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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Malignant Pleural Mesothelioma

Version 2.2015

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

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

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2015 Updates Malignant Pleural Mesothelioma

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Updates in Version 2.2015 of the NCCN Guidelines for Malignant Pleural Mesothelioma from version 1.2015 include:

MPM-B 1 of 2

- **The first-line combination chemotherapy regimen of pemetrexed/cisplatin/bevacizumab followed by maintenance bevacizumab added as a treatment option for unresectable MPM.**

MPM-B 2 of 2

- **Reference 2 added.**

MS-1

- **Discussion updated to reflect the changes in the algorithm.**

Updates in Version 1.2015 of the NCCN Guidelines for Malignant Pleural Mesothelioma from version 1.2014 include:

MPM-2

- **Surgical evaluation: PFTs clarified with the addition of "including DLCO."**

MPM-3

- **Induction chemotherapy: "Observation" added after pleurectomy/decortication.**

MPM-B

- **Reference 12 added: 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.**

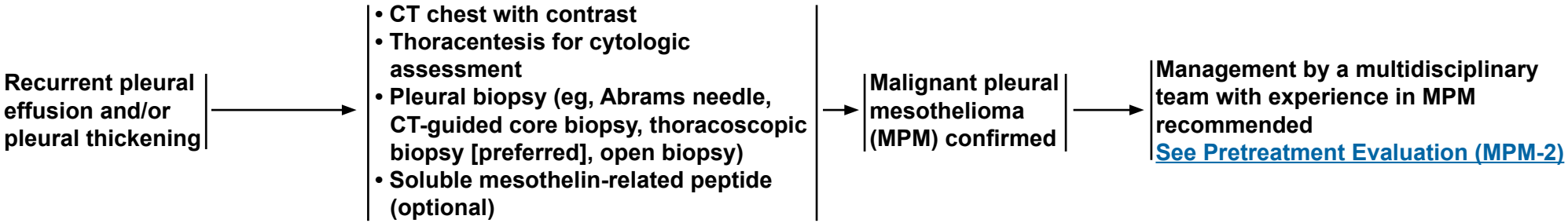
MPM-C

- **Bullet 3 modified: 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.**
- **Bullet 4 modified: The surgical choices are: 1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor; and 2) extrapleural pneumonectomy (EPP), which is defined as en-bloc resection of the pleura, lung, ipsilateral diaphragm, and, often, pericardium. Mediastinal node sampling should be performed~~. The,~~ *with a* goal ~~is~~ to obtain a*t least* 3 nodal stations~~, if technically feasible~~.**
- **Bullet 5 modified: Numerous studies have defined sarcomatoid ~~and mixed tumors~~ as a poor prognostic factor~~s~~ *for any surgical or non-surgical treatment of MPM and is a contraindication to* ~~after~~ EPP.**
- **Bullet 6 modified: 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 ~~should be the first option.~~and EPP *are each reasonable surgical treatment options and should* ~~may~~ be considered in select patients for complete gross cytoreduction.**
- **Bullet 7 modified: If N2 disease *or a mixed histology tumor* is identified, *prognosis with surgery (and other therapy) is substantially diminished.* Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.**
- **Bullet 8 added: If technically appropriate for even more advanced disease, lung sparing operations like pleurectomy/decortication reduces the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection.**
- **Bullet 9 added: 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.**
- **References 3–5 added.**

MPM-D (2 of 3)

- **Recommended Doses for Conventionally Fractionated Radiation Therapy: Treatment type clarified, Postoperative *after EPP*.**

INITIAL EVALUATION[a]



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

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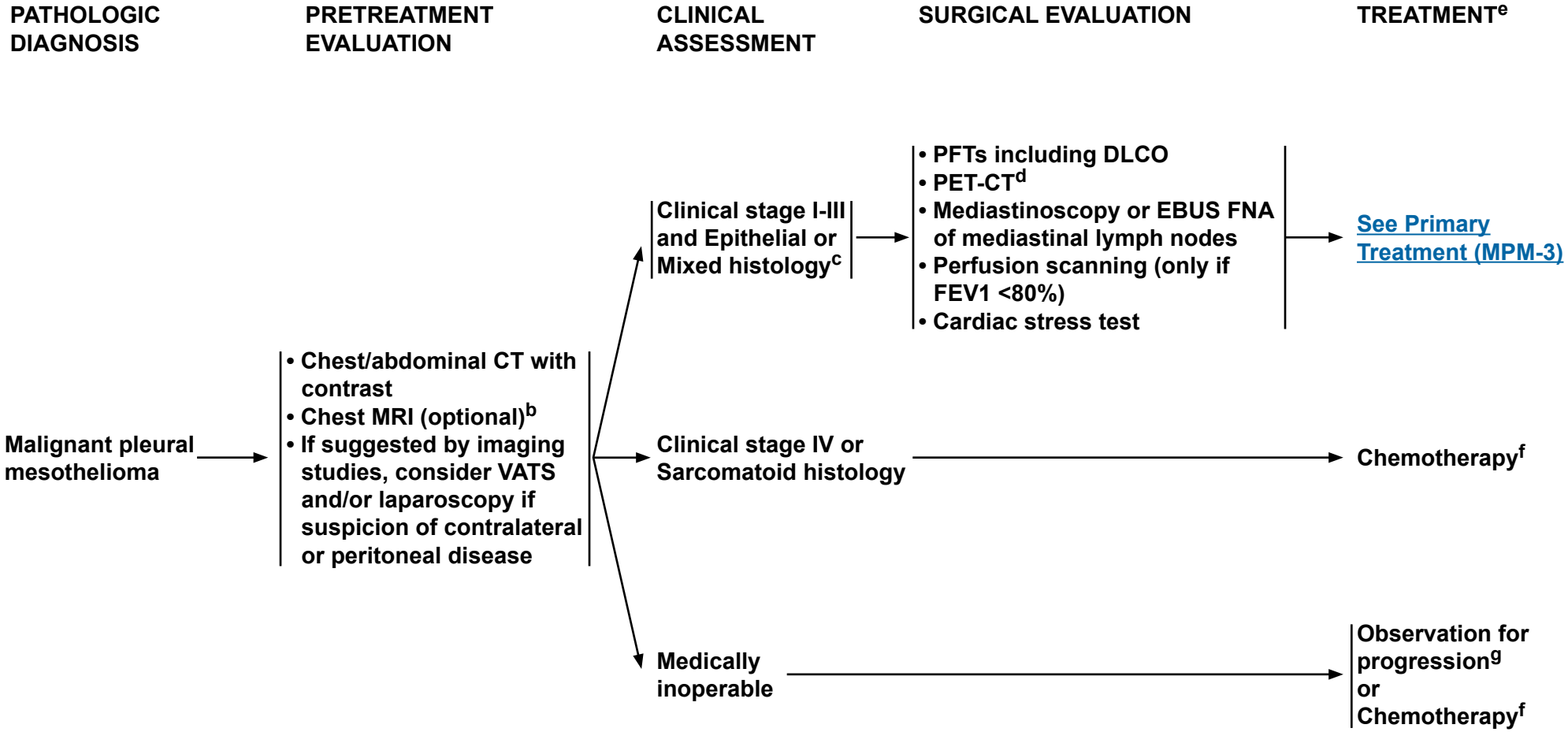

[b]For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[c]Assessment by multidisciplinary team with experience in malignant pleural mesothelioma.
[d]PET-CT should be performed before any pleurodesis.
[e]See Principles of Supportive Care (MPM-A).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

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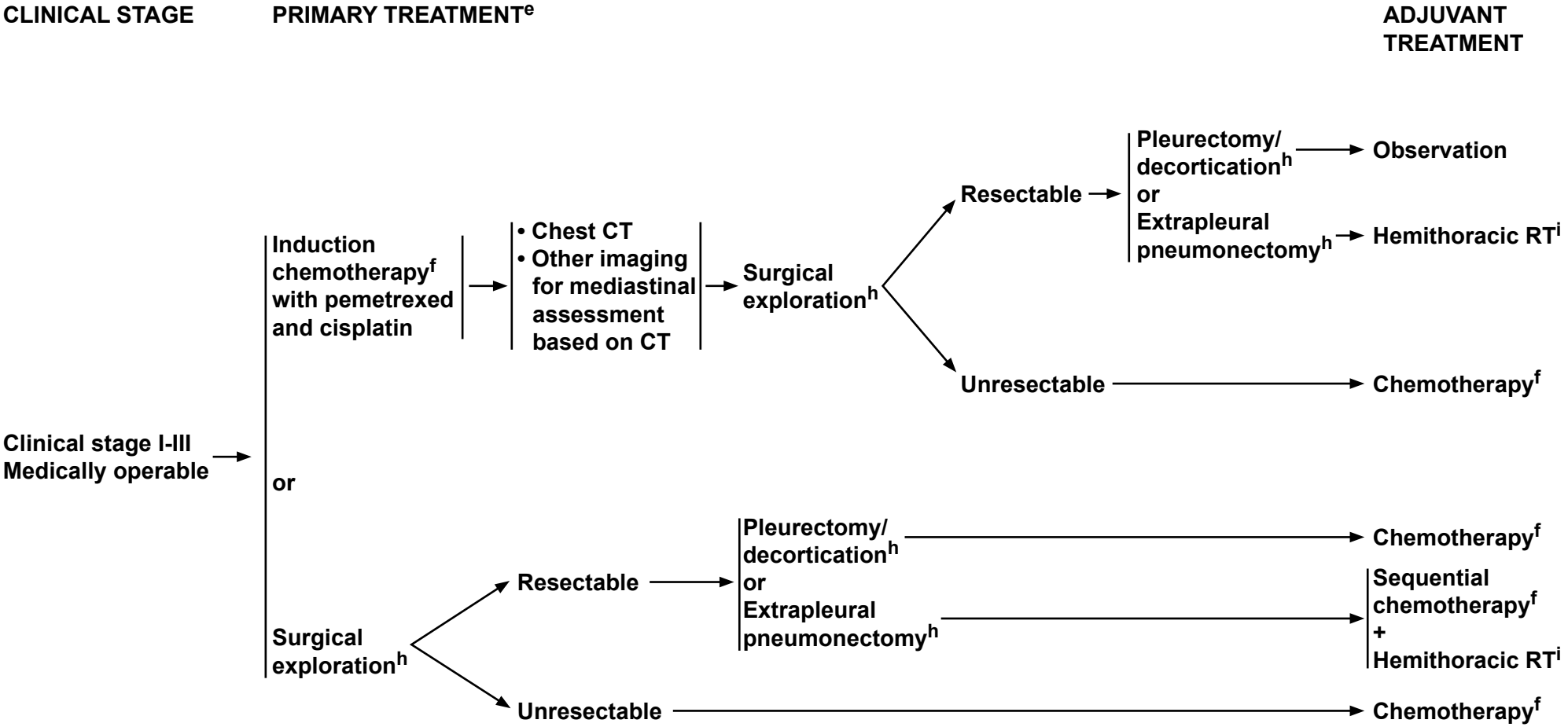

[e] See Principles of Supportive Care (MPM-A).
[f] See Principles of Chemotherapy (MPM-B).
[h] See Principles of Surgery (MPM-C).
[i] See Principles of Radiation Therapy (MPM-D).

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PRINCIPLES OF SUPPORTIVE CARE

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

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

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PRINCIPLES OF CHEMOTHERAPY (1 of 2)

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

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

SECOND-LINE CHEMOTHERAPY

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

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

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PRINCIPLES OF CHEMOTHERAPY (2 of 2)
References

[1]Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-2644.
[2]Zalcman G, Mazières J, Margery J, et al. Bevacizumab 15mg/kg plus cisplatin-pemetrexed (CP) triplet versus CP doublet in Malignant Pleural Mesothelioma (MPM): Results of the IFCT-GFPC-0701 MAPS randomized phase 3 trial [abstract]. J Clin Oncol 2015; 33:Abstract 7500.
[3]Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma. Ann Oncol 2008;19:370-373.
[4]Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol 2006;24:1443-1448.
[5]Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma. J Thorac Oncol 2008;3:756-763.
[6]Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 2002;87:491-496.
[7]Van Haarst JM, Baas J, Manegold CH, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer 2002; 86:342-345.
[8]Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol 2008;3:764-771.
[9]Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. Lancet 2008;371:1685-1694.
[10]Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol 2008;26:1698-1704.
[11]Zucal PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung Cancer 2012;75:360-367.
[12]Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer 2009;63:94-97.
[13]Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-274.
[14]Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. Ann Oncol 2005;16:923-927.
[15]van Meerbeeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999;85:2577-2582.
[16]Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agents. Lung Cancer 2009;64:211-218.

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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.**
- **The surgical choices are: 1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor; and 2) extrapleural pneumonectomy (EPP), which is defined as en-bloc resection of the pleura, lung, ipsilateral diaphragm, and often pericardium. Mediastinal node sampling should be performed with a goal to obtain at least 3 nodal stations.**
- **Numerous studies have defined sarcomatoid as a poor prognostic factor for any surgical or non-surgical treatment of MPM and is a contraindication to EPP.**
- **For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid), PD may be safer than EPP but it is unclear which operation is oncologically better. There is controversy regarding choice of procedure that needs to be weighed, taking into account tumor histology, distribution, patient pulmonary reserve, and availability of adjuvant and intraoperative strategies. P/D and EPP are each reasonable surgical treatment options and should be considered in select patients for complete gross cytoreduction.[2-5]**
- **If N2 disease or a mixed histology tumor is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.**
- **If technically appropriate for even more advanced disease, lung sparing operations like pleurectomy/decortication reduces the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection.**
- **Intraoperative adjuvant therapy, such as heated chemotherapy or photodynamic therapy, is still under investigation but may be considered as part of a reasonable multidisciplinary approach to this locally aggressive disease.**
- **After recovery from surgery, patients should be referred for adjuvant therapy, which may include chemotherapy and radiation therapy (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 (1 of 3)

General Principles

- Recommendations regarding RT should be made by a radiation oncologist.
- The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed in a multidisciplinary team, including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- For patients with resectable MPM who undergo EPP, adjuvant RT can be recommended for patients with good performance status (PS) to improve local control.[1-6]
- PET scanning for treatment planning can be used as indicated.
- RT can be used to prevent instrument-tract recurrence after pleural intervention.
- RT is an effective palliative treatment for relief of chest pain associated with mesothelioma.
- When there is limited or no resection of disease, delivery of high-dose RT to the entire hemithorax in the setting of an intact lung has not been shown to be associated with significant survival benefit, and the toxicity is significant.[1,5,6] RT under such circumstances or after P/D is usually not recommended, but may be considered with caution under strict dose limits of organs at risk or IRB-approved protocols.
- Acronyms and abbreviations related to RT are the same as listed in the principles of RT for non-small cell lung cancer.
  See NCCN Guidelines for Non-Small Cell Lung Cancer.

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment.
  See Recommended Doses for Conventionally Fractionated Radiation Therapy (MPM-D 2 of 3).
- The dose of radiation for adjuvant therapy following EPP should be 50–60 Gy in 1.8–2.0 Gy based on the margin status. A dose of 54 Gy given to the entire hemithorax, the thoracotomy incision, and sites of chest drains was well-tolerated.[6,7] When it is challenging to deliver 50 Gy, every effort should be made to deliver a minimum dose of 40 Gy.[1]
- A dose ≥60 Gy should be delivered to macroscopic residual tumors if the doses to adjacent normal structures are limited to their tolerances. In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall.[8-10]
- Daily doses of 4 Gy appear to be more efficacious than fractions of less than 4 Gy in providing relief from chest pain associated with mesothelioma,[9,11] although the optimal daily and total dose of RT for palliative purposes remains unclear.
- For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.[8,12] For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam radiation in combination with surgery.

See Radiation Techniques (MPM-D 2 of 3)

See References (MPM-D 3 of 3)

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PRINCIPLES OF RADIATION THERAPY (2 of 3)

Recommended Doses for Conventionally Fractionated Radiation Therapy

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

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

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤1; good functional pulmonary status; good function of contralateral kidney confirmed by renal scan; and absence of disease in abdomen, contralateral chest, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.

Radiation Techniques

- Use of conformal radiation technology is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.
- CT simulation-guided planning with conventional photon/electron RT is recommended.[7] Intensity-modulated radiation therapy (IMRT) is a promising treatment technique that allows for a more conformal high-dose RT and improved coverage to the hemithorax. IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol. When IMRT is applied, the NCI and ASTRO/ACR IMRT guidelines should be strictly followed.[13,14] Special attention should be paid to minimize radiation to the contralateral lung,[15] as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.[16] The mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.[17]
- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
- The clinical target volume (CTV) for adjuvant RT after EPP should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
- Extensive elective nodal irradiation (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
- The planning target volume (PTV) should consider the target motion and daily setup errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

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PRINCIPLES OF RADIATION THERAPY (3 of 3) - References

[1]Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2005;63:1045–1052.
[2]Gupta V, Krug LM, Laser B, et al. Patterns of local and nodal failure in malignant pleural mesothelioma after extrapleural pneumonectomy and photon-electron radiotherapy. J Thorac Oncol 2009;4:746–750.
[3]Bölükbas S, Manegold C, Eberlein M, et al. Survival after trimodality therapy for malignant pleural mesothelioma: Radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. Lung Cancer 2011;71:75–81.
[4]Hasani A, Alvarez JM, Wyatt JM, et al. Outcome for patients with malignant pleural mesothelioma referred for trimodality therapy in Western Australia. J Thorac Oncol 2009;4:1010–1016.
[5]Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg 1997;63:334–338.
[6]Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2001;122:788–795.
[7]Yajnik S, Rosenzweig KE, Mychalczak B, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2003;56:1319–1326.
[8]Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. Chest. 1995;108:754–758.
[9]de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura—a single-institution experience with 189 patients. Int J Radiat Oncol Biol Phys 1999;43:511–516.
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[12]Di Salvo M, Gambaro G, Pagella S, et al. Prevention of malignant seeding at drain sites after invasive procedures (surgery and/or thoracoscopy) by hypofractionated radiotherapy in patients with pleural mesothelioma. Acta Oncol 2008;47:1094–1098.
[13]Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. Med Phys 2011;38:5067–5072.
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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1.

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

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

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

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

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

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

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

Mesothelioma is a rare cancer that is estimated to occur in approximately 2,500 people in the United States every year.[1,2] These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) focus on malignant pleural mesothelioma (MPM), which is the most common type; mesothelioma can also occur in the lining of other sites (eg, peritoneum, pericardium, tunica vaginalis testis).[3-5] The disease is difficult to treat, because most patients have advanced disease at presentation. Median overall survival is approximately 1 year; cure is rare.[6-8] MPM occurs mainly in older men (median age at diagnosis, 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20–40 years later).[9,10]

The incidence of MPM is leveling off in the United States, because asbestos use has decreased since the 1970s; however, the United States still has more reported cases and deaths than anywhere else in the world.[11-13] The mortality burden from asbestos-related diseases in the United States did not change from 1999 to 2010.[14] Worldwide, estimates are that about 17 Potential Years of Life are Lost (PYLL) in patients who die from mesothelioma.[15] Although asbestos is no longer mined in the United States, it is still imported.[13] The incidence of MPM is increasing in other countries such as Russia, Western Europe, China, and India.[1,12,16-20] Mortality rates from MPM are highest in the United Kingdom, Netherlands, and Australia; mortality rates are increasing in Japan, Argentina, and Brazil.[7,16,21] Russia, China, Brazil, and Canada are the top producers of asbestos.[22] Although most mesothelioma is linked to asbestos exposure, reports suggest that ionizing radiation may also cause mesothelioma, such as in patients previously treated with mantle radiation for Hodgkin lymphoma.[23-31] Recent data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma.[32-34] Genetic factors may also play a role in MPM, with some families carrying a germline mutation in the BRCA1 Associated Protein 1 (*BAP1*) gene.[35,36] Smoking is not a risk factor for mesothelioma.[37] However, patients who smoke and have been exposed to asbestos are at increased risk for lung cancer. In addition, patients who smoke should be encouraged to quit because smoking impedes treatment (eg, delays wound healing after surgery) (http://www.smokefree.gov/) (see the NCCN Guidelines® for Smoking Cessation, available at NCCN.org).[38]

The histologic subtypes of mesothelioma include epithelioid (most common), sarcomatoid, and biphasic or mixed epithelioid and sarcomatoid.[2,39] Patients with epithelioid histology have better outcomes than those with either mixed (biphasic) or sarcomatoid histologies. Some patients who have been exposed to asbestos only have benign pleural disease, although they may have significant chest pain.[40,41] Although screening for mesothelioma has been studied in patients at high risk (ie, those with asbestos exposure), these NCCN Guidelines do not recommend screening for MPM because it has not been shown to decrease mortality (see *Initial Evaluation* in the NCCN Guidelines® for Malignant Pleural Mesothelioma).[22,42-44] Note that data and guidelines about screening for lung cancer with low-dose CT do not apply to MPM; there are no data to suggest that screening improves survival for patients with MPM.[22,45]

This Discussion text describes the recommendations in the algorithms in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithms. Additional supplementary material in the NCCN Guidelines includes the *Principles of Supportive Care, Principles of Chemotherapy*, *Principles of Surgery*, and *Principles of Radiation Therapy.* These NCCN Guidelines for Malignant Pleural Mesothelioma

were developed and are updated by panel members who are also on the panel for the NCCN Guidelines for Non-Small Cell Lung Cancer. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2015. The *Principles of Surgery* were extensively revised for the 2015 update. The NCCN Guidelines for Malignant Pleural Mesothelioma are updated at least once a year.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Malignant Pleural Mesothelioma, an electronic search of the PubMed database was performed to obtain key literature on mesothelioma published between July 2013 and September 2014 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 II; Clinical Trial, Phase III; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 11 citations, and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Diagnosis

Patients with suspected MPM often have dyspnea and chest pain; they can also have pleural effusion, fatigue, insomnia, cough, chest wall mass, loss of appetite, and weight loss (see the NCCN Guidelines for Adult Cancer Pain).[21,46,47] Patients with MPM often have a high symptom burden when compared with patients who have other types of cancer. In patients with recurrent pleural effusion and/or pleural thickening, the recommended initial evaluation for suspected MPM includes: 1) CT of the chest with contrast; 2) thoracentesis for cytologic assessment of the effusion; and 3) pleural biopsy (eg, thoracoscopic biopsy [preferred]) (see *Initial Evaluation* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[21,22,48-50] However, cytologic samples are often negative even when patients have MPM.[51,52] Fine-needle aspiration (FNA) is not recommended for diagnosis.[21] Talc pleurodesis or pleural catheter may be needed for management of pleural effusion.[53-57] Soluble mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status;[58-61] osteopontin does not appear to be as useful for diagnosis.[62-66] Other potential diagnostic biomarkers are being assessed.[67-71]

It can be difficult to distinguish malignant from benign pleural disease and also to distinguish MPM from other malignancies such as metastatic adenocarcinoma, sarcoma, or other metastases to the pleura.[17,72-75] On CT, thymoma can mimic MPM; however, pleural effusion does not typically occur with thymoma. Cytologic samples of pleural fluid are often negative.[51,52,76] Calretinin, WT-1, D2-40, and cytokeratin (CK) 5/6 are useful immunohistochemical markers for the diagnosis of MPM, as are markers that typically are positive in pulmonary adenocarcinoma and negative in mesothelioma (eg, thyroid transcription factor 1 [TTF-1], carcinoembryonic antigen [CEA]) (see *Protocol for the Examination of Specimens From Patients With*

Malignant Pleural Mesothelioma from the College of American Pathologists [CAP] on the CAP website).[51,72,74,77]

Management

The NCCN Guidelines recommend that patients with MPM be managed by a multidisciplinary team with experience in MPM. Treatment options for patients with MPM include surgery, radiation therapy (RT), and/or chemotherapy;[2] select patients (ie, clinical stages I–III, medically operable, good performance status [PS]) are candidates for multimodality therapy.[78-82] Definitive RT alone is not recommended for unresectable MPM (see *Treatment* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[83,84] 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. Video-assisted thoracic surgery (VATS) or laparoscopy can be considered if contralateral or peritoneal disease is suspected.[85] When indicated, PET-CT scans should be obtained before pleurodesis if possible, because talc produces pleural inflammation, which can affect the FDG avidity (ie, false-positive result).[86-88] If surgical resection is being considered, mediastinoscopy or endobronchial ultrasonography (EBUS) FNA of the mediastinal lymph nodes is recommended.[89,90] The following tests may be performed if suggested by imaging: 1) laparoscopy to rule out transdiaphragmatic extension (eg, extension to the peritoneum is indicative of stage IV [unresectable] disease); and 2) chest MRI.

Staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system (see Table 1 in the NCCN Guidelines for Malignant Pleural Mesothelioma), which was approved by the AJCC.[91,92] Most patients have advanced disease at presentation. However, it is difficult to accurately stage patients before surgery. Understaging is common with PET-CT.[88,93] However, PET-CT is useful for determining whether metastatic disease is present.[93,94] Patients with clinical stage I to III MPM can be evaluated for surgery using pulmonary function tests (PFTs) including 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). Surgical resection is recommended for patients with clinical stage I to III MPM who are medically operable and can tolerate the surgery. Multimodality therapy (ie, chemotherapy, surgery, RT) is recommended for patients with clinical stages I to III MPM who are medically operable (see *Treatment* in the NCCN Guidelines for Malignant Pleural Mesothelioma). Chemotherapy alone is recommended for those who are not operable, those with clinical stage IV MPM, or those with sarcomatoid histology (see *Chemotherapy* in this Discussion and *Principles of Chemotherapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma). Pleural effusion can be managed using thoracoscopic talc pleurodesis or placement of a drainage catheter.[53,57,95-97] Therapeutic/palliative thoracentesis can also be used to remove pleural fluid and thus decrease dyspnea either before treatment or for patients who are not candidates for more aggressive treatment.[21]

Surgery

It is essential that patients receive a careful assessment before surgery is performed. Surgical resection for patients with MPM can include either 1) pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the

involved pleura and all gross tumor; or 2) extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium (see *Principles of Surgery* in the NCCN Guidelines for Malignant Pleural Mesothelioma).[98] Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[98] Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained. The surgical goal for MPM is cytoreductive surgery to achieve macroscopic complete resection.[99,100]

The choice of surgery for MPM is controversial, because data from randomized controlled trials are not available.[2,21,101-107] EPP would often be required to remove all gross tumor in patients with stages II to III MPM.[47] Neither EPP nor P/D will yield an R0 resection.[2,108,109] However, EPP is associated with higher morbidity and mortality.[102,110] P/D (ie, lung-preserving surgery) is safer than EPP.[110-117] A retrospective analysis (n = 663) suggested that survival was greater after P/D than after EPP, but this may have been confounded by patient selection.[2,115] A recent meta-analysis suggested a trend in favor of overall survival for extended PD when compared with EPP.[102] Lung-sparing options, such as P/D, reduce the risk for perioperative mortality and yield either equal or better long-term survival than non-surgical therapy in patients with more advanced disease.[108,118]

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.[119] 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.[120] An Australian retrospective study (540 patients) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and treatment with pemetrexed.[121] The NCCN Panel and other clinicians recommend surgery for select patients who require a complete cytoreduction (ie, good PS, no comorbidities, patients with stage II–III disease, favorable histology [ie, epithelioid], no N2 disease), but surgery is not usually recommended for patients at high risk (eg, unfavorable histology [eg, sarcomatoid, mixed tumors]).[6,104,122]

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.[102,115,119,123,124] 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, as well as availability of adjuvant and intraoperative strategies.[6,124] For patients with operable early-stage disease (confined to the pleural envelope [stage I], no N2 lymph node involvement), surgery should be considered for select patients.[82,115,116,125,126,127] 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.[111] P/D may also be useful for symptom control (eg, patients with entrapped lung syndrome).[22] The NCCN Panel does not recommend surgery for patients with stage IV MPM or sarcomatoid histology; chemotherapy is recommended for these patients (see *Chemotherapy* in this Discussion and *Treatment* in the NCCN Guidelines for Malignant Pleural Mesothelioma). In addition, surgery is generally not recommended for patients with N2 disease or

mixed histology tumor unless performed at a center of expertise or in a clinical trial.

Chemotherapy

Chemotherapy is recommended either alone for medically inoperable patients with MPM or as part of a multimodality regimen for patients with medically operable MPM (see *Treatment* and *Principles of Chemotherapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma). Patients with medically operable stage I to III MPM can receive chemotherapy either before or after surgery. Chemotherapy alone is recommended for patients with medically inoperable stages I to IV MPM and those with sarcomatoid histology.[103,128,129] Pemetrexed-based chemotherapy can also be used for malignant peritoneal mesothelioma and for tunica vaginalis testis mesothelioma.[3]

A combined first-line regimen using cisplatin/pemetrexed (category 1) is considered the gold standard for MPM and is currently the only regimen approved by the U.S. Food and Drug Administration.[130,131] A phase III 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).[130] Based on this trial and the FDA approval, the NCCN Panel recommends cisplatin/pemetrexed (category 1) for patients with MPM. A recent multicenter phase III randomized trial (IFCT-GFPC-0701 MAPS) compared adding bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) versus cisplatin/pemetrexed alone for patients with unresectable MPM and PS 0-2 who did not have bleeding or thrombosis.[132] 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=.76; *P*=.012). More grade 3 hypertension (0% vs. 23%), grade 3 proteinuria (0% vs. 3.1%), and grade 3-4 arterial thrombotic events (0% vs. 2.7%) were observed in patients receiving the triplet arm. For the 2015 interim update (Version 2.2015), the NCCN Panel added a new recommendation (category 2A) for this bevacizumab, cisplatin, and pemetrexed regimen based on this trial (see *Principles of Chemotherapy* in the NCCN Guidelines for Malignant Pleural Mesothelioma).

Other acceptable first-line combination chemotherapy options recommended by NCCN include: 1) pemetrexed/carboplatin, which was assessed in 3 large phase II studies (median survival = 12.7, 14, and 14 months, respectively);[133-135] or 2) gemcitabine/cisplatin, which was also assessed in phase II studies (median survival = 9.6–11.2 months).[136-138] Gemcitabine/cisplatin may be useful for patients who cannot take pemetrexed. A comparison of 1,704 patients with medically inoperable MPM treated with cisplatin/pemetrexed or carboplatin/pemetrexed as part of an expanded access trial found that outcomes with the regimens were similar.[139] The carboplatin/pemetrexed regimen is a better choice for patients with poor PS and/or comorbidities.

Acceptable first-line single-agent options include pemetrexed or vinorelbine.[140-142] Second-line chemotherapy options include pemetrexed (if not administered first line) (category 1), vinorelbine, or gemcitabine.[141,143-148] Data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed.[149] Limited data are available to guide second-line therapy, although several agents are in clinical trials.[150-153]

Trimodality therapy using chemotherapy, surgery, and hemithoracic RT has been used in patients with MPM.[78-81] Median survival of up to 29 months has been reported for patients who complete trimodality therapy.[79] Nodal status and response to chemotherapy can affect

survival.[79,82] In patients who do not receive induction chemotherapy before EPP, postoperative sequential chemotherapy with hemithoracic RT is recommended. Intraoperative adjuvant therapies—such as hyperthermic pleural lavage, photodynamic therapy, or heated chemotherapy—are under investigation.[150,154-161]

Radiation Therapy

The *Principles of Radiation Therapy* are described in the algorithm and are summarized in this Discussion (see the NCCN Guidelines for Malignant Pleural Mesothelioma). The NCCN Guidelines for Non-Small Cell Lung Cancer are also a useful resource. In patients with MPM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended (see next paragraph). RT can also be used as palliative therapy for relief of chest pain or metastases in bone or in the brain (see the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).[21,83,162] The dose of radiation should be based on the purpose of treatment.[163] 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.[125,164-166] Patients are candidates for RT if they have good PS, pulmonary function, and kidney function (see *Principles of Radiation Therapy* in the algorithm). However, in patients with limited or no resection of disease (ie, in the setting of an intact lung), high-dose RT to the entire hemithorax has not been shown to improve survival and the toxicity is significant.[83] RT can also be used to prevent instrument-tract recurrence after pleural intervention.[109,125,167-170]

CT simulation–guided planning with conventional photon/electron RT is recommended. 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 algorithm). A dose of 60 Gy or more should be delivered to macroscopic residual tumors, if the doses to normal adjacent structures are limited to their tolerances (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at NCCN.org). In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall,[171-173] although this is controversial.[174-176]

Intensity-modulated RT (IMRT) allows a more conformal high-dose RT and improved coverage to the hemithorax at risk.[83,164,165,177,178] The NCI and ASTRO/ACR IMRT guidelines are recommended (http://rrp.cancer.gov/content/docs/imrt.doc).[179-181] The ICRU-83 (International Commission on Radiation Units & Measurements Report 83) recommendations are also a useful resource.[182,183] RT to the contralateral lung should be minimized,[83,165,184] because fatal pneumonitis may occur with IMRT if strict limits are not applied.[185-187] The mean lung dose should be kept as low as possible, preferably less than 8.5 Gy.[188] The volume of contralateral lung receiving low-dose RT (eg, 5 Gy) should be minimized.[189,190] For patients with chest pain from mesothelioma, total doses of 20 to 40 Gy appear to be effective in providing relief from pain;[21,171,172] the optimal dose of RT for palliative purposes remains unclear.[163,191] 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%.[177] However, 13 patients had grade 3+ surgical complications and one patient died from treatment.

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