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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Malignant Pleural Mesothelioma

Version 1.2011

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NCCN Guidelines™ Version 1.2011 Panel Members
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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NCCN Guidelines™ Version 1.2011 Updates Malignant Pleural Mesothelioma

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Summary of the changes in the 1.2011 version of the Malignant Pleural Mesothelioma Guidelines from the 1.2010 version include:

MPM-2
- FDG-PET changed to PET-CT. Note also added that this should be performed prior to pleurodesis.
- Clinical stage I-III: note added that this is epithelial or mixed histology.

MPM-3
- Clinical stage I, medically inoperable: Chemotherapy was added as a treatment option.

MPM-4
- Performance status removed from clinical stage.
- Post-surgical therapy: Sequential RT followed by chemotherapy added as an option for adjuvant treatment.

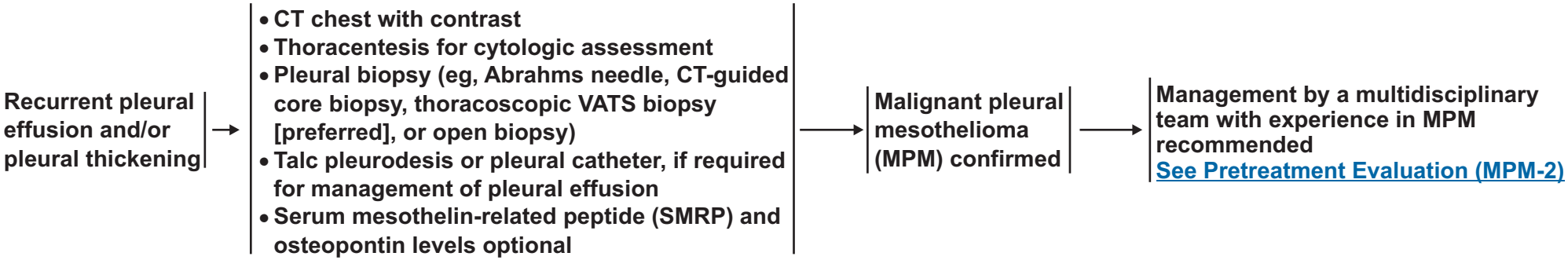
MPM-B
- Bullet 2 is new: “For patients being considered for surgery, a single port thoracoscopy on the line of the potential incision is recommended.”
- Bullet 5: “low nodal burden” changed to “no N2 lymph node involvement” and “EPP is the best option” changed to “EPP may be the best option.”

MPM-C 1 of 3
- General Principles
  Bullet 3: “after EPP” was added to the end of the statement.
- Radiation Dose and Volume
  Bullet 5: “For prophylactic radiation after surgical procedure...” was changed to “For prophylactic radiation to surgical sites...”
  Bullet 7: The following sentence was added, “RT under such circumstances or after pleurectomy/decortication may be considered with caution under strict dose limits of organs at risk or IRB approved protocols.”

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INITIAL EVALUATION

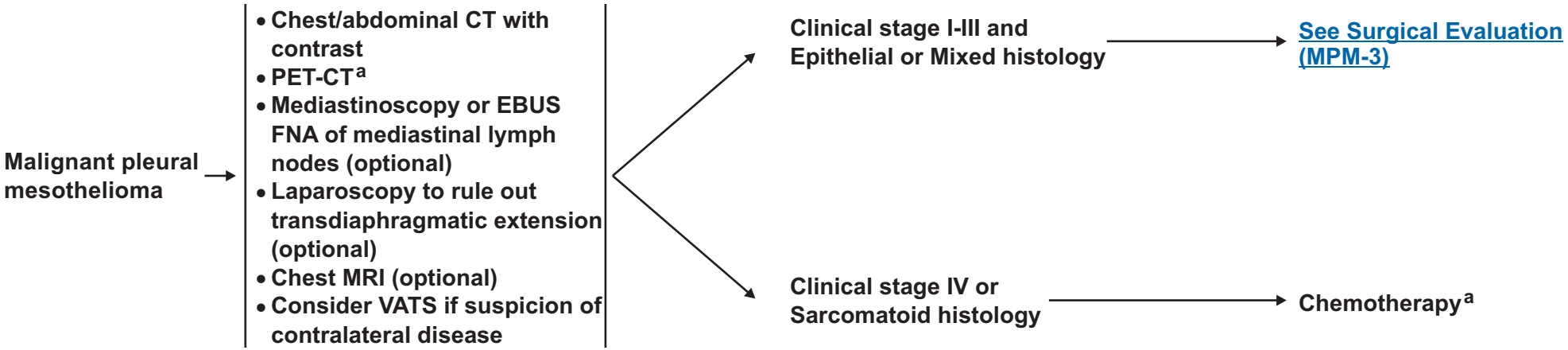


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PATHOLOGIC DIAGNOSIS | **PRETREATMENT EVALUATION** | **CLINICAL ASSESSMENT**



[a] Should be performed before any pleurodesis.
[b] See Principles of Chemotherapy (MPM-A).

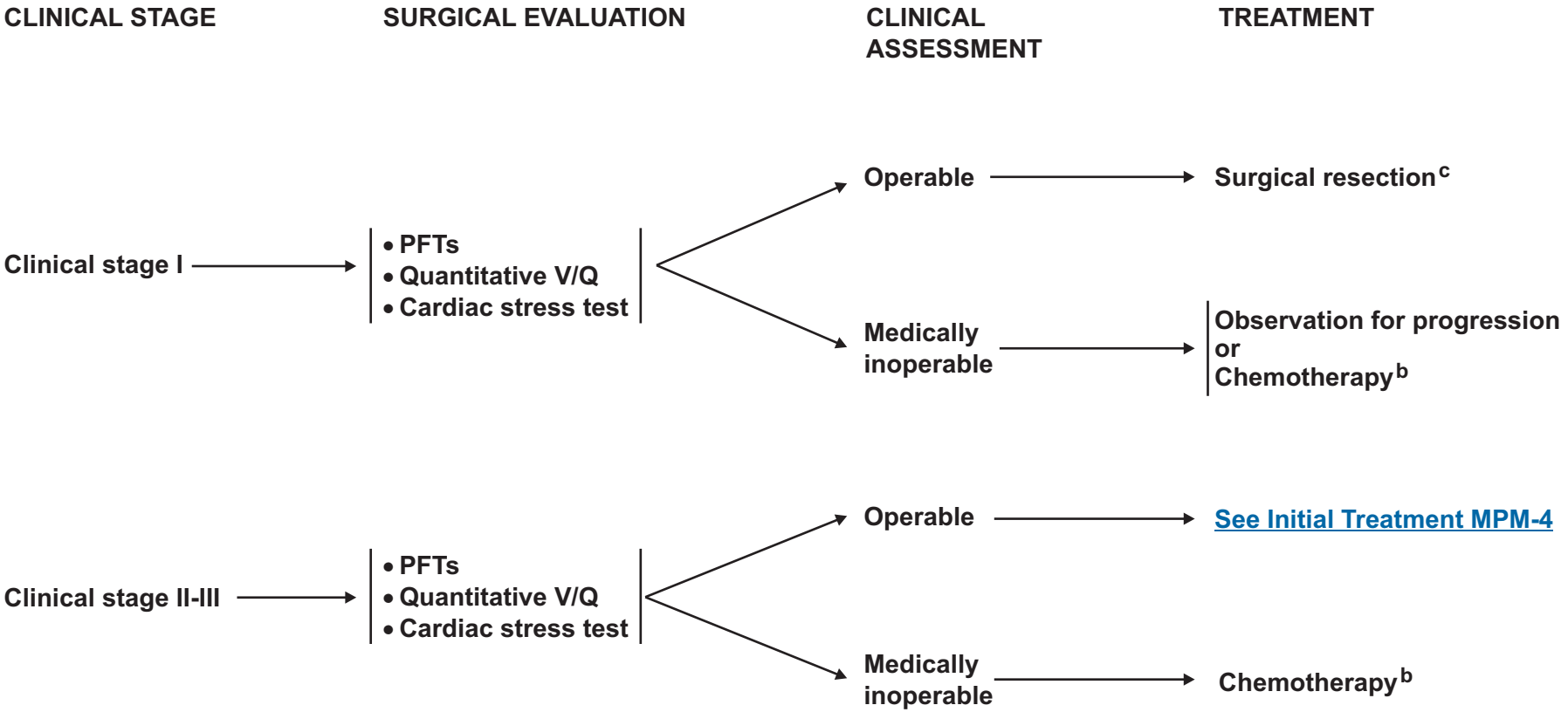
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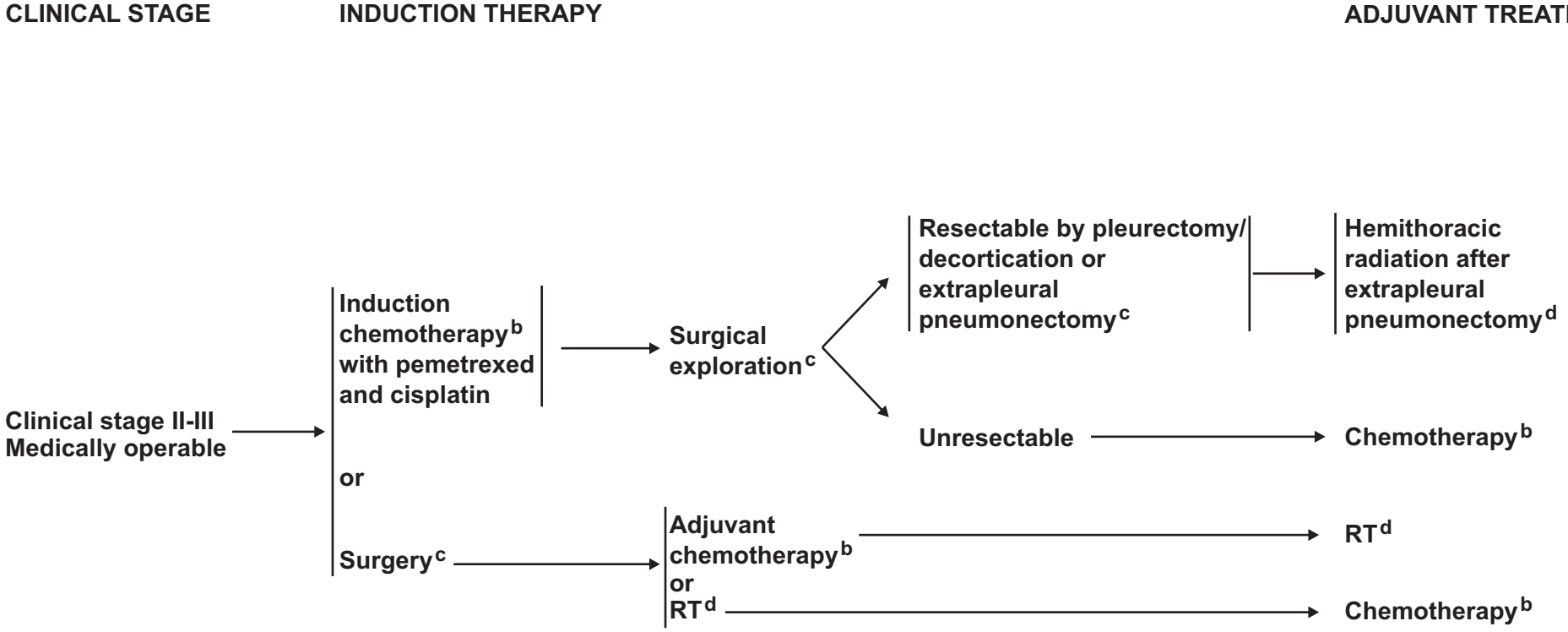


[b] See Principles of Chemotherapy (MPM-A).
[c] See Principles of Surgical Resection (MPM-B).

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[b] See Principles of Chemotherapy (MPM-A).
[c] See Principles of Surgical Resection (MPM-B).
[d] See Principles of Radiation Therapy (MPM-C).

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PRINCIPLES OF CHEMOTHERAPY

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS	SECOND-LINE CHEMOTHERAPY
Pemetrexed 500 mg/m^2 day 1 Cisplatin 75 mg/m^2 day 1 Administered every 3 weeks (category 1)[1]	**Pemetrexed (if not administered as first-line)[8] Vinorelbine[9] Gemcitabine**
Pemetrexed 500 mg/m^2 day 1 Carboplatin AUC 5 day 1 Administered every 3 weeks[2,3]	
Gemcitabine 1000-1250 mg/m^2 day 1, 8, 15 Cisplatin 80-100 mg/m^2 day 1 Administered in 3-4 week cycles[4,5]	
Pemetrexed 500 mg/m^2 every 3 weeks[6]	
Vinorelbine 25-30 mg/m^2 weekly[7]	

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[2] 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;19:370-3.
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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) 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. A mediastinal node dissection 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.**
- **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.**

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PRINCIPLES OF RADIATION THERAPY (1 of 3)

General Principles

- All patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists for a multimodality treatment recommendation.
- The best timing of delivering RT after surgical intervention and/or in conjunction with chemotherapy, should be discussed in a multidisciplinary team.
- For patients with resectable MPM, adjuvant RT is recommended after EPP.[1-6]
- 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 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.[1,5,6] RT under such circumstances or after pleurectomy/decortication 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 should be 50 – 60 Gy in 1.8-2.0 Gy based on the margin status. A dose of 54 Gy to the entire hemithorax, the thoracotomy incision, and sites of chest drains was tolerated.[6] The dose of adjuvant radiation appeared to significantly influence overall results. Those who receive doses higher than 40 Gy might survive longer than those who receive doses less than 40 Gy ($P = 0.001$).[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.[7-9]
- 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,[8,10] 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.[7,11] 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 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 30 Gy	 ≥ 4 Gy 3 Gy	 1-2 weeks 2 weeks
Prophylactic radiation to prevent surgical tract recurrence	21 Gy	7 Gy	1-2 weeks

Radiation Techniques

- Use of modern 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.
- 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. 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,[12] as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.[13] The mean lung dose should be kept as low as possible, preferably < 8.5 Gy. The low dose volume should be minimized.[14]

See General Principles and Radiation Dose and Volume MPM-C 1 of 3
See References MPM-C 3 of 3

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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;63:1045-52.

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[11]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.

[12]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.

[13]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.

[14]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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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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 01/27/10

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

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.[1] Although mesothelioma can also occur in the peritoneum and pericardium, this NCCN guideline focuses on malignant pleural mesothelioma (MPM), which is the most common type of mesothelioma. The disease is deadly and 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).[2,3] The incidence of MPM is leveling off in the United States, because asbestos use has been restricted since the 1970s; however, the incidence is still increasing in other countries such as Western Europe and Australia.[4-7] Although most mesothelioma is linked to asbestos exposure, reports suggest that radiotherapy may also cause mesothelioma.[8-11] The histologic subtypes of mesothelioma include epithelioid (most common), biphasic or mixed, and sarcomatoid.[1] The NCCN Non-Small Cell Lung Cancer panel developed this new guideline on MPM for 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.[12] In patients with recurrent pleural effusion and/or pleural thickening, initial evaluation for suspected MPM may include 1) computed tomography (CT) of the chest with contrast; 2) thoracentesis for cytologic assessment; 3) thoracoscopic video-assisted thoracic surgery (VATS) biopsy (preferred), CT-guided biopsy, or pleural biopsy (e.g., Abrahm's needle); 4) talc pleurodesis or pleural catheter, if required for management of pleural effusion; and 5) serum mesothelin-related peptide (SMRP) or osteopontin levels, which are optional.[13,14] 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.[4,15,16]

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;[1] select patients (clinical stages II-III, medically operable, performance status 0) are candidates for multimodality therapy.[17-21] Definitive RT alone is not recommended for unresected MPM.[22,23] Appropriate patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and

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pulmonologists to assess if they are candidates for multimodality treatment.

Pretreatment evaluation for patients with MPM includes 1) chest and abdominal CT with contrast; 2) FDG--positron emission tomography (PET); and 3) VATS can be considered if there is a suspicion of contralateral disease. The following tests are optional: 1) mediastinoscopy or endobronchial ultrasonography (EBUS) fine-needle aspiration (FNA) of the mediastinal lymph nodes; 2) laparoscopy to rule out transdiaphragmatic extension; 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).[24]

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. Patients with clinical stage I MPM who are medically operable can have surgical resection; those who are not operable can be observed for progression. Patients with clinical stages II-III MPM who are medically operable can have trimodality therapy; chemotherapy alone is recommended for those who are not operable. Patients with clinical stage IV MPM or sarcomatoid histology are candidates for chemotherapy.

Pleural effusion can be managed using thoracoscopic talc pleurodesis or pleuroperitoneal shunts.[25-28] 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 extensive multimodality treatment.

Surgery

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. The choice of surgery for MPM is controversial.[1,29] EPP would often be required to remove all gross tumor in patients with stages II-III MPM.[12] However, EPP is associated with higher morbidity and mortality; therefore, P/D may be a better option for some patients.[30-33] In addition, neither EPP nor P/D will yield an R0 resection.[1,34] A recent 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.[1,30] It is essential that patients receive a careful surgical assessment before surgery is done.

For patients with operable early-stage disease (stage I), P/D is recommended if a complete resection can be done otherwise EPP can be considered for patients with good performance status and no comorbidities.[35] For patients with operable advanced disease (stage II-III), EPP is an option for those with good performance status and no comorbidities. The NCCN Panel does not recommend surgery for patients with stage IV MPM or sarcomatoid histology.

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 algorithm for specific regimens). Patients with stage II-III MPM can receive chemotherapy either before or after surgery. Patients with medically inoperable stages II-III MPM and those with stage IV or sarcomatoid histology should receive chemotherapy alone.[36]

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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.[37,38] A phase III randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; data showed that the combined regimen increased survival when compared with cisplatin alone (12.1 versus 9.3 months, *P* = .02).[37] Other acceptable first-line combination chemotherapy options recommended by NCCN include 1) pemetrexed and carboplatin, which was assessed in 2 large phase II studies (median survival = 12.7 and 14 months, respectively);[39,40] or 2) gemcitabine and cisplatin, which was also assessed in phase II studies (median survival = 9.6 to 11.2 months).[41,42]

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.[43] 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.[44-46] Second-line chemotherapy options include pemetrexed (if not administered first line), vinorelbine, or gemcitabine.[47-49] There are limited data to guide second-line therapy.

Recently, trimodality therapy using chemotherapy, EPP, and hemithoracic RT has been used in patients with MPM.[17-20] Median survival of 29 months has been reported for patients who complete trimodality therapy.[18,19] Nodal status and response to chemotherapy can impact survival.[18,21] In a small retrospective series, trimodality therapy using EPP did not improve survival when compared with patients who did not receive EPP.[34]

Radiation Therapy

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. 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. Adjuvant RT is recommended for patients with resectable MPM to improve local control and to prevent instrument-tract recurrence after pleural intervention.[19,34,50-53]

After extrapleural pneumonectomy, adjuvant RT significantly reduced the local recurrence rate.[53] 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.[22]

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 dose of radiation for adjuvant therapy should be 50-60 Gy (1.8-2.0 Gy/fraction) based on the margin status. A total dose of 54 Gy to the entire hemithorax, thoracotomy incision, and sites of chest drains was tolerated.[51,53] The dose of adjuvant RT appears to significantly influence overall results. Those who receive doses higher than 40 Gy might survive longer than those who receive doses less than 40 Gy (*P*=.001).[50] A dose of 60 Gy or more should be delivered to macroscopic residual tumors, if the doses to normal adjacent structures are limited. 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,[54-56] although this is controversial.[57-59]

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Intensity-modulated RT (IMRT) is promising technique for mesothelioma that allows a more conformal high-dose RT and improved coverage to the hemithorax at risk.[22] When IMRT is used, the NCI/ASTRO IMRT guidelines should be strictly followed http://www.astro.org/Research/ResearchHighlights/documents/Imrt.pdf. Radiation to the contralateral lung should be minimized,[22,60] because the risk of fatal pneumonitis with IMRT is excessively high if strict limits are not applied.[61-63] 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.[64]

To prevent surgical tract recurrence after surgical procedures, the recommended prophylactic radiation dose is a total dose of 21 Gy (7 Gy in 3 fractions).[54,56] Some investigators have treated patients with residual tumors using brachytherapy or intraoperative external-beam RT in combination with surgery.

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,[54,55] although the optimal daily and total dose of RT for palliative purposes remain unclear.

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