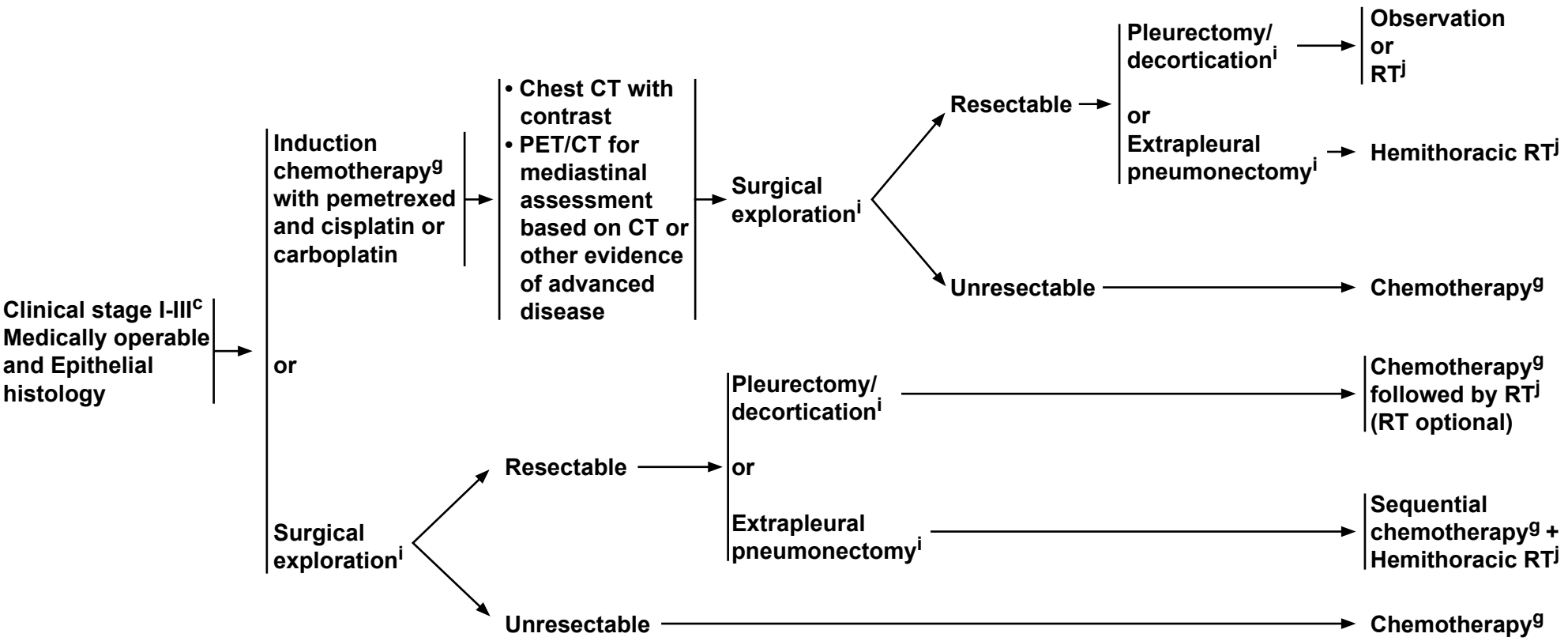

[c]If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.

[g]See Principles of Systemic Therapy (MPM-A).

[h]See Principles of Supportive Care (MPM-B).

[i]See Principles of Surgery (MPM-C).

[j]See Principles of Radiation Therapy (MPM-D).

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PRINCIPLES OF SYSTEMIC THERAPY

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 (category 1)[2,]**

- **Pemetrexed* 500 mg/m² day 1**
  Carboplatin AUC 5 day 1[3-5]
  ± bevacizumab 15 mg/kg day 1[6]
  Administered every 3 weeks for 6 cycles
  ± maintenance bevacizumab 15 mg/kg (if bevacizumab given in combination with pemetrexed and carboplatin) every 3 weeks until disease progression**

- **Gemcitabine 1000–1250 mg/m² days 1, 8, and 15**
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[7,8]

- **Pemetrexed* 500 mg/m² every 3 weeks[9]**

- **Vinorelbine 25–30 mg/m² weekly[10]**

SUBSEQUENT SYSTEMIC THERAPY

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

- **Vinorelbine[13,14]**

- **Gemcitabine[14-16]**

- **Nivolumab ± ipilimumab[17,18] (category 2B)**

- **Pembrolizumab[19]**

References on MPM-A (2 of 2)

*Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[20]
**The combination regimen of pemetrexed/cisplatin/bevacizumab or pemetrexed/carboplatin/bevacizumab is only for unresectable disease.

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PRINCIPLES OF SYSTEMIC THERAPY
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 2016;387:1405-1414.
[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]Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer 2013;109:552-558.
[7]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.
[8]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.
[9]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.
[10]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.
[11]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.
[12]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.
[13]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.
[14]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.
[15]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.
[16]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.
[17]Scherpereel A, Mazieres J, Greiller L, et al. Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase 2 trial [abstract]. J Clin Oncol 2017;35: Abstract LBA8507.
[18]Zalcman G, Mazieres J, Greillier L, et al. Second or 3rd line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Updated results of the IFCT-1501 MAPS2 randomized phase 2 trial [abstract]. Ann Oncol 2017;28: Abstract LBA58_PR.
[19]Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncology 2017;18:623-630.
[20]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.

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PRINCIPLES OF SUPPORTIVE CARE

- **Pleural effusions: Talc pleurodesis or pleural catheter, if required for management of pleural effusion[1]**
- **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**

[1]If PET/CT is to be done, 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.

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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 ± en-bloc resection of pericardium and/or diaphragm with reconstruction; 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 and mixed histology as poor prognostic factors for any surgical or non-surgical treatment of MPM and are contraindications to EPP or P/D.**
- **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 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 reduce the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection. P/D can provide excellent symptomatic control of recurrent pleural effusions.**
- **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.

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PRINCIPLES OF RADIATION THERAPY

General Principles

- Recommendations regarding RT should be made by a board-certified 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.
- Prophylactic RT may prevent instrument-tract recurrence after pleural intervention.[7]
- 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 after P/D is usually not recommended. Hemithoracic intensity-modulated RT (IMRT) after P/D may be considered in centers with experience and expertise in these methods.[8]
- 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.
- Advanced technologies may be used, such as image-guided RT (IGRT) for treatment involving IMRT/SRS/SBRT.

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment. See Recommended Doses for 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.[6,9] 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.[10-12]
- 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,[11,13] although the optimal daily and total dose of RT for palliative purposes remains unclear.
- 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)

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PRINCIPLES OF RADIATION THERAPY

Recommended Doses for Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
Postoperative after EPP			
Negative margins	50–54 Gy	1.8–2 Gy	5–6 weeks
Microscopic-macroscopic positive margins	54–60 Gy	1.8–2 Gy	6–7 weeks
Palliative			
Chest wall pain from recurrent nodules	20–40 Gy or 30 Gy	≥4 Gy 3 Gy	1–2 weeks 2 weeks
Multiple brain or bone metastasis	30 Gy	3 Gy	2 weeks
Post pleurectomy/decortication			
Negative margins	45 Gy–50.4 Gy	1.8 Gy–2.0 Gy	5–6 weeks
Microscopic positive margins	50 Gy–54 Gy	1.8 Gy–2.0 Gy	5–6 weeks

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 (IMRT) is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.[7,14]
- CT simulation-guided planning using either IMRT or conventional photon/electron RT is acceptable.[8] 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.[15,16] Special attention should be paid to minimize radiation to the contralateral lung,[17] as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.[18] The mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.[19]
- 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 or P/D 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.

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PRINCIPLES OF RADIATION THERAPY

[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]Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. Lancet Oncol 2016;17:1094-1104.
[8]Rimner A, Zauderer MG, Gomez DR, et al. Phase II study of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) as part of lung-sparing multimodality therapy in patients with malignant pleural mesothelioma. J Clin Oncol 2016;34:2761-2768.
[9]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.
[10]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.
[11]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.
[12]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.
[13]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.
[14]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.
[15]Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. Med Phys 2011;38:5067-5072.
[16]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.
[17]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.
[18]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.
[19]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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1. **Definitions for T, N, M**

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 involvement of: -visceral pleura -mediastinal pleura -diaphragmatic 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 metastases
N1	Metastasis to the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1	N0	M0
Stage IB	T2-T3	N0	M0
Stage II	T1-T2	N1	M0
Stage IIIA	T3	N1	M0
Stage IIIB	T1-T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise indicated.

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Overview

Mesothelioma is a rare cancer that is estimated to occur in approximately 2500 people in the United States every year.[1-4] These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) focus on malignant pleural mesothelioma (MPM), which is the most common type (81%). Mesothelioma can also occur in the lining of other sites, such as the peritoneum (9%), pericardium, and tunica vaginalis testis.[5-7] MPM is difficult to treat, because most patients have advanced disease at presentation. Median overall survival is approximately 1 year in patients with MPM, and 5-year overall survival is about 10%; cure is rare.[8-11] 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).[12-14]

These NCCN Guidelines® for Malignant Pleural Mesothelioma were first published in 2010 and have been subsequently updated every year. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2018, which are described in greater detail in this revised Discussion text; recent references have been added. Additional supplementary material in the NCCN Guidelines for Malignant Pleural Mesothelioma includes the *Principles of Systemic Therapy*, *Principles of Supportive Care, 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 incidence of MPM is decreasing in men 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.[2,15-17] The mortality burden from asbestos-related diseases in the United States did not change from 1999 to 2015.[8,18] Although asbestos is no longer mined in the United States, it is still imported.[17] The incidence of MPM is increasing in other countries such as Russia, Western Europe, China, and India.[3,16,19-24] Mortality rates from MPM are highest in the United Kingdom, Netherlands, and Australia; mortality rates are increasing in Poland, Spain, China, Japan, Argentina, Republic of Korea, and Brazil.[10,19,20,25] Russia, China, Brazil, and Canada are the top producers of asbestos.[26]

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.[27-37] Data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma.[38-41] Genetic factors may also play a role in MPM, with rare families carrying a germline mutation in the BRCA1 Associated Protein 1 (*BAP1*) gene.[38,42-46] Smoking is not a risk factor for mesothelioma.[47] 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) (see the NCCN Guidelines® for Smoking Cessation, available at www.NCCN.org).[48]

The histologic subtypes of mesothelioma include epithelioid (most common), sarcomatoid, and biphasic (mixed) epithelioid and sarcomatoid.[4,49,50] Patients with epithelioid histology have better outcomes than those with either mixed or sarcomatoid histologies. Some patients who have been exposed to asbestos only have benign pleural disease, although they may have significant chest pain.[51,52] 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).[26,53-59] 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 with low-dose CT improves survival for patients with MPM.[26,60]

Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature on mesothelioma 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 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 (available at www.NCCN.org).

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 www.NCCN.org).[25,61,62] Patients with MPM often have a high symptom burden when compared with patients who have other types of cancer. Patients often present without distant metastases because symptoms such as chest pain and/or dyspnea are associated with local disease; CNS metastases are uncommon.[53] 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).[25,26,53,63-67] However, cytologic samples are often negative even when patients have MPM.[68,69] Fine-needle aspiration (FNA) is not recommended for diagnosis.[25] Talc pleurodesis or pleural catheter may be needed for management of pleural effusion.[53,70-74] Soluble mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status;[75-78] osteopontin does not appear to be as useful for diagnosis.[53,79-83] Other potential diagnostic biomarkers are being assessed.[54-56,84-88]

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.[21,89-96] 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.[53,68,69,97,98] 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]).[68,90,93,95,99,100]

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;[4] select patients (ie, clinical stages I–III, medically operable, epithelial histology, good performance status [PS]) are candidates for multimodality therapy.[101-105] Definitive RT alone is not recommended for unresectable MPM; chemotherapy alone is recommended in this setting for patients with PS 0 to 2 (see *Treatment* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[106,107] 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.[63,64,108] Video-assisted thoracoscopic surgery (VATS) or laparoscopy can be considered if contralateral or peritoneal disease is suspected.[109] PET/CT scans should be obtained before pleurodesis if practical, because talc produces pleural inflammation, which can affect the FDG avidity (ie, false-positive result).[110-112] However, PET/CT scans are mainly used to assess for metastatic disease. If surgical resection is being considered, mediastinoscopy or endobronchial ultrasonography (EBUS) FNA of the mediastinal lymph nodes is recommended.[113,114] 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 wall, spinal, diaphragmatic, or vascular involvement.

Surgical staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system (see *Staging* in the NCCN Guidelines for Malignant Pleural Mesothelioma), which was approved by the AJCC.[115-117] The AJCC cancer staging system was recently updated (8th edition) and became effective on January 1, 2018.[118] Some of the recent changes in the AJCC staging for MPM include: 1) T3 and T4 are now classified as stage IIIB, regardless of N status; 2) former N3 nodes are now classified as N2; 3) former N2 nodes are now classified as N1; and 4) T1a and T1b are now classified as T1.[53,118,119] Clinical staging only is done for patients who are not candidates for surgery. It is difficult to clinically stage patients using CT or MRI; therefore, patients who have surgery may be upstaged.

Most patients have advanced disease at presentation. However, it is difficult to accurately stage patients before surgery. Understaging is common with PET/CT.[112,120] However, PET/CT is useful for determining whether metastatic disease is present.[120,121] Consideration of surgical resection is recommended for patients with clinical stage I to III MPM (epithelial histology) 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 (epithelial

histology) 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 or mixed 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 for progression 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.[53,70,74,122-124] 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.[25]

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).[125] Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[125] Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). The surgical goal for MPM is cytoreductive surgery to achieve macroscopic complete resection by removing all visible or palpable tumors.[126,127] 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.[4,25,53,128-135] Neither EPP nor P/D will yield an R0 resection.[4,136,137] EPP would often be required to remove all gross tumor in patients with stages II to III MPM (epithelial histology).[62] However, EPP is associated with higher morbidity and mortality.[130,138] P/D (ie, lung-preserving surgery) is safer than EPP.[138-145] 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.[4,143] A meta-analysis suggested a trend in favor of overall survival for extended PD when compared with EPP.[130] Lung-sparing options, such as P/D, reduce the risk for perioperative mortality when compared with EPP and yield either equal or better long-term survival than non-surgical therapy in patients with more advanced disease.[136,146]

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.[147] 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.[148] An Australian retrospective study (540 patients) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and treatment with pemetrexed.[149]

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.[130,143,147,150,151] 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.[9,151] 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.[139] P/D may also be useful for symptom control (eg, patients with entrapped lung syndrome, recurrent pleural effusions).[26] The NCCN Panel does not recommend surgery for patients with stage IV MPM, sarcomatoid histology, or mixed 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 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 (epithelial histology) 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 or mixed histology.[131,152-154] Pemetrexed-based chemotherapy can also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[5,155] Trimodality therapy—using chemotherapy, surgery, and hemithoracic RT—has been used in patients with MPM.[101-104,156-159] Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.[102,159] Nodal status and response to chemotherapy can affect survival.[102,105] 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—have also been studied.[160-169]

First-Line Therapy

A combined first-line regimen using cisplatin/pemetrexed (category 1) is recommended for MPM and is currently the only regimen approved by the FDA.[170-173] 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).[172] Based on this trial and the FDA approval, the NCCN Panel recommends cisplatin/pemetrexed (category 1) for patients with MPM. A 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 to 2 who did not have bleeding or thrombosis.[174] 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 1) bevacizumab, cisplatin, and pemetrexed followed by maintenance bevacizumab for bevacizumab-eligible patients with unresectable MPM based on this trial (see *Principles of Chemotherapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[174] Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity.[53]

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);[175-177] or 2) gemcitabine/cisplatin, which was also assessed in phase 2 studies (median survival = 9.6–11.2 months).[178-180] Gemcitabine/cisplatin may be useful for patients who cannot take pemetrexed. A comparison of 1704 patients with medically inoperable MPM treated with cisplatin/pemetrexed or carboplatin/pemetrexed as part of an expanded access trial found that outcomes with the regimens were similar.[181] For the 2018 update, the NCCN Panel deleted the caveat that carboplatin/pemetrexed regimen is a better choice for patients with poor PS and/or comorbidities, because panel members feel this regimen can also be used for patients with good PS based on clinical trial data.[181] Acceptable first-line single-agent options include pemetrexed or vinorelbine for patients who are not candidates for platinum-based combination therapy.[182-184] A phase 2 trial assessed adding bevacizumab to carboplatin/pemetrexed with or without maintenance bevacizumab as first-line therapy for patients with unresectable MPM.[185] Overall survival was 15.3 months; 34% (26/76) of patients had a partial response and 58% (44/76) had stable disease. Bowel perforation occurred in 4% of patients, grade 3 to 4 fatigue occurred in 8%; there were 3 toxic deaths. Maintenance bevacizumab (maximum, 1 year) was administered to patients without progression and/or severe toxicities. For the 2018 update, the NCCN Panel now recommends (category 2A) adding bevacizumab to carboplatin/pemetrexed with or without maintenance bevacizumab as a new first-line therapy option for patients with unresectable MPM based on this trial.

Subsequent Therapy

Limited data are available to guide second-line and beyond (subsequent) systemic therapy.[169,186-189] Recent data suggest that immune checkpoint inhibitors may be useful as subsequent systemic therapy for patients with MPM.[190-197] Human immune-checkpoint–inhibitor antibodies, such as pembrolizumab and nivolumab, inhibit the programmed death-1 (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.[198] Nivolumab and pembrolizumab inhibit PD-1 receptors.[198] Testing for PD-L1 is not required for prescribing nivolumab for subsequent therapy.

Immune-related adverse events, such as pneumonitis, may occur with nivolumab or pembrolizumab (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[199-201] Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events. Nivolumab or pembrolizumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or

life-threatening immune-mediated adverse events when indicated (see prescribing information). CTLA-4 decreases T-cell activity. Ipilimumab is a monoclonal antibody that inhibits CTLA-4 and thus improves T-cell activity. Ipilimumab can also cause immune-mediated adverse events such as hepatitis and endocrinopathies.

A phase 2 randomized trial (IFCT-1501 MAPS2; n = 125) is assessing nivolumab with or without ipilimumab as subsequent therapy for patients with MPM.[192] Updated results from this trial indicate that median overall survival was not reached in the nivolumab/ipilimumab arm and was 13.6 months with nivolumab alone (95% CI, 6.7 months–not reached).[193] The 12-month overall survival rates were 58% with the nivolumab/ipilimumab arm and 51% with the nivolumab alone. The overall response rate was 27.8% (95% CI, 15.8%–39.7%) with nivolumab/ipilimumab versus 18.5% (95% CI, 8.2%–28.9%) with nivolumab alone. Positive PD-L1 levels were not associated with overall survival. There were more grade 3 to 5 adverse events in the nivolumab/ipilimumab arm when compared with the nivolumab alone arm (16.4% vs. 9.5%); 3 treatment-related deaths were reported in the nivolumab/ipilimumab arm (one each: metabolic encephalopathy, fulminant hepatitis, acute renal failure).

A phase 1b trial (KEYNOTE-028) is assessing pembrolizumab as subsequent therapy for 25 patients with PD-L1–positive MPM (>1% PD-L1 expression levels). Preliminary data indicate a partial response rate of 20% (5/25) (95% CI, 6.8–40.7); 52% (13/25) of patients had stable disease.[190] The median response duration was 1 year (95% CI, 3.7 months–not reached). Grade 3 adverse events were reported in 20% (5/25) of patients. Updated results from this trial indicate a median overall survival of 18 months (95% CI, 9.4–not reached); the 12-month overall survival rate was 62.6%.[191] The overall response rate was 28% (7/25); 48% (12/25) of patients had stable disease. Grade 3 to 4 drug-related adverse events occurred in 5 (20%) patients. No treatment-related deaths or need for discontinuing pembrolizumab have been reported in the KEYNOTE-028 trial.

A phase 2 trial in 34 patients is assessing pembrolizumab as subsequent therapy for patients with MPM or peritoneal mesothelioma; patients were not selected for PD-L1 expression.[53] Preliminary data indicate a median PFS of 6.2 months (95% CI, 3.2–8.2); the median overall survival has not been reached. A partial response occurred in 21% (7/34) of patients, stable disease in 56% (19/34), and progression in 18% (6/34). Response did not correlate with PD-L1 expression. Early death occurred in 6% (2/34) of patients; grade 5 toxicity included autoimmune hepatitis (3%) and unknown (3%). Grade 3 to 4 toxicity included pneumonitis (6%), fatigue (6%), adrenal insufficiency (6%), colitis (3%), confusion (3%), hyponatremia (3%), and neutropenia (3%).

Based on these trials, the NCCN Panel recommends the following subsequent immunotherapy options for patients with MPM: 1) pembrolizumab (category 2A); or 2) nivolumab with or without ipilimumab (category 2B).[53,190-193] For the 2018 update, the NCCN Panel revised the recommendation for nivolumab with ipilimumab to be category 2B (from category 2A) based on the toxicities of the regimen. The NCCN Panel also recommends other subsequent systemic therapy options including pemetrexed (if not administered first line) (category 1), vinorelbine, or gemcitabine.[183,186,202-207] Data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed.[186,208]

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 for treatment (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 www.NCCN.org).[25,106,209] The dose of radiation should be based on the purpose of treatment.[210] 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.[211-214] 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.[106]

It has been controversial whether immediate (prophylactic) RT is useful for preventing instrument-tract recurrence after pleural intervention.[215-220] A French trial reported that prophylactic RT was useful for preventing recurrence, but 2 more recent trials did not find any benefit.[215,219,220] A phase 3 randomized trial (SMART trial) compared prophylactic radiotherapy with deferred radiotherapy to assess the rate of recurrences in patients who had had procedures for MPM.[221] Patients in the deferred RT arm did not receive RT until procedure-tract metastases were evident. Data showed that there was no difference in procedure-tract recurrence in the prophylactic RT (9% [9/102]) versus deferred RT (16% [16/101]) arms (odds ratio [OR], 0.51 [95% CI, 0.19–1.32]). In addition, prophylactic RT did not improve the quality of life, decrease chest pain, or decrease the need for analgesic drugs. However, if patients did not receive chemotherapy, prophylactic RT did decrease the risk for procedure-tract metastases (OR, 0.16 [95% CI, 0.02–0.93]; P = .021). For the 2018 update, the NCCN Panel revised the recommendations for use of prophylactic RT to prevent instrument-tract recurrence after pleural intervention based on the SMART trial.[103,137,214,221-224] The recommendation was softened to state that RT *may* prevent instrument-tract recurrence after pleural intervention; previously the recommendation had stated that RT can be used to prevent recurrence (see *Principles of Radiation Therapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma). The prophylactic RT doses were also deleted, because panel members felt they were overly prescriptive and only included one regimen when several regimens are cited in the literature.[215,219-221]

CT simulation–guided planning using either intensity-modulated RT (IMRT) or conventional photon/electron RT is acceptable.[159,211,213,225] 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 www.NCCN.org). The volume of postoperative radiation should cover the surgical bed within the thorax.[103,137,214,222-224] The optimal dose of RT for palliative purposes remains unclear.[210,226] For patients with chest pain from mesothelioma, total doses of 20 to 40 Gy appear to be effective in providing relief from pain.[25,215,216]

IMRT allows a more conformal high-dose RT and improved coverage to the hemithorax at risk.[106,211,212,227,228] Advanced technologies, such as image-guided RT may be used for treatments involving IMRT, stereotactic radiosurgery, or stereotactic body radiation therapy. The NCI and ASTRO/ACR IMRT guidelines are recommended.[229-231] The ICRU-83 (International Commission on Radiation Units & Measurements Report 83) recommendations are also a useful resource.[232,233] RT to the contralateral lung should be minimized,[106,212,234] because fatal pneumonitis may occur with IMRT if strict limits are not applied.[235-237] The mean lung dose should be kept as low as possible, preferably less than 8.5 Gy.[238] The volume of contralateral lung receiving low-dose RT (eg, 5 Gy) should be minimized.[239,240] 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%.[227] However, 13 patients had grade 3+ surgical complications and one patient died from treatment.

Summary

These NCCN Guidelines focus on MPM, which is the most common type of mesothelioma. This Discussion text for MPM 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. Revisions for the 2018 update are described in this Discussion and outlined in the algorithm (see *Summary of the Guidelines Updates* in the NCCN Guidelines for Malignant Pleural Mesothelioma). For example, one of the recommended first-line combination chemotherapy regimens is carboplatin/pemetrexed (category 2A), and this regimen was revised by adding an option for bevacizumab with or without maintenance bevacizumab based on phase 2 trial data. Nivolumab with or without ipilimumab are options for subsequent systemic therapy regimens; the category for these regimens was revised to category 2B from category 2A based on updated trial data. The RT recommendations for MPM were also revised with the 2018 update. For example, the NCCN Panel has softened the recommendation for using prophylactic RT to prevent instrument-tract recurrence after pleural intervention based on recent trial data. The NCCN Guidelines now state that RT *may* prevent instrument-tract recurrence after pleural intervention. The cancer staging for MPM has also been updated for 2018 to reflect the new staging guidelines from the AJCC, which became effective on January 1, 2018.

References

1. Special Section – Rare Cancers in Adults. American Cancer Society. Cancer Facts & Figures 2017. Available at: https://tinyurl.com/yb4joe3c.

2. Howlader N, Noone AM, Krapcho M. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute. Available at: https://seer.cancer.gov/csr/1975_2014/.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. Mazurek JM, Syamlal G, Wood JM, et al. Malignant mesothelioma mortality - United States, 1999-2015. MMWR Morb Mortal Wkly Rep 2017;66:214-218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28253224.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. Abdel-Rahman O. Global trends in mortality from malignant mesothelioma; analysis of WHO mortality database (1994-2013). Clin Respir J 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29424961.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. Chang ET, Lau EC, Mowat FS, Teta MJ. Therapeutic radiation for lymphoma and risk of second primary malignant mesothelioma. Cancer Causes Control 2017;28:971-979. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28755241.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. 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.

38. Carbone M, Kanodia S, Chao A, et al. Consensus report of the 2015 Weinman International Conference on Mesothelioma. J Thorac Oncol 2016;11:1246-1262. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27453164.

39. 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.

40. 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.

41. 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.

42. Betti M, Casalone E, Ferrante D, et al. Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma. Cancer Lett 2017;405:38-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28687356.

43. 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.

44. 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.

45. 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.

46. 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.

47. 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.

48. 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.

49. 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.

50. 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.

51. 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.

52. 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.

53. Kindler HL, Ismaila N, Armato SG, 3rd, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018:JCO2017766394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29346042.

54. Felten MK, Khatab K, Knoll L, et al. Changes of mesothelin and osteopontin levels over time in formerly asbestos-exposed power industry workers. Int Arch Occup Environ Health 2014;87:195-204. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23423281.

55. Casjens S, Weber DG, Johnen G, et al. Assessment of potential predictors of calretinin and mesothelin to improve the diagnostic performance to detect malignant mesothelioma: results from a population-based cohort study. BMJ Open 2017;7:e017104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29025836.

56. Johnen G, Gawrych K, Raiko I, et al. Calretinin as a blood-based biomarker for mesothelioma. BMC Cancer 2017;17:386. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28558669.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

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

63. 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.

64. 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.

65. 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.

66. 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.

67. 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.

68. 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.

69. 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.

70. 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.

71. 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.

72. 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.

73. 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.

74. 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.

75. 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.

76. 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.

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.

84. 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.

85. 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.

86. 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.

87. 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.

88. 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.

89. Churg A, Attanoos R, Borczuk AC, et al. Dataset for reporting of malignant mesothelioma of the pleura or peritoneum: recommendations from the International Collaboration on Cancer Reporting (ICCR). Arch Pathol Lab Med 2016;140:1104-1110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27031777.

90. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2017 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2018;142:89-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28686500.

91. Marchevsky AM, LeStang N, Hiroshima K, et al. The differential diagnosis between pleural sarcomatoid mesothelioma and spindle cell/pleomorphic (sarcomatoid) carcinomas of the lung: evidence-based guidelines from the International Mesothelioma Panel and the MESOPATH National Reference Center. Hum Pathol 2017;67:160-168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28782639.

92. 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.

93. 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.

94. 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.

95. 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.

96. 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.

97. 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.

98. 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.

99. Dacic S, Butnor KJ, Baker TP, et al. Protocol for the examination of specimens from patients with malignant pleural mesothelioma. Based on AJCC/UICC TNM, 8th edition. Protocol web posting date: June 2017: Collage of American Pathologists; 2017. Available at: https://tinyurl.com/yajz9bpb.

100. 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:

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

111. 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.

112. 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.

113. 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.

114. 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.

115. Bonomi M, De Filippis C, Lopci E, et al. Clinical staging of malignant pleural mesothelioma: current perspectives. Lung Cancer (Auckl) 2017;8:127-139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28860886.

116. 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.

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

118. Amin MB, Greene FL, Byrd DR. AJCC Cancer Staging Manual, 8th edition: Springer International Publishing; 2017:1-1024.

119. Rusch VW, Chansky K, Kindler HL, et al. The IASLC mesothelioma staging project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. J Thorac Oncol

2016;11:2112-2119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27687962.

120. 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.

121. 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.

122. 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.

123. 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.

124. 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.

125. 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.

126. 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.

127. 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.

128. Taioli E, van Gerwen M, Mihalopoulos M, et al. Review of malignant pleural mesothelioma survival after talc pleurodesis or surgery. J Thorac Dis 2017;9:5423-5433. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29312753.

129. 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.

130. 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.

131. 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.

132. 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.

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

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

135. 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.

136. 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.

137. 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.

138. 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.

139. 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.

140. 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.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. 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.

147. 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.

148. 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.

149. 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.

150. 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.

151. 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.

152. 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.

153. 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.

154. 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.

155. Kim JS, Lim SY, Hwang J, et al. A case report of primary pericardial malignant mesothelioma treated with pemetrexed and cisplatin. J Korean Med Sci 2017;32:1879-1884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28960045.

156. Kapeles M, Gensheimer MF, Mart DA, et al. Trimodality treatment of malignant pleural mesothelioma: an institutional review. Am J Clin Oncol 2018;41:30-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26353120.

157. Nelson DB, Rice DC, Niu J, et al. Long-term survival outcomes of cancer directed surgery for malignant pleural mesothelioma: propensity score matching analysis. J Clin Oncol 2017;35:3354-3362. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28817374.

158. Vogl SE. Guarantee-time bias and benefits of surgery for pleural mesothelioma. J Clin Oncol 2018;36:624-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29303626.

159. 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.

160. Srinivasan G, Sidhu GS, Williamson EA, et al. Synthetic lethality in malignant pleural mesothelioma with PARP1 inhibition. Cancer Chemother Pharmacol 2017;80:861-867. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28756516.

161. 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.

162. 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.

163. 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.

164. 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.

165. 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.

166. 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.

167. 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.

168. 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. 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.

174. 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 2016;387:1405-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26719230.

175. 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.

176. 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.

177. 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.

178. 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.

179. 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.

180. 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.

181. 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.

182. 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.

183. 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.

184. 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.

185. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer 2013;109:552-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23860535.

186. 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.

187. 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.

188. 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.

189. 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.

190. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol 2017;18:623-630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28291584.

191. Alley EW, Lopez J, Santoro A, et al. OA13.03 Long-term overall survival for patients with malignant pleural mesothelioma on pembrolizumab enrolled in KEYNOTE-028 [abstract]. J Thorac Oncol 2017;12:S294. Available at: http://www.jto.org/article/S1556-0864(16)31543-X/fulltext.

192. Scherpereel A, Mazieres J, Greiller L, et al. Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase 2 trial [abstract]. J Clin Oncol 2017;35:Abstract LBA8507. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA8507.

193. Zalcman G, Mazieres J, Greillier L, et al. Second or 3rd line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Updated results of the IFCT-1501 MAPS2 randomized phase 2 trial [abstract]. Ann Oncol 2017;28:Abstract LBA58_PR. Available at: https://tinyurl.com/ych67u3c.

194. 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: https://tinyurl.com/y9xqndc4.

195. 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://tinyurl.com/ybrdtp2c.

196. 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.

197. 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.

198. Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non small cell lung cancer: two year outcomes from two randomized, open label, phase III trials (CheckMate 017 and CheckMate 057). J Clin Oncol 2017;35:3924-3933. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29023213.

199. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor related pneumonitis in patients with advanced cancer: a systematic review and meta analysis. JAMA Oncol 2016;2:1607-1616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27540850.

200. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2017;35:709-717. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27646942.

201. Sgambato A, Casaluce F, Sacco PC, et al. Anti PD-1 and PDL-1 immunotherapy in the treatment of advanced non-small cell lung cancer (NSCLC): a review on toxicity profile and its management. Curr Drug

Saf 2016;11:62-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26412670.

202. 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.

203. 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.

204. 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.

205. 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.

206. 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.

207. 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.

208. 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.

209. 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.

210. 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.

211. 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.

212. 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.

213. 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.

214. 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.

215. 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.

216. 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.

217. 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.

218. 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.

219. 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.

220. 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.

221. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. Lancet Oncol 2016;17:1094-1104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27345639.

222. 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.

223. 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.

224. 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.

225. 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.

226. 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.

227. 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.

228. 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.

229. 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.

230. 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.

231. 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.

232. 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.

233. 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.

234. 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.

235. 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.

236. 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.

237. 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.

238. 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.

239. 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.

240. 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.