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Malignant Pleural Mesothelioma, Version 3.2016:

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights focus on recent updates to the NCCN Guidelines for Malignant Pleural Mesothelioma (MPM). These NCCN Guidelines Insights discuss systemic therapy regimens and surgical controversies for MPM. The NCCN panel recommends cisplatin/

pemetrexed (category 1) for patients with MPM. The NCCN panel also now recommends bevacizumab/cisplatin/pemetrexed as a first-line therapy option for patients with unresectable MPM who are candidates for bevacizumab. The complete version of the NCCN Guidelines for MPM, available at NCCN.org, addresses all aspects of management for MPM including diagnosis, evaluation, staging, treatment, surveillance, and therapy for recurrence and metastasis; NCCN Guidelines are intended to assist with clinical decision-making.

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 Guidelines Insights focus on malignant pleural mesothelioma (MPM), which is the most common type; mesothelioma can also occur in the lining of other sites, such as the peritoneum, pericardium, and tunica vaginalis testis. Histologic subtypes of mesothelioma include epithelioid (most common), sarcomatoid, and biphasic (mixed) epithelioid and sarcomatoid (see MPM-2, above).[2–4] Patients with epithelioid histology have better outcomes than those with either sarcomatoid or biphasic (mixed) histologies. MPM is difficult to treat, because most patients have pleural dissemination at presentation. Median overall survival for MPM is approximately 1 year; cure is rare.[5–7] 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).[8–10] Reports of MPM have also been described following radiation therapy (RT) for other malignancies, including breast cancer and Hodgkin lymphoma.[11–13] Patients with suspected MPM often have dyspnea and chest pain; they may also have pleural effusion, fatigue, insomnia, cough, chest wall mass, loss of appetite, and weight loss.[14–16] Patients with MPM often have a high symptom burden; therefore, supportive care is important for patients, especially management of pleural effusions.[14,17–21] A phase III randomized trial is currently assessing whether early palliative care will improve survival in patients with MPM.[22] The NCCN panel recommends palliative RT for chest pain, bronchial or esophageal obstruction, or other symptomatic sites (see MPM-D, pages 830 and 831).[14,23,24]

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, RT, and/or chemotherapy[2]; select patients with clinical stages I–III disease who are medically operable and have good performance status (PS) are candidates for multimodality therapy.[25–29] These NCCN Guidelines Insights focus on systemic therapy regimens and surgical controversies for MPM. Surgery for MPM is controversial, because sufficient data from randomized controlled trials are limited.[14,30–33] Some surgical procedures, such as extrapleural pneumonectomy (EPP), are associated with greater morbidity than others, such as pleurectomy/decortication (P/D); therefore, EPP is are not recommended for patients with MPM who have sarcomatoid histology. When comparing EPP with P/D, it is not clear which surgical procedure will yield better oncologic outcomes.[14]

Systemic Therapy

Many patients with MPM receive systemic therapy either alone or as part of multimodality therapy. Because most patients present with unresectable or medically inoperable MPM, they are not candidates for surgery, although a board-certified thoracic surgeon with experience in multimodality mesothelioma management should make the decision regarding resectability (see “Surgery,” page 831). The NCCN Guidelines currently recommend 4 combination systemic therapy options for patients with MPM, depending on clinical characteristics such as PS, histology, and whether patients are medically operable or inoperable. Three of the combination regimens are recommended as first-line therapy options for patients with unresectable clinical stage IV, sarcomatoid histology, or medically inoperable MPM or for those who refuse surgery (see MPM-B, page 828). The 3 combination regimens include (1) cisplatin/pemetrexed (category 1), (2) carboplatin/pemetrexed, and (3) cisplatin/gemcitabine.[34–45] Pemetrexed-based regimens are typically used, with gemcitabine recommended only for patients who cannot receive pemetrexed. These 3 combination regimens can also be used as adjuvant therapy for patients as part of multimodality therapy.[46] Several regimens can also be used as induction therapy as part of a modality regimen, including cisplatin/pemetrexed.[46] The fourth combination regimen is bevacizumab/cisplatin/pemetrexed, which is only recommended for patients with unresectable disease and should only be considered for patients who are candidates to receive bevacizumab.[47] For patients with clinical stage IV MPM, sarcomatoid histology, or medically inoperable MPM who are asymptomatic and have a minimal burden of disease, observation may be considered if chemotherapy is planned at the time of symptomatic or radiographic progression (see MPM-2, page 827).[48,49] Best supportive care is recommended for patients with PS 3 to 4 who have clinical stage IV MPM, sarcomatoid histology, or medically inoperable MPM.

The NCCN panel recommends cisplatin/pemetrexed (category 1) based on a phase III randomized trial and FDA approval.[50] The phase III trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; the combined regimen increased survival by 2.8 months compared with cisplatin alone (12.1 vs 9.3 months; P=.02). Patients receiving cisplatin/pemetrexed had less pain and dyspnea than those receiving cisplatin alone. Other recommended first-line combination chemotherapy options include (1) pemetrexed/carboplatin, which was assessed in 3 large phase II studies (median survival, 12.7, 14, and 14 months, respectively) and a large expanded access nonrandomized study[34,51–53]; or (2) gemcitabine/cisplatin, which was assessed in phase II studies (median survival, 9.6–14.7 months).[35,36,40,54,55] The carboplatin/pemetrexed regimen is a better choice for patients with poor PS or comorbidities.[51] Gemcitabine/cisplatin is only recommended for patients who cannot take pemetrexed. First-line single-agent options include pemetrexed or vinorelbine, which are recommended only for patients who cannot receive platinum-doublet therapy.[48,56,57] New agents are being assessed in the frontline setting for MPM.[43,58–61]

A recent multicenter phase III randomized trial assessed the addition of bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) compared with cisplatin/pemetrexed alone for patients 75 years of age or younger with unresectable MPM and PS 0 to 2

who did not have significant cardiovascular history, including history of stroke or transient ischemic attack.[47] Most patients (97%) were PS 0 to 1. Overall survival was increased in the bevacizumab plus chemotherapy arm by 2.7 months when compared with chemotherapy alone: bevacizumab triplet arm (median, 18.8 months; 95% CI, 15.9–22.6) compared with cisplatin/pemetrexed (16.1 months; 95% CI, 14.0–17.9; hazard ratio, 0.77; 95% CI, 0.62–0.95; P=.0167). Grade 3 to 4 adverse events were reported in 71% of patients (158 of 222) receiving the bevacizumab regimen when compared with 62% (139 of 224) of those receiving cisplatin/pemetrexed alone. More grade 3 or higher hypertension (23% vs 0%), grade 3 proteinuria (3.1% vs 0%), and grade 3 to 4 thrombotic events (6% vs 1%) were observed in patients receiving the triplet arm. Based on this trial, the NCCN panel added a recommendation (category 2A) in 2015 (Version 2) for the bevacizumab/cisplatin/pemetrexed regimen.

Recommended second-line chemotherapy options include pemetrexed (if not administered first-line) (category 1), vinorelbine, or gemcitabine (see MPM-B, page 828).[57,58,62–67] If patients experienced a good response to first-line pemetrexed, data suggest that repeating pemetrexed is effective, especially in those who achieved a treatment-free interval of at least 3 months.[58,68–70] Several agents are in clinical trials.[58,61,68,71–73] Preliminary data suggest that immune checkpoint inhibitors and agents targeting mesothelin may be useful in MPM.[74–79]

Surgery

For patients with MPM, the goals of surgery may differ depending on the needs of the patient. Surgery will be recommended in select patients with good PS and epithelioid or mixed histology if a complete gross cytoreduction can be achieved, with the goal to increase survival.[46,80] However, palliative surgery and/or RT may be recommended to relieve pain, free a trapped lung, decrease pleural effusions, and/or improve respiration.[14] As previously mentioned, most patients with MPM are not candidates for surgery because they present with unresectable or medically inoperable disease. Board-certified thoracic surgeons with expertise in managing MPM should decide whether a patient has unresectable or resectable MPM and should perform the surgical resection if indicated. Surgery is not usually recommended for patients with anticipated short-term survival and/or at high risk of morbidity and mortality, poor PS, or comorbidities, as well as unfavorable oncologic outcomes due to unfavorable histology such as sarcomatoid.[5,81–83] The NCCN Guidelines do not recommend surgery for patients with clinical stage IV MPM who have locally advanced unresectable tumors (T4), N3 disease, and/or distant metastases (see Table 1 in the complete version of these guidelines, available at NCCN.org). In addition, patients with N2 disease, mixed histology, or sarcomatoid histology should not routinely be resected outside of a clinical trial and in a center with MPM experience (see MPM-C, page 829).

Surgical resection for patients with MPM can include either P/D (also known as *total pleurectomy* or *lung-sparing surgery*), which is complete removal of the involved pleura and all gross tumor, or EPP, which is en bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium.[84] Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[84] Mediastinal nodal

dissection is recommended in patients with either P/D or EPP; at least 3 nodal stations should be obtained.

Trimodality therapy—chemotherapy, EPP, and hemithoracic RT—has been shown to benefit select patients with epithelioid histology, good PS, and low-volume disease on the basis of single-arm phase II studies at centers with experience.[14,25–28,46] Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.[26,46] Lung-sparing options, such as P/D, decrease the risk for perioperative mortality and yield either equal or better long-term survival than nonsurgical therapy in patients with more advanced disease.[85,86] However, the choice of surgery for MPM is controversial, because data from randomized controlled trials are not available.[14,30–33]

A retrospective analysis (n=663) suggested that survival was greater after P/D than EPP, but this may have been confounded by patient selection.[2,80] A recent meta-analysis suggested a trend in favor of overall survival for extended PD when compared with EPP.[30] The Mesothelioma and Radical Surgery (MARS) trial assessed whether patients treated with induction chemotherapy would accept randomization either to EPP with hemithoracic radiation or to no further treatment; 112 were patients enrolled in the trial, and 50 patients were randomized.[87] In this trial, overall 30-day mortality was 18.7% (3 of 16 patients). Median survival was 14.4 months in the EPP arm and 19.5 months in the no-EPP arm. The authors concluded that EPP was not beneficial because of the high rate of surgical mortality when compared with chemotherapy alone treatment. 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.[88]

Neither P/D nor EPP will achieve an R0 resection[2,85,89]; it is not clear which surgical procedure will yield better oncologic outcomes.[14] When compared with P/D, EPP is associated with more morbidity and more short-term mortality.[30,90–92] Some surgeons prefer to use P/D, because they feel it is a safer procedure.[33,80,90,93–97] Some surgeons mainly use P/D for palliation.[14]

The surgical goal for MPM is cytoreductive surgery to achieve macroscopic complete resection by removing all visible or palpable tumors.[84,98,99] If macroscopic complete resection is not possible, such as in patients with multiple sites of chest wall invasion, then surgery should be aborted. However, to help with postoperative management, surgery should be continued if most of the gross disease can be removed and if there will be a minimal impact on morbidity (see MPM-C, page 829). The NCCN panel feels that P/D and EPP are both reasonable surgical options that should be considered in select patients to achieve complete gross cytoreduction.[30,80,87,91,100] For patients having surgery, either preoperative chemotherapy or postoperative chemotherapy (with or without adjuvant hemithoracic RT, depending on which surgical procedure is used) is recommended in the NCCN Guidelines.[14,46] Surgical procedures can also be done to obtain diagnostic samples and to provide palliative benefit.[14] Palliative surgical procedures include pleurodesis to decrease pleural effusions and P/D to debulk the tumor with the goals of relieving pain and decreasing pleural effusions.[14,20,101] Video-assisted thoracic surgery (VATS) has a

diagnostic role and a palliative role (eg, pleurodesis) in patients with MPM, but it is not an accepted technique for P/D.[84]

Summary

These NCCN Guidelines Insights discuss surgical controversies and systemic therapy regimens for MPM. The NCCN Guidelines recommend that patients with MPM be managed by a multidisciplinary team with experience in MPM. Patients with suspected MPM often have dyspnea and chest pain; they may also have pleural effusion, fatigue, insomnia, cough, chest wall mass, loss of appetite, and weight loss. Patients with MPM often have a high symptom burden; therefore, supportive care is important for patients, especially management of pleural effusions. The NCCN panel recommends palliative RT for chest pain, bronchial or esophageal obstruction, or other symptomatic sites. Treatment options for patients with MPM include surgery, RT, and/or chemotherapy; select patients with clinical stages I to III disease who are medically operable and have good PS are candidates for multimodality therapy. Board-certified thoracic surgeons with expertise in managing MPM should decide whether a patient has resectable MPM and should perform the surgical resection if indicated. Surgery is not usually recommended for patients with anticipated short-term survival and/or at high risk of morbidity and mortality, poor PS, or comorbidities, as well as unfavorable oncologic outcomes because of unfavorable histology such as sarcomatoid. The choice of surgery for MPM is controversial, because data from randomized controlled trials are not available. Neither P/D nor EPP will achieve an R0 resection; it is not clear which surgical procedure will yield better oncologic outcomes. The NCCN panel feels that P/D and EPP are both reasonable surgical options that should be considered in select patients to achieve complete gross cytoreduction.

The NCCN Guidelines currently recommend 4 combination systemic therapy options for patients with MPM. Three of the combination regimens are recommended as first-line therapy for patients with unresectable, metastatic, sarcomatoid histology, or medically inoperable MPM or those who refuse surgery. The 3 regimens include (1) cisplatin/pemetrexed (category 1), (2) carboplatin/pemetrexed, and (3) cisplatin/gemcitabine. The NCCN panel now also recommends bevacizumab/cisplatin/pemetrexed as a first-line therapy option for patients with unresectable MPM who are candidates for bevacizumab. Observation may be considered if chemotherapy is planned at the time of symptomatic or radiographic progression for select patients with clinical stage IV, sarcomatoid histology, or medically inoperable MPM who are asymptomatic and have a minimal burden of disease.

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NCCN Categories of Evidence and Consensus

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

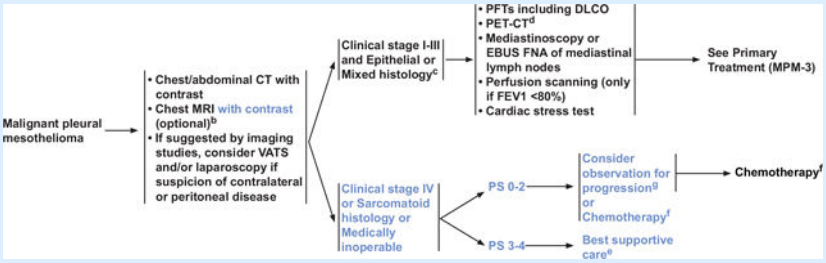
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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.

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



PRINCIPLES OF CHEMOTHERAPY (1 of 2)

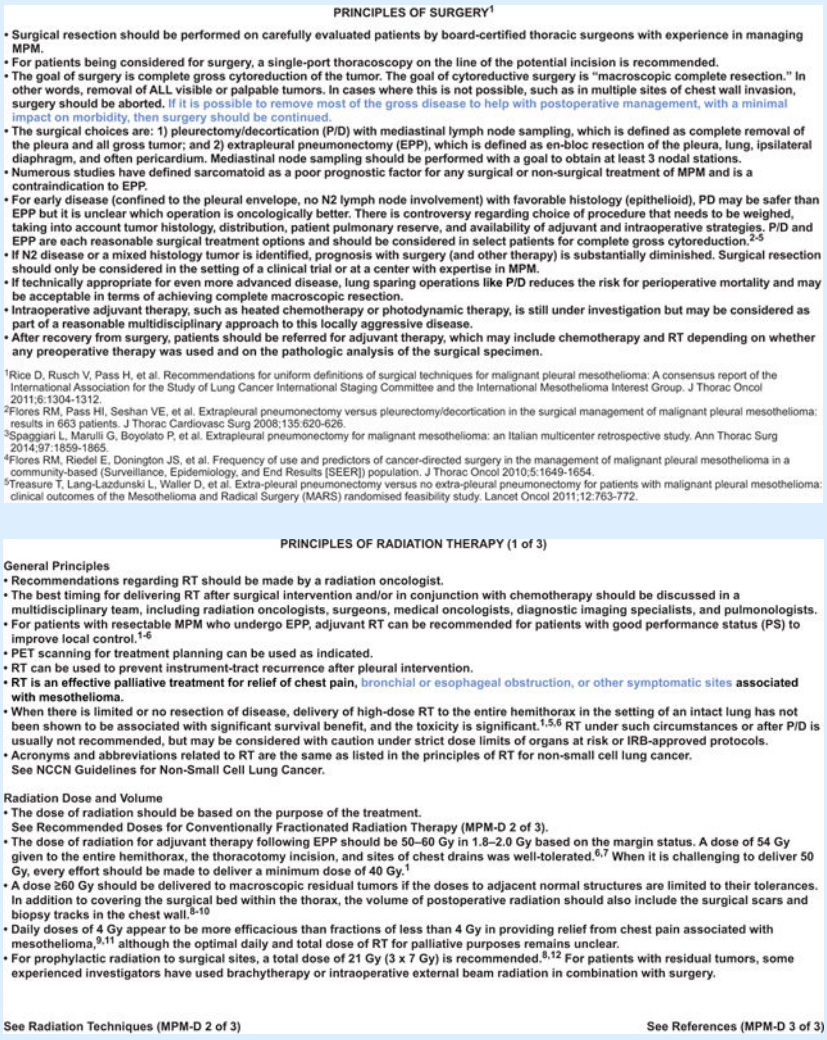
FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- 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.



PRINCIPLES OF SURGERY[1]

- Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons with experience in managing MPM.
- For patients being considered for surgery, a single-port thoracoscopy on the line of the potential incision is recommended.
- The goal of surgery is complete gross cytoreduction of the tumor. The goal of cytoreductive surgery is "macroscopic complete resection." In other words, removal of ALL visible or palpable tumors. In cases where this is not possible, such as in multiple sites of chest wall invasion, surgery should be aborted. If it is possible to remove most of the gross disease to help with postoperative management, with a minimal impact on morbidity, then surgery should be continued.
- The surgical choices are: 1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor; 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 P/D 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 RT depending on whether any preoperative therapy was used and on the pathologic analysis of the surgical specimen.

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[3]Spaggiari L, Marulli G, Boyolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. Ann Thorac Surg 2014;97:1859-1865.
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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, bronchial or esophageal obstruction, or other symptomatic sites associated with mesothelioma.
- When there is limited or no resection of disease, delivery of high-dose RT to the entire hemithorax in the setting of an intact lung has not been shown to be associated with significant survival benefit, and the toxicity is significant.[1,5,6] RT under such circumstances 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)

Recommended Doses for Conventionally Fractionated Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
Postoperative after EPP			
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	20–40 Gy	≥4 Gy	1–2 weeks
Chest wall pain from recurrent nodules	or 30 Gy	3 Gy	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 week

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 using either intensity-modulated radiation therapy (IMRT) or conventional photon/electron RT is acceptable.[7] 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 patien's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

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

See References MPM-D (3 of 3)