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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NCCN Guidelines Version 2.2018
Malignant Pleural Mesothelioma

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ф Diagnostic/Interventional radiology
¥ Patient advocate
Þ Internal medicine
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National Comprehensive Cancer Network®

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
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Principles of Systemic Therapy (MPM-A)
Principles of Supportive Care (MPM-B)
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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.**

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.

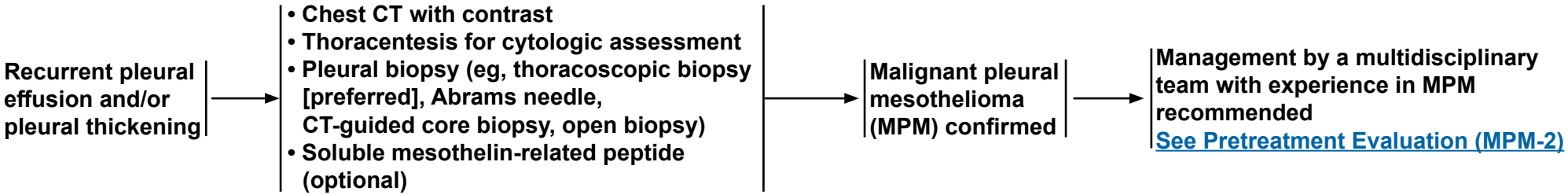
  Bullet 5 has been modified: RT ~~can be used to~~ *may* prevent instrument-tract recurrence after pleural intervention.

  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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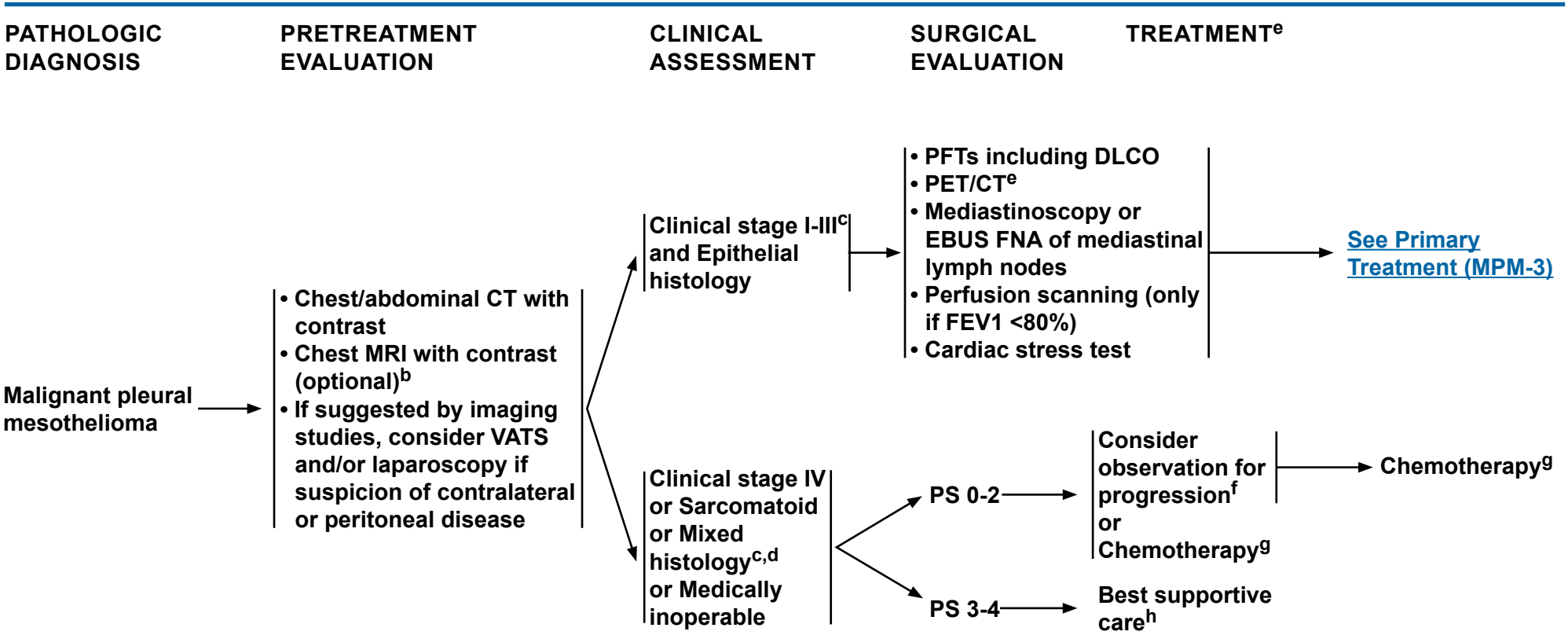

[b]For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[c]If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at 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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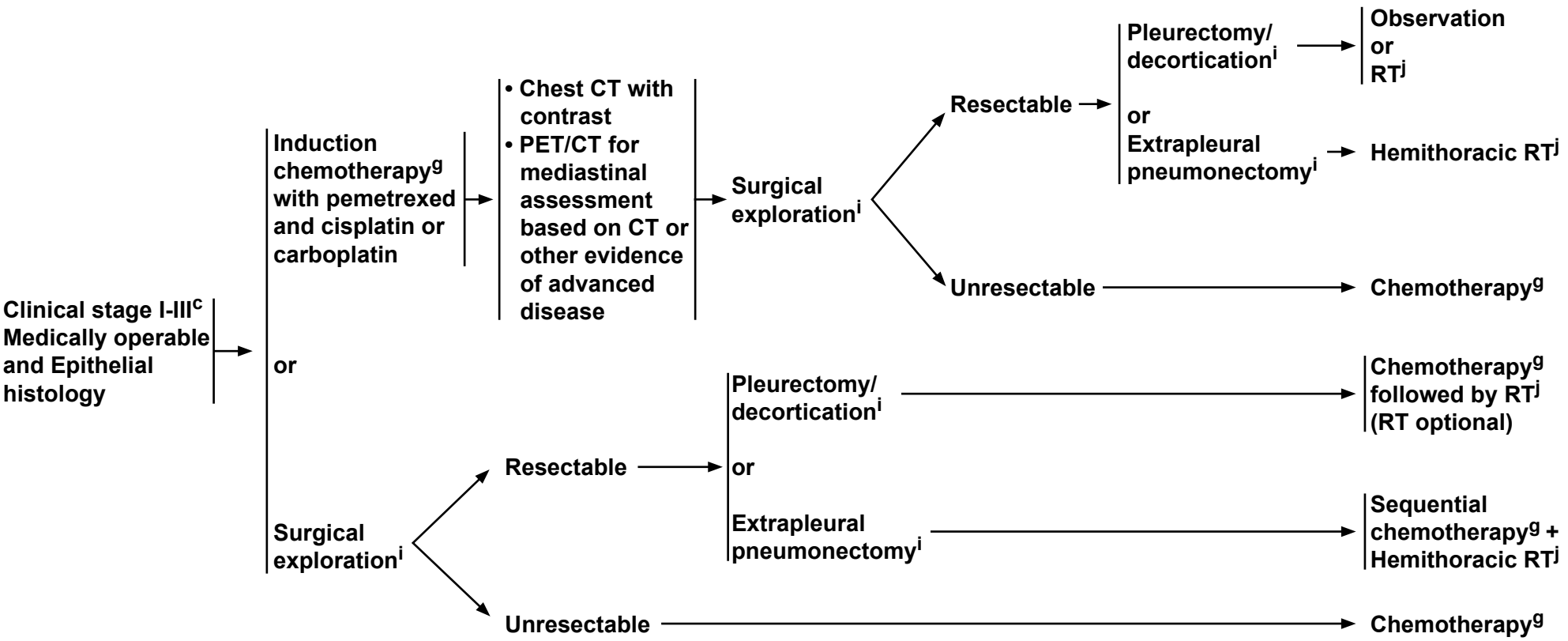

[c]If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.

[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.
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[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.
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[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.
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[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.
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[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.
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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.

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