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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)**

# **Malignant Pleural Mesothelioma**

Version 1.2012

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## Malignant Pleural Mesothelioma

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**Clinical Trials:** The 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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Summary of changes in the 1.2012 version of the Malignant Pleural Mesothelioma Guidelines from the 2.2011 version include:

### MPM-1

- Initial Evaluation, 3rd bullet: “VATS” deleted.
- Initial Evaluation, 5th bullet: “osteopontin levels” deleted.
- Footnote “a” added to the page: “Recommend obtaining PET/CT before pleurodesis.”

### MPM-2

- “Optional” deleted from “Mediastinoscopy or EBUS FNA of mediastinal lymph nodes”
- Deleted: “Laparoscopy to rule out transdiaphragmatic extension.”
- The qualifier “If suggested by imaging studies” added before the last bullet.
- Footnote “c” is new to the page: “For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.”
- Surgical Evaluation: “Quantitative V/Q” deleted and replaced with “Perfusion scanning if FEV1 < 80%”.

### MPM-3

- Previous pages MPM-3 and MPM-4 combined.
- Treatment recommendations for clinical stage I combined with clinical stage II-III.
- After Induction chemotherapy with pemetrexed and cisplatin, the following tests added: “Chest CT” and “other imaging for mediastinal assessment based on CT.”
- Primary treatment: surgery changed to surgical exploration.
- Adjuvant treatment recommendations after surgical exploration changed to the same following surgical exploration after induction chemotherapy.

### MPM-A

- Reference added for second-line gemcitabine.

### MPM-B

- Bullet 4 modified: “The surgical choices are (1) pleurectomy/decortication (P/D) *with mediastinal lymph node sampling...*” and “Mediastinal node dissection *sampling* should be performed.”
- Bullet 5: reference added.

### MPM-C 1 of 3

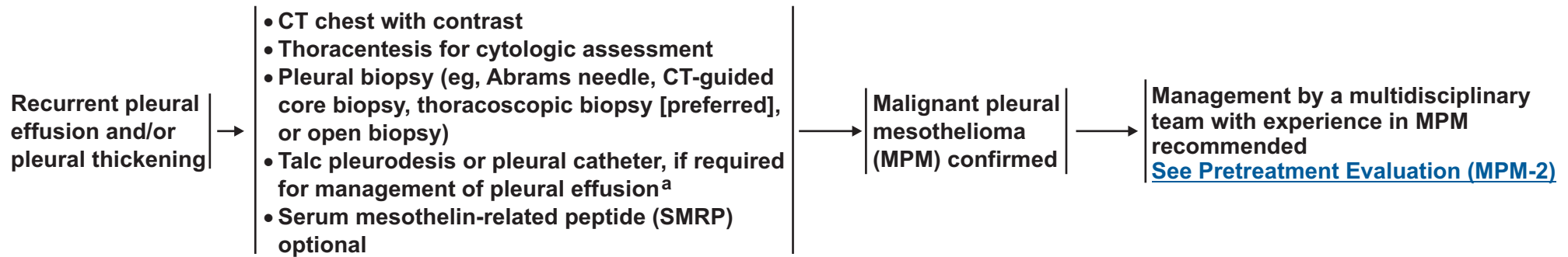
- General Principles, bullet 1 modified: *Recommendations regarding radiation therapy should be made by a radiation oncologist. All patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists for a multimodality treatment recommendation.*
- General Principles, bullet 2 modified: The best timing of 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.*
- General Principles, bullet 3 modified: For patients with resectable MPM, *who undergo extrapleural pneumonectomy (EPP), adjuvant RT is can be recommended for patients with good performance status to improve local control after EPP.*
- General Principles, bullet 7 modified: *After EPP, when extrapleural pneumonectomy, adjuvant RT significantly reduces the local recurrence rate. 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. RT under such circumstances or after pleurectomy/decortication is usually not recommended but may be considered with caution under strict dose limits of organs at risk or IRB approved protocols.*
- Radiation Dose and Volume, bullet 2 modified: 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. *When it is challenging to deliver 50 Gy, every effort should be made to deliver* The dose of adjuvant radiation appeared to significantly influence overall results. *Those who receive doses higher than a minimum dose of 40 Gy might survive longer than those who receive doses less than 40 Gy (P = 0.001)*

Summary of changes in the 1.2012 version of the Malignant Pleural Mesothelioma Guidelines from the 2.2011 version include:

### [MPM-C 2 of 3](#)

- **Recommended Doses for Conventionally Fractionated Radiation Therapy:** The following doses added for Palliative treatment of chest wall pain from recurrent nodules: 30 Gy in 3 fractions for 2 weeks.
- **The following statement added:** After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS  $\leq$  1, FEV1  $>$  80%, and good functional pulmonary status; renal scan must confirm good function of contralateral kidney, restaging PET/CT or CAP CT should confirm absence of disease in contralateral chest, abdomen, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.
- **Radiation Techniques, bullet 1 modified:** Use of ~~modern conformal~~ radiation technology ~~(such as 4DCT, IMRT, IGRT, tomotherapy and proton therapy with sophisticated radiation planning and delivery)~~ is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.
- **Radiation Techniques, bullet 2 modified:** CT simulation guided planning with conventional photon/electron RT is recommended. IMRT is a promising treatment technique that allows a more conformal high-dose RT and improved coverage to the hemithorax. *IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol.*
- **The last 4 bullets are new to the page:**
  - The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
  - The clinical tumor volume (CTV) for adjuvant RT after EPP should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
  - Extensive elective nodal irradiation (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
  - The planning target volume (PTV) should consider the target motion and daily set-up errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of daily set-up of each clinic.

**INITIAL EVALUATION**



<sup>a</sup>Recommend obtaining PET/CT before pleurodesis.

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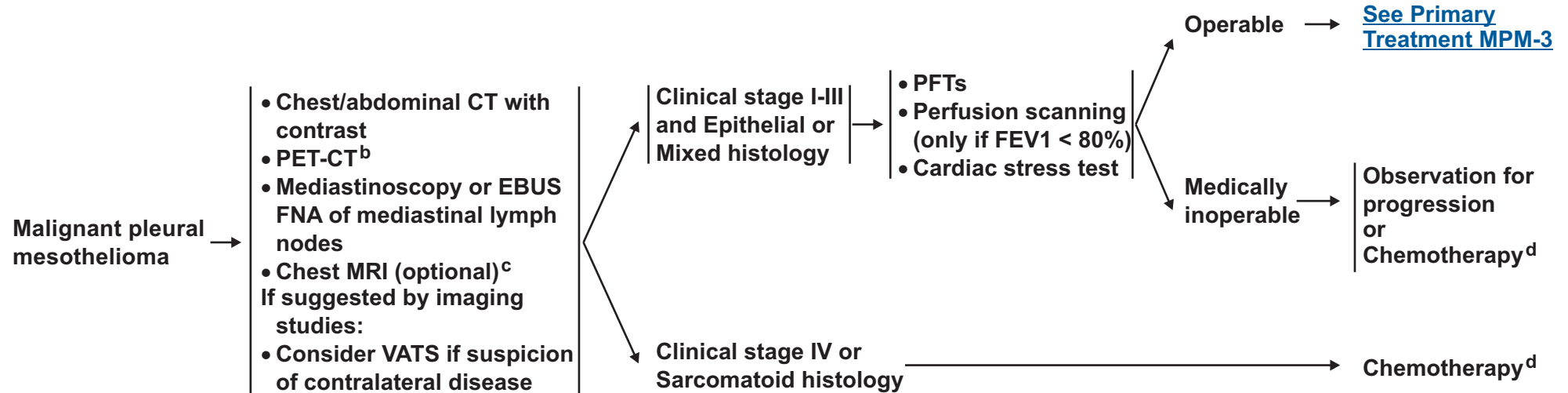
**PATHOLOGIC  
DIAGNOSIS**

**PRETREATMENT  
EVALUATION**

**CLINICAL  
ASSESSMENT**

**SURGICAL EVALUATION**

**TREATMENT**

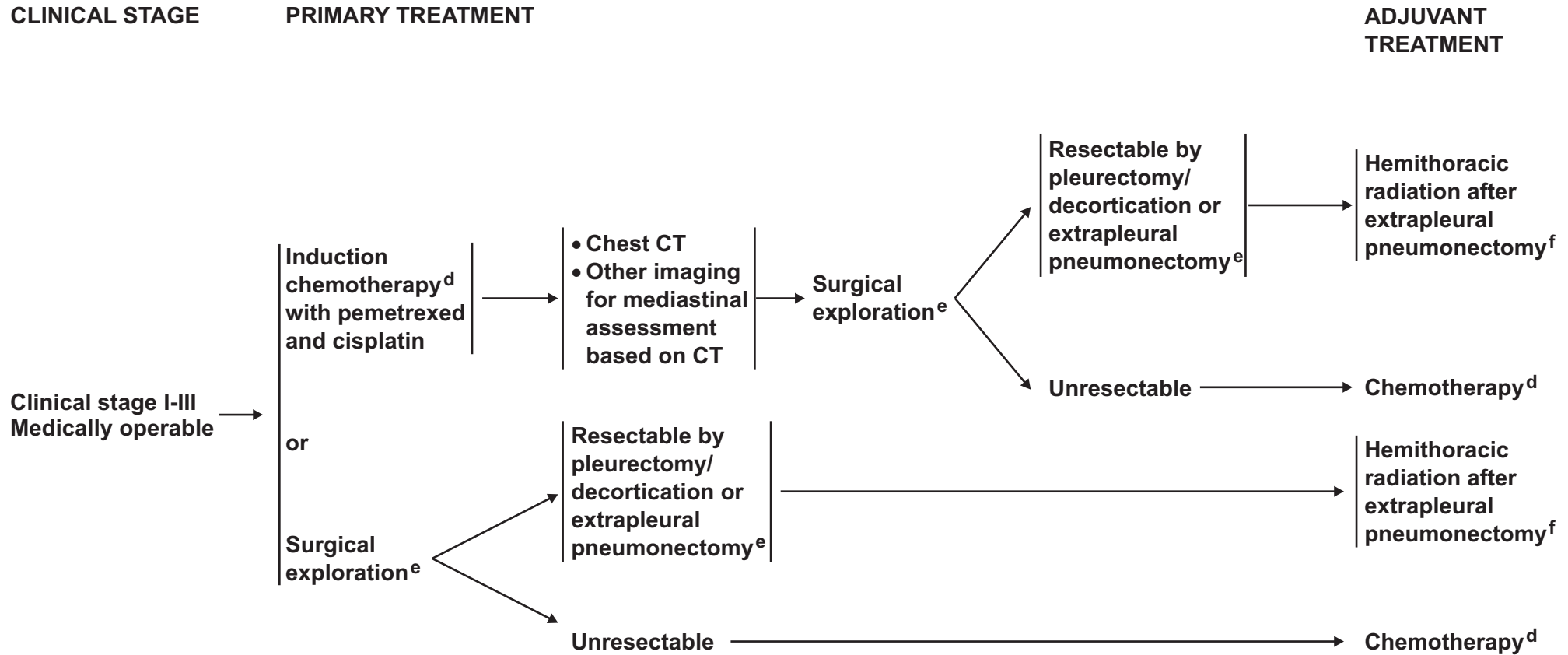


<sup>b</sup>Should be performed before any pleurodesis.

<sup>c</sup>For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.

<sup>d</sup>[See Principles of Chemotherapy \(MPM-A\).](#)

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<sup>d</sup> See Principles of Chemotherapy (MPM-A).

<sup>e</sup> See Principles of Surgical Resection (MPM-B).

<sup>f</sup> See Principles of Radiation Therapy (MPM-C).

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### PRINCIPLES OF CHEMOTHERAPY

#### FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

**Pemetrexed 500 mg/m<sup>2</sup> day 1**  
**Cisplatin 75 mg/m<sup>2</sup> day 1**  
**Administered every 3 weeks (category 1)<sup>1</sup>**

**Pemetrexed 500 mg/m<sup>2</sup> day 1**  
**Carboplatin AUC 5 day 1**  
**Administered every 3 weeks<sup>2,3</sup>**

**Gemcitabine 1000-1250 mg/m<sup>2</sup> day 1, 8, 15**  
**Cisplatin 80-100 mg/m<sup>2</sup> day 1**  
**Administered in 3-4 week cycles<sup>4,5</sup>**

**Pemetrexed 500 mg/m<sup>2</sup> every 3 weeks<sup>6</sup>**

**Vinorelbine 25-30 mg/m<sup>2</sup> weekly<sup>7</sup>**

#### SECOND-LINE CHEMOTHERAPY

**Pemetrexed (if not administered as first-line)<sup>8</sup>**  
**Vinorelbine<sup>9</sup>**  
**Gemcitabine<sup>10</sup>**

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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.

<sup>4</sup>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.

<sup>5</sup>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.

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

<sup>7</sup>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.

<sup>8</sup>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.

<sup>9</sup>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.

<sup>10</sup>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.

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## PRINCIPLES OF SURGICAL RESECTION

- **Surgical resection should be performed on carefully evaluated patients by board certified thoracic surgeons.**
- **For patients being considered for surgery, a single port thoracoscopy on the line of the potential incision is recommended.**
- **The goal of surgery is complete gross cytoreduction of the tumor. In cases where this is not possible such as multiple sites of chest wall invasion, surgery should be aborted.**
- **The surgical choices are (1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling which is defined as complete removal of the pleura and all gross tumor; and (2) extrapleural pneumonectomy (EPP) which is defined as en-bloc resection of the pleura, lung, ipsilateral diaphragm, and often pericardium. Mediastinal node sampling should be performed.**
- **For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid) in good risk patients, EPP may be the best option. For advanced disease (high nodal disease, areas of local invasion), mixed histology, and/or high-risk patients, pleurectomy/decortication may be a better choice.<sup>1</sup>**
- **After recovery from surgery, patients should be referred for adjuvant therapy which may include chemotherapy and radiation therapy depending on whether any preoperative therapy was used and on the pathological analysis of the surgical specimen.**

<sup>1</sup>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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## PRINCIPLES OF RADIATION THERAPY (1 of 3)

### General Principles

- **Recommendations regarding radiation therapy 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 extrapleural pneumonectomy (EPP), adjuvant RT is can be recommended for patients with good performance status to improve local control.<sup>1-6</sup>**
- **The goal of adjuvant RT is to improve local control.**
- **RT can be used to prevent instrument-tract recurrence after pleural intervention.**
- **RT is an effective palliative treatment for relief of chest pain associated with mesothelioma.**
- **After EPP, 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.<sup>1,5,6</sup> RT under such circumstances or after pleurectomy/decortication is usually not recommended but may be considered with caution under strict dose limits of organs at risk or IRB approved protocols.**
- **Acronyms and abbreviations related to RT are the same as listed in the principles of RT for non-small cell lung cancer.**  
[See NCCN Non-Small Cell Lung Cancer Guidelines.](#)

### 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-C 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.<sup>6,7</sup> When it is challenging to deliver 50 Gy, every effort should be made to deliver a minimum dose of 40 Gy.<sup>1</sup>**
- **A dose  $\geq$  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.<sup>8-10</sup>**
- **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,<sup>9,11</sup> although the optimal daily and total dose of RT for palliative purposes remain unclear.**
- **For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.<sup>8,12</sup> For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam radiation in combination with surgery.**

[See Radiation Techniques MPM-C 2 of 3](#)

[See References MPM-C 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
Preoperative	45-50 Gy	1.8-2 Gy	4-5 weeks
Postoperative			
Negative margins	50-54 Gy	1.8-2 Gy	4-5 weeks
Microscopic-macroscopic positive margins	54-60 Gy	1.8-2 Gy	5-6 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
Prophylactic radiation to prevent surgical tract recurrence	21 Gy	7 Gy	1-2 weeks

[See General Principles and Radiation Dose and Volume MPM-C 1 of 3](#)

[See References MPM-C 3 of 3](#)

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤ 1, FEV1 > 80%, and good functional pulmonary status; renal scan must confirm good function of contralateral kidney, restaging PET/CT or CAP CT should confirm absence of disease in contralateral chest, abdomen, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.

#### Radiation Techniques

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

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### PRINCIPLES OF RADIATION THERAPY (3 of 3) - References

- <sup>1</sup>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;63:1045-52.
- <sup>2</sup>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;4:746-50.
- <sup>3</sup>Böläkbas 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* 2009 Sep 16 [Epub ahead of print].
- <sup>4</sup>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;4:1010-6.
- <sup>5</sup>Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 1997;63:334-8.
- <sup>6</sup>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;122:788-95.
- <sup>7</sup>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.
- <sup>8</sup>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;108:754-8.
- <sup>9</sup>de Graff-Strukowska L, van der Zee J, van Putten, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura--a single institution experience with 189 patients. *Int J Radiat Oncol Biol Phys* 1999;43:511-6.
- <sup>10</sup>de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma. *Chest* 2002;121:480-7.
- <sup>11</sup>Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: a review of a 5-year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990;13:4-9.
- <sup>12</sup>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;47:1094-8.
- <sup>13</sup>Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2007;84:1685-92.
- <sup>14</sup>Allen AM, Czerminska M, Janne PA, et al. Fatal pneumonitis associated with intensity modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640-5.
- <sup>15</sup>Krayenbuehl J, Oertel S, Davis JB, Ciernik IF. Combined photon and electron three-dimensional conformal versus intensity-modulated radiotherapy with integrated boost for adjuvant treatment of malignant pleural mesothelioma after pleuropneumonectomy. *Int J Radiat Oncol Biol Phys* 2007;69:1593-9. Epub 2997 Oct 10.

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# NCCN Guidelines™ Version 1.2012 Staging Malignant Pleural Mesothelioma

**Table 1.**  
**International Mesothelioma Interest Group (IMIG) Staging System for Diffuse Malignant Pleural Mesothelioma\***

<b>T</b>	<b>Primary Tumor</b>
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

<b>N</b>	<b>Regional Lymph Nodes</b>
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to the ipsilateral bronchopulmonary 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
<b>M</b>	<b>Distant Metastasis</b>
M0	No distant metastasis
M1	Distant metastasis

**Stage Grouping**  
**Stage**

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

\*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 and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit [www.springer.com](http://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

This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/04/11

#### 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.**

### Overview

Mesothelioma is a rare cancer that is estimated to occur in about 2,500 people in the United States every year.<sup>1, 2</sup> This NCCN guideline focuses on malignant pleural mesothelioma (MPM), which is the most common type; mesothelioma can also occur in other sites (e.g., the peritoneum, pericardium, and tunica vaginalis testis). The disease is difficult to treat; median overall survival is only about 1 year. MPM occurs mainly in older men (median age, 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20-40 years later).<sup>3, 4</sup>

The incidence of MPM is leveling off in the United States, because asbestos use has decreased since the 1970s; however, the incidence is increasing in other countries (such as Western Europe, China, and India).<sup>1, 5-9</sup> Mortality rates from MPM are highest in the United Kingdom,

Netherlands, and Australia; mortality rates are increasing in several countries (such as Japan, Argentina, and Brazil).<sup>5</sup> Although most mesothelioma is linked to asbestos exposure, reports suggest that radiotherapy may also cause mesothelioma.<sup>10-14</sup>

The histologic subtypes of mesothelioma include epithelioid (most common), biphasic or mixed, and sarcomatoid.<sup>2</sup> Patients with epithelioid histology have better outcomes than those with either mixed (biphasic) or sarcomatoid histologies. There are very rare subtypes of pleural mesothelioma (i.e., multicystic, well-differentiated papillary) that are relatively indolent; some clinicians feel they can be followed without immediate therapy. Although screening for mesothelioma has been studied in high-risk patients (i.e., those with asbestos exposure), the NCCN guidelines do not currently recommend screening for MPM.<sup>15, 16</sup> The NCCN Non-Small Cell Lung Cancer panel developed this guideline for MPM in 2010.

### Diagnosis

Patients with suspected MPM often have symptoms (such as dyspnea and chest pain) and can also have pleural effusion, cough, chest wall mass, weight loss, fever, and sweating.<sup>17</sup> In patients with recurrent pleural effusion and/or pleural thickening, the recommended initial evaluation for suspected MPM includes 1) computed tomography (CT) of the chest with contrast; 2) thoracentesis for cytologic assessment; and 3) pleural biopsy (e.g., thoroscopic video-assisted thoracic surgery [VATS] biopsy [preferred]) (see “Initial Evaluation” in the NCCN MPM algorithm).<sup>18, 19</sup> However, cytologic samples are often negative even when patients have MPM. Talc pleurodesis or pleural catheter, may be needed for management of pleural effusion.<sup>20</sup> Serum mesothelin-related peptide (SMRP) or osteopontin levels may also be assessed.<sup>21, 22</sup>

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.<sup>6, 23, 24</sup> On CT, thymoma can mimic MPM; however, pleural effusion does not typically occur with thymoma. Diagnosis is difficult, because cytologic samples of pleural fluid are often negative.<sup>25</sup> Calretinin, WT-1, 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 (e.g., thyroid transcription factor 1 [TTF-1], carcinoembryonic antigen [CEA]) (see also the College of American Pathologists protocol

[http://www.cap.org/apps/docs/committees/cancer/cancer\\_protocols/2011/Mesothelioma\\_11protocol.pdf](http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Mesothelioma_11protocol.pdf)).<sup>23</sup>

### 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;<sup>2</sup> select patients (clinical stages II-III, medically operable, good performance status) are candidates for multimodality therapy.<sup>26-30</sup> Definitive RT alone is not recommended for unresected MPM (see “Principles of Radiation Therapy” in the NCCN MPM algorithm).<sup>31, 32</sup> 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 done 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–positron emission tomography (PET)-CT. VATS can be considered if there is a suspicion of contralateral disease. If possible, it is recommended that PET-CT be done before pleurodesis because of concerns that the inflammation from the pleurodesis can affect the FDG avidity.<sup>33</sup> If surgical resection is being considered, the following tests may be done as deemed necessary: 1) mediastinoscopy or endobronchial ultrasonography (EBUS) fine-needle aspiration (FNA) of the mediastinal lymph nodes; 2) laparoscopy to rule out transdiaphragmatic extension (e.g., extension to the peritoneum is indicative of stage IV [unresectable] disease); and 3) chest magnetic resonance imaging (MRI).

Staging is done using the International Mesothelioma Interest Group (IMIG) TNM staging system, which was approved by the American Joint Committee on Cancer (AJCC) (see Table 1).<sup>34</sup> Most patients have advanced disease at presentation. However, it is difficult to accurately stage patients before surgery; understaging is common with PET-CT.<sup>33,35</sup> However, PET-CT is useful for determining whether metastatic disease is present.<sup>35, 36</sup>

Patients with clinical stage I-III MPM can be evaluated for surgery using pulmonary function tests (PFTs), quantitative ventilation/perfusion (V/Q) tests, and cardiac stress tests (see “Surgical Evaluation” in the NCCN MPM algorithm). Surgical resection is recommended for patients with clinical stage I MPM who are medically operable and can tolerate the surgery. Patients with clinical stage I MPM who are not operable have 2 options: 1) observation for progression; 2) chemotherapy (see the section on “Chemotherapy” in this Discussion and the “Principles of Chemotherapy” in the NCCN MPM algorithm). Trimodality therapy (i.e., chemotherapy, surgery, and RT) is recommended for patients with clinical stages II-III MPM who are medically operable (see the NCCN MPM algorithm). Chemotherapy alone is recommended for those who

are not operable, those with clinical stage IV MPM, or those with sarcomatoid histology.

Pleural effusion can be managed using thoroscopic talc pleurodesis or placement of a drainage catheter.<sup>20, 37-39</sup> Therapeutic thoracentesis can also be used to remove pleural fluid and thus decrease dyspnea either prior to treatment or for patients who are not candidates for more aggressive treatment.

### Surgery

It is essential that patients receive a careful assessment before surgery is done. Surgical resection for patients with MPM can include either 1) pleurectomy/decortication (P/D), 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 Surgical Resection” in the NCCN MPM algorithm). Mediastinal nodal dissection is recommended in patients having either P/D or EPP. In medically operable patients, the decision about whether to do a P/D or an EPP may not be made until surgical exploration.

The choice of surgery for MPM is controversial, because data from randomized controlled trials are not available yet.<sup>2, 40</sup> EPP would often be required to remove all gross tumor in patients with stages II-III MPM.<sup>17</sup> In addition, neither EPP nor P/D will yield an R0 resection.<sup>2, 41</sup> However, EPP is associated with higher morbidity and mortality; therefore, P/D may be a better option for some patients.<sup>42-45</sup> A retrospective analysis (n=663) found that the type of surgery did not affect survival regardless of whether patients had early-stage or advanced stage disease.<sup>2, 42</sup> A randomized trial is currently assessing whether surgery improves survival when compared with chemotherapy treatment alone.<sup>46</sup>

For patients with operable early-stage disease (confined to the pleural envelope [stage I], no N2 lymph node involvement), EPP may be the best option for patients with favorable histology (i.e., epithelioid), good performance status, and no comorbidities.<sup>30, 42, 43, 47</sup> PD may be a better choice for those with operable advanced disease (stages II-III), mixed (biphasic) histology, and/or high-risk factors (poor performance status, comorbidities).<sup>48</sup> The NCCN Panel does not recommend surgery for patients with stage IV MPM or sarcomatoid histology; chemotherapy is recommended for these patients (see next section and “Clinical Assessment” in the NCCN MPM algorithm).

### Chemotherapy

Chemotherapy is recommended either alone for medically inoperable patients with MPM or as part of a regimen for patients with medically operable MPM (see “Principles of Chemotherapy” for specific regimens in the NCCN MPM algorithm). Patients with medically operable stage II-III MPM can receive chemotherapy either before or after surgery (see the NCCN MPM algorithm). Chemotherapy alone is recommended for patients with medically inoperable stages I-IV MPM and those with sarcomatoid histology.<sup>49</sup>

A combined first-line regimen using cisplatin and pemetrexed (category 1) is considered the gold standard for MPM and is currently the only regimen approved by the Food and Drug Administration for mesothelioma.<sup>50, 51</sup> A phase III randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; the combined regimen increased survival when compared with cisplatin alone (12.1 versus 9.3 months,  $P = .02$ ).<sup>50</sup> Other acceptable first-line combination chemotherapy options recommended by NCCN include 1) pemetrexed and carboplatin, which was assessed in 3 large phase II studies (median survival = 12.7, 14, and 14 months, respectively);<sup>52-54</sup> or 2) gemcitabine and cisplatin, which

was also assessed in phase II studies (median survival = 9.6 to 11.2 months).<sup>55, 56</sup> Gemcitabine and 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.<sup>57</sup> The carboplatin/pemetrexed regimen is a better choice for patients with poor performance status and/or comorbidities. Acceptable first-line single-agent options include pemetrexed or vinorelbine.<sup>58-60</sup> Second-line chemotherapy options include pemetrexed (if not administered first line), vinorelbine, or gemcitabine.<sup>61-63</sup> There are limited data to guide second-line therapy.<sup>64</sup>

Recently, trimodality therapy using chemotherapy, EPP, and hemithoracic RT has been used in patients with MPM.<sup>26-29</sup> Median survival of up to 29 months has been reported for patients who complete trimodality therapy.<sup>27</sup> Nodal status and response to chemotherapy can impact survival.<sup>27, 30</sup> In a small retrospective series, trimodality therapy using EPP did not improve survival when compared with patients who did not receive EPP.<sup>41</sup>

### Radiation Therapy

The Principles of Radiation Therapy are described in the NCCN Mesothelioma algorithm and are summarized here; the NCCN Non-Small Cell Lung Cancer algorithm is also a useful resource. In patients with MPM, RT can be used as part of a multimodality regimen or as palliative therapy for relief of chest pain or metastases in bone or brain; RT alone is not recommended (see next paragraph).<sup>31</sup> The dose of radiation should be based on the purpose of treatment. The most appropriate timing of delivering RT (i.e., after surgical intervention, in

conjunction with chemotherapy) should be discussed in a multidisciplinary team.

After EPP, adjuvant RT has been shown to significantly reduce the local recurrence rate.<sup>65</sup> However, when there is limited or no resection of disease (i.e., 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.<sup>31</sup> RT can also be used to prevent instrument-tract recurrence after pleural intervention.<sup>28, 41, 65-68</sup>

CT simulation guided planning with conventional photon/electron RT is recommended. 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 MPM 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 Table 3 in the NCCN Non-Small Cell Lung Cancer algorithm). 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,<sup>69-71</sup> although this is controversial.<sup>72-74</sup>

Intensity-modulated RT (IMRT) allows a more conformal high-dose RT and improved coverage to the hemithorax at risk.<sup>31, 75</sup> The NCI/ASTRO IMRT guidelines are recommended <http://www.astro.org/Research/ResearchHighlights/documents/Imrt.pdf>. The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) guidelines are also useful [http://www.icru.org/index.php?option=com\\_content&task=view&id=171](http://www.icru.org/index.php?option=com_content&task=view&id=171). Radiation to the contralateral lung should be minimized,<sup>31, 75, 76</sup> because the risk of fatal pneumonitis with IMRT is excessively high if strict limits are not applied.<sup>77-79</sup> The mean lung dose should be kept as low as



possible, preferably less than 8.5 Gy. The volume of contralateral lung receiving low-dose RT (e.g., 5 Gy) should be minimized.<sup>80</sup>

For patients with chest pain from mesothelioma, daily doses of 4 Gy appear to be effective in providing relief from pain,<sup>69, 70</sup> however, the optimal dose of RT for palliative purposes remains unclear.<sup>81</sup>



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