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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Mesothelioma: Pleural

Version 1.2025 — November 21, 2024

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

See NCCN Categories of Evidence and Consensus.

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See NCCN Categories of Preference.

Updates in Version 1.2025 of the NCCN Guidelines for Mesothelioma: Pleural from Version 2.2024 include:

PM-2
- Clinical Assessment
  - Clinical stage I-IIIA changed to Clinical stage I
  - Clinical stage IIIB-IV changed to Clinical stage II–IV and epithelioid histology, sarcomatoid or biphasic histology (any stage)
    - Performance status stratification removed (see new footnote c)
- Treatment
  - Clinical stage I and epithelioid histology
    - New treatment options
      - Systemic therapy and consider pleural IMRT (preferred)
        - Systemic therapy for progression
      - Observation
        - Systemic therapy for progression
- Footnote c added: Best supportive care is recommended for patients presenting with PS 3–4. See Principles of Supportive Care (PM-B).
- Footnote e added: Pleural IMRT should only be performed in carefully selected patients at centers with experience in this technique. See Principles of Radiation Therapy (PM-D).
- Footnote g added: The benefit of surgical resection in pleural mesothelioma is unclear and there is no evidence that patient survival is improved with surgery when combined with systemic therapy versus systemic therapy alone.

PM-3
- This is a new page, replacing the previous PM-3 page.

PM-C 1 of 3
- First-Line Therapy
  - Epithelioid, biphasic or sarcomatoid
    - Cisplatin + gemcitabine changed to (Cisplatin or carboplatin) + gemcitabine
- Footnote removed: Carboplatin is recommended for patients who are not candidates for cisplatin.

PM-C 2 of 3
- Reference 12 added: Favaretto AG, Aversa SML, Paccagnella A, et al. Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric phase II study. Cancer 2003;97:2791-2797.

PM-D 1 of 3
- Bullet 6 modified: A randomized phase III trial in patients with non-metastatic pleural mesothelioma who underwent non-radical lung-sparing surgery found substantially greater overall survival with ~~radical hemithoracic~~ *sequential pleural* intensity-modulated RT (IMRT) compared to palliative RT. ~~Hemithoracic~~ *Sequential* pleural IMRT after P/D in the presence of an intact lung may be considered in centers with experience and expertise in these methods, given the technical difficulty of this treatment.
- The following bullets were removed:
  - For patients with resectable pleural mesothelioma who undergo EPP, adjuvant RT can be recommended for patients with good performance status (PS) to improve local control.
  - The dose of radiation for adjuvant therapy following EPP should be 45–60 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 45 Gy, every effort should be made to deliver a minimum dose of 40 Gy.

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Mesothelioma: Pleural from Version 2.2024 include:

PM-D 2 of 3

- Recommended Doses for Radiation Therapy
  - Treatment type removed: Postoperative after EPP
  - Statement below table removed: 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
  - Bullet 4: EPP removed.
  - Bullet removed: A minimum technological standard is CT-planned 3D conformal RT (3D-CRT) using photon or photon/electron beams.

PM-D 3 of 3

- References removed:
  - Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2005;63:1045-1052.
  - Gupta V, Krug LM, Laser B, et al. Patterns of local and nodal failure in malignant pleural mesothelioma after extrapleural pneumonectomy and photon-electron radiotherapy. J Thorac Oncol 2009;4:746-750.
  - Bölükbas S, Manegold C, Eberlein M, et al. Survival after trimodality therapy for malignant pleural mesothelioma: Radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. Lung Cancer 2011;71:75-81.
  - Hasani A, Alvarez JM, Wyatt JM, et al. Outcome for patients with malignant pleural mesothelioma referred for trimodality therapy in Western Australia. J Thorac Oncol 2009;4:1010-1016.
  - Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg 1997;63:334-338.
  - Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2001;122:788-795.
  - 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.

PM-E

- Bullet 6 modified: For early-stage disease (confined to the pleural envelope, no ~~N2~~ *clinical evidence for* lymph node involvement) with favorable histology (epithelioid), P/D may *be considered* ~~safer than EPP~~ but it is unclear ~~which operation is oncologically better~~ *whether there is benefit over systemic therapy alone*. There is controversy regarding ~~choice of procedure~~ *a decision for surgical resection* that needs to be weighed, taking into account tumor histology, distribution, the patient's pulmonary reserve, and availability of adjuvant and intraoperative strategies. P/D ~~and EPP are each reasonable~~ *is the preferred* surgical treatment option~~s~~ and ~~should~~ *can* be considered in select patients for complete gross cytoreduction. *EPP may be selected in certain cases that require careful consideration of the total treatment plan that includes the patient and multidisciplinary team.*

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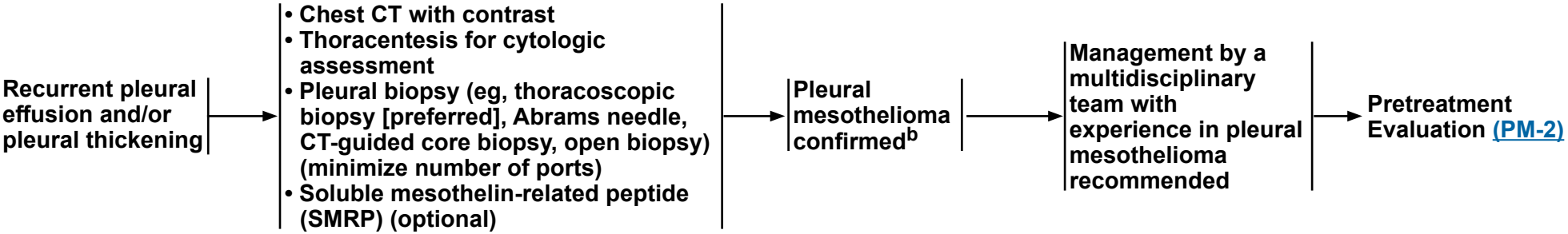
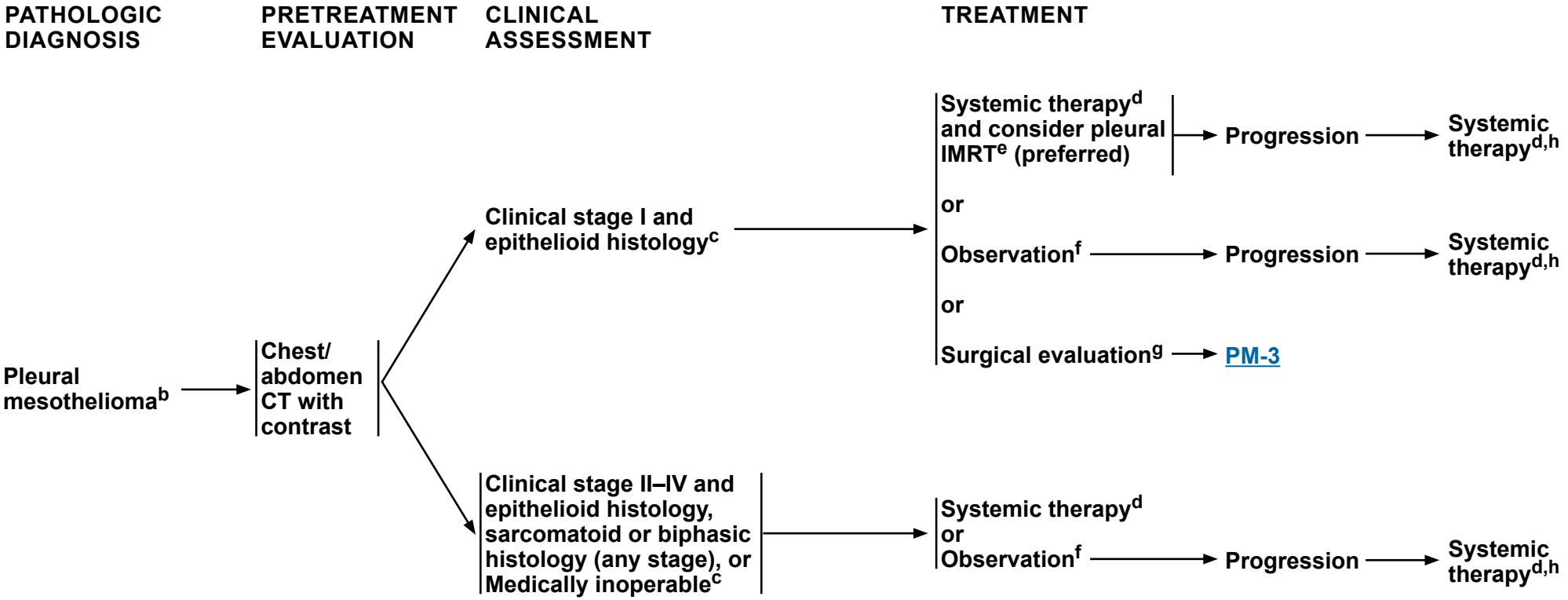
INITIAL EVALUATION[a]



[a] There are no data to suggest that screening improves survival.
[b] Principles of Pathologic Review (PM-A).

Note: All recommendations are category 2A unless otherwise indicated.

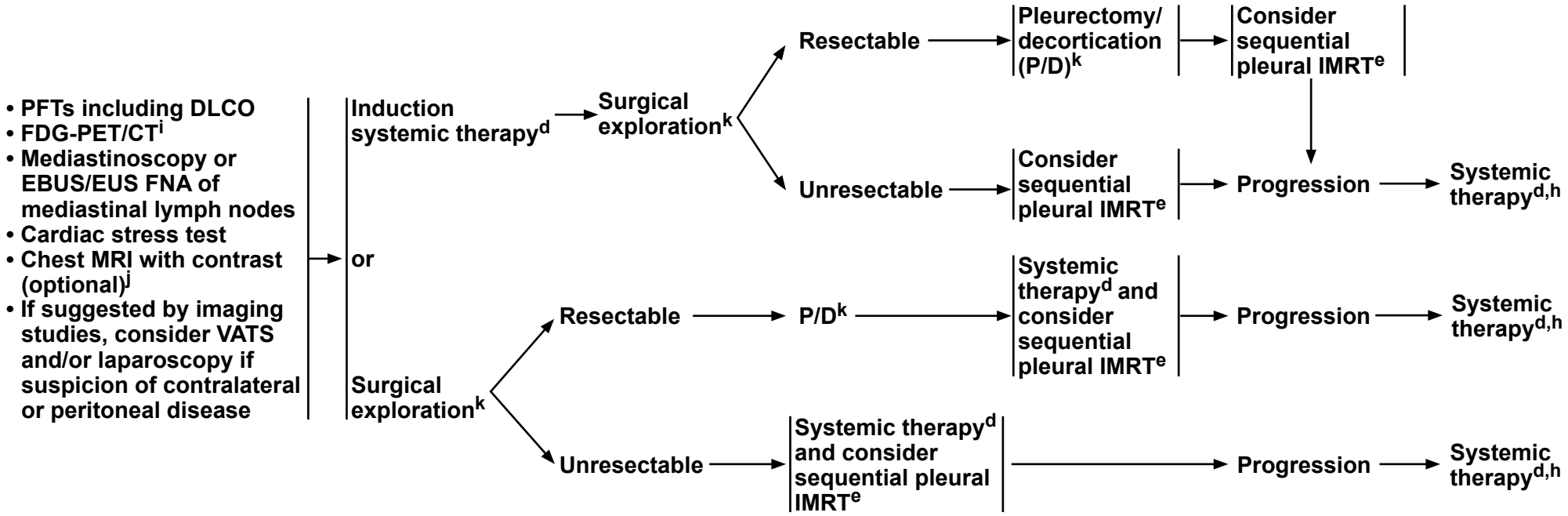


[b] Principles of Pathologic Review (PM-A).
[c] Best supportive care is recommended for patients presenting with PS 3–4. See Principles of Supportive Care (PM-B).
[d] Principles of Systemic Therapy (PM-C).
[e] Pleural intensity-modulated radiation therapy (IMRT) should only be performed in carefully selected patients at centers with experience in this technique. See Principles of Radiation Therapy (PM-D).
[f] Observation may be considered for patients who are asymptomatic with minimal burden of disease if systemic therapy is planned at the time of symptomatic or radiographic progression.
[g] The benefit of surgical resection in pleural mesothelioma is unclear and there is no evidence that patient survival is improved with surgery when combined with systemic therapy versus systemic therapy alone.
[h] Principles of Supportive Care (PM-B).

Note: All recommendations are category 2A unless otherwise indicated.

CLINICAL STAGE I AND EPITHELIOID HISTOLOGY SURGICAL EVALUATION[g]

TREATMENT[h]



[d] Principles of Systemic Therapy (PM-C).
[e] Pleural IMRT should only be performed in carefully selected patients at centers with experience in this technique. See Principles of Radiation Therapy (PM-D).
[g] The benefit of surgical resection in pleural mesothelioma is unclear and there is no evidence that patient survival is improved with surgery when combined with systemic therapy versus systemic therapy alone.
[h] Principles of Supportive Care (PM-B).
[i] If FDG-PET/CT is to be done, recommend obtaining FDG-PET/CT before pleurodesis. Confirm diagnosis of pleural mesothelioma prior to pleurodesis. If pleural mesothelioma is suspected, consider evaluation by a multidisciplinary team with expertise in pleural mesothelioma.
[j] For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[k] Principles of Surgery (PM-E).

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW

Pathologic Evaluation

- Mesothelioma originates from the cells in the serosal lining that surrounds the body cavities. Of all mesotheliomas, ~85% arise from the pleura, ~15% arise from the peritoneum, and the remainder (<1%) originate from the pericardium or the tunica vaginalis.[1]
- In the United States, diffuse pleural mesothelioma affects ~3,000 patients each year, with an annual incidence of ~1 in 100,000.[2,3]
- The purpose of the pathologic evaluation of mesothelioma is based on the pathologic assessment of tumor tissue, which can be obtained from core biopsy sampling, pleurectomy, or other more extensive resections such as extrapleural pneumonectomy (EPP). Given its rarity and overlapping microscopic features with other conditions, the histologic diagnosis of diffuse mesothelioma can be challenging.
- To establish a pathologic diagnosis of mesothelioma, diagnostic tools that are used clinically include histologic assessment, immunohistochemistry (IHC), cytogenetics, and molecular techniques (such as targeted next-generation sequencing [NGS], fluorescence in situ hybridization [FISH], and single-nucleotide polymorphism arrays). Despite the multiple diagnostic toolkits, the diagnosis relies primarily on proper histologic assessment and IHC.
- The new edition of the World Health Organization (WHO) Classification of Thoracic Tumors by the International Agency for Research on Cancer (IARC) introduced the following changes for 2021 from the previous 2015 edition:[1,4]
  - New entity: mesothelioma in situ
  - New terminology: diffuse pleural mesothelioma (instead of diffuse *malignant* pleural mesothelioma)
  - New terminology: localized pleural mesothelioma (instead of localized *malignant* pleural mesothelioma)
  - New terminology: well-differentiated papillary mesothelial tumor (WDPMT, instead of well-differentiated papillary mesothelioma)
  - Genetic tumor syndromes involving the thorax: *BAP1* tumor predisposition syndrome is a hereditary cancer syndrome caused by heterozygous germline pathogenic variants in the *BAP1* (BRCA1-associated protein 1) gene.
- The descriptions below refer to diffuse mesothelioma, which will be named *mesothelioma* for the purpose of simplicity.

Mesothelioma Classification

- Mesothelioma is classified into three histologic types: epithelioid, biphasic (mixed), and sarcomatoid, which have significant prognostic value.[1]
- The determination of histologic types is based on the cytologic features of the tumor:
  - *Epithelioid mesothelioma* is characterized by epithelioid-to-round cells.
  - *Sarcomatoid mesothelioma* is characterized by spindled cells with tapered nuclei.
  - *Biphasic mesothelioma* contains both epithelioid and sarcomatoid components in various proportions, with each comprising at least 10% of the tumor.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW

Mesothelioma Classification (continued)

- Within each histologic type, mesothelioma can be divided into several subtypes and patterns based on its cytologic, architectural, and background stromal features.[5]
  - Other rare variants of epithelioid mesothelioma include clear cell, signet ring cell, rhabdoid, deciduoid, and small cell.[6-8] Tumor cells are arranged in diverse architectural patterns that include tubulopapillary, trabecular, solid, acinar, micropapillary, or adenomatoid.
  - In sarcomatoid mesothelioma, subtypes described include conventional/spindle cell, desmoplastic,[9,10] and lymphohistiocytoid.[11-13] A subset of sarcomatoid mesothelioma exhibits heterologous differentiation with osteosarcomatous, chondrosarcomatous, and/or rhabdomyosarcomatous elements.[10]
  - The assignment of histologic type can be challenging, given the intertumoral and intratumoral morphologic heterogeneity. Appropriate type classification of mesothelioma is nonetheless important, given the prognostic significance of different histologic types.
  - Studies comparing the concordance between histologic type in initial biopsies with subsequent resections have shown that the accuracy of typing increases with a higher number of biopsies.[14] While sarcomatoid histology in biopsies is highly predictive of sarcomatoid histology in resections, epithelioid histology in biopsies is not entirely specific and is changed to biphasic or sarcomatoid types in resections in up to 20% of patients.[14]

Histologic Criteria for Mesothelioma

- In mesothelioma, the goals of histologic assessment are to confirm the pathologic diagnosis and to determine the histologic type, which allows for prognostication and treatment planning. For the diagnosis of mesothelioma, one needs to establish each of the three conditions below:
  - ***The lesion is diffuse and not solitary***. Correlation with clinical and radiologic findings is needed to confirm that the distribution of the tumor is diffuse rather than solitary. While almost all (>99%) mesotheliomas are diffuse, rare cases of *localized pleural mesothelioma* have been described, which are solitary, have a different pathogenesis, and harbor a relatively less aggressive clinical course.[15-18]
  - ***The lesional cells are mesothelial***. Given the morphologic overlap between mesothelioma and diverse mimics such as carcinomas, IHC can be used to confirm the presence of mesothelial differentiation in the tumor cells. Other tools such as cytogenetics and molecular analysis may also be helpful in some instances (see next page).
  - ***The lesional cells are malignant***. Histologic assessment is integral to establish that the mesothelial cells are malignant. Morphologic features that distinguish mesothelioma from reactive conditions include: 1) invasion into adjacent tissue, such as adipose or fibrous tissue, and skeletal muscle; 2) full-thickness serosal involvement; and 3) formation of expansile nodules (considered as a type of fibrous tissue invasion). The presence of tissue invasion is considered to be the most reliable criterion in distinguishing mesothelioma from reactive mesothelial proliferations.[19,20] On the other hand, "worrisome" features such as necrosis, cytologic atypia, and mitoses should be interpreted with caution, since each can be present in reactive pleuritis and do not necessarily indicate malignancy.
- Interpretation can be difficult when there is limited diagnostic tissue, tangential sectioning, artifacts from histologic processing, and/or entrapment of adjacent structures mimicking invasion.[19,21] For a mesothelial proliferation that is suspicious for, but not definitive for malignancy, one may report the findings as "atypical mesothelial proliferation" and recommend rebiopsy and/or close follow-up.
- In the distinction between mesothelioma and benign, reactive mesothelial proliferations, the role of ancillary studies has been limited until recently, where BAP1 or MTAP IHC and *CDKN2A* copy number assessment by FISH may aid in the distinction in some instances (see next page).[22]

Continued

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry

Markers to Confirm Mesothelial Differentiation

- IHC is integral to the pathologic diagnosis of mesothelioma in clinical practice.
- Useful IHC markers include: 1) positive markers to confirm mesothelial differentiation, such as WT1, calretinin, and D2-40; and 2) negative markers to exclude mimics, such as polyclonal carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), and claudin-4.[23-25] One of the caveats is that no individual IHC marker is entirely sensitive and specific. Therefore, it is recommended that a panel including at least two mesothelial markers (eg, calretinin, WT1, D2-40) and two carcinoma markers (eg, claudin-4, TTF-1, polyclonal CEA) should be used to establish the diagnosis.[26]
- Broad-spectrum keratins (eg, AE1/AE3, pancytokeratin, MNF116) are not specific and are expressed in both mesothelioma and carcinomas.
- Sarcomatoid mesothelioma often shows focal to absent expression for most mesothelial markers, with the most sensitive marker being D2-40/podoplanin.[27]
- Recently, GATA3 has been explored as a potential diagnostic marker for sarcomatoid mesotheliomas since GATA3 is expressed in only ~10%–20% of sarcomatoid carcinoma[28] and strongly expressed in all sarcomatoid/desmoplastic mesotheliomas.[29]

Markers to Confirm a Mesothelial Malignant Proliferation

- Although the distinction between diffuse or localized mesothelioma and reactive mesothelial proliferations primarily relies on histologic assessment, this can be challenging in some cases.
- BAP1, MTAP IHC, and *CDKN2A* (p16) FISH are established markers for diagnosing mesothelioma.[22]
  - BAP1 IHC is a specific (though not sensitive) marker to distinguish mesothelioma from reactive mesothelial proliferations.
  - *BAP1* is a tumor suppressor implicated in the pathogenesis of mesothelioma, uveal melanoma, cholangiocarcinoma, and clear cell renal cell carcinoma.[30] Recurrent somatic and/or germline mutations in *BAP1* are present in mesothelioma. As a surrogate for *BAP1* genomic status, BAP1 IHC is used as a diagnostic marker for mesothelioma, whereas reactive proliferations have intact BAP1 nuclear staining. Complete absence of expression or cytoplasmic staining is considered a loss of BAP1 expression. Aberrant BAP1 protein expression, defined as absence of nuclear BAP1 staining, is present in ~50%–70% of mesothelioma epithelioid type[31-37] but in <20% of sarcomatoid type.[38]
  - MTAP IHC has been used as a diagnostic marker for mesothelioma.[39] *MTAP* is located near *CDKN2A* on the chromosomal region 9p21. Loss of cytoplasmic MTAP staining is considered a surrogate for chromosomal 9p loss as determined by concurrent *CDKN2A* FISH testing[39] and has been reported in ~40%–60% of mesothelioma but rarely in reactive proliferations.[35-37]
  - Although MTAP alone is not sensitive, combined use of BAP1 and MTAP IHC may improve sensitivity and specificity.[35-37] Since ~10%–20% of lung adenocarcinomas have MTAP loss,[36] MTAP IHC is not useful for distinction between mesothelioma and lung carcinoma.
- Additional IHC markers such as 5-hydroxymethyl cytosine (5-HMC), enhancer of zeste homolog 2 (EZH2), cyclin D1, and programmed death ligand 1 (PD-L1), and *NF2* by FISH are all potentially useful to distinguish mesothelioma from reactive mesothelial proliferations, but need further study since their utility in clinical practice remains unclear.[22]

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry (continued)

Markers as Potential Prognostic and Predictive Markers

- Recent studies explored IHC targets as potential prognostic and predictive markers.
  - Patients with pleural mesothelioma, epithelioid type, with loss of BAP1 by IHC and retained p16 expression by IHC have prolonged survival in both univariate and multivariate analyses.[40]
  - Patients with mesothelioma with germline *BAP1* mutations have a prolonged survival.[41,42]
  - *ALK* rearrangements by IHC found in rare patients with peritoneal mesothelioma[43-46] have shown dramatic response with ALK inhibitor therapies.[47,48]
- PD-L1 (CD274), a negative regulator of immune checkpoint, represents a target in immunotherapy, with PD-L1 IHC evaluated as a predictive biomarker in diverse tumor types.[49]
- The utility of PD-L1 IHC as a predictive marker for immune checkpoint inhibitors and the optimal assessment criteria in mesothelioma remain unclear.

Cytogenetic Features

- Most mesotheliomas are characterized by complex numerical and structural karyotypic alterations.[50]
- Although no specific chromosomal abnormalities are pathognomonic for mesothelioma, loss of chromosomal region 9p including *CDKN2A* or 22q including *NF2* is noted in a subset of tumors.
  - Homozygous loss of *CDKN2A* by FISH testing is present in ~60% of mesotheliomas.[51-53]
  - While detection of *CDKN2A* loss can aid in the distinction of mesothelioma from reactive mesothelial proliferations, *CDKN2A* loss alone is not useful in separating mesothelioma from other tumor types, since *CDKN2A* loss can be found in a substantial fraction of sarcomatoid mesotheliomas, sarcomatoid carcinomas, and sarcomas.[54]
  - Hemizygous loss of *NF2* by FISH is present in ~50% of pleural mesotheliomas.[55]
- A rare subset of pleural mesothelioma harbors a peculiar near-haploid karyotype, with extensive loss of heterozygosity involving nearly all chromosomes except chromosomes 5 and 7.[56]

Molecular Features

- Most mesotheliomas are characterized by recurrent mutations in tumor suppressors and epigenetic regulators, including *BAP1, NF2, TP53, SETD2*, and other genes.[56-60] Consistent with its histomorphologic heterogeneity, mesothelioma shows an impressive molecular diversity.
- Alterations are identified in multiple pathways in the regulation of cell cycle, RNA processing, histone regulation, and cell growth.[58] *BAP1* is one of the most frequently altered genes; mechanisms of *BAP1* inactivation include point mutations, copy number loss, inactivating structural rearrangements, and minute chromosomal deletions.[56-58,61-63]
- Furthermore, a small subset of pleural mesothelioma harbors unusual genetic alterations: Genomic near-haploidization was described in rare pleural mesotheliomas that harbor mutations in *TP53* and/or *SETDB1*.[56]
- Peritoneal mesothelioma has distinct molecular features compared to pleural mesothelioma.[64]

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW

Molecular Features (continued)

- Oncogenic *EWSR1::ATF1* fusion has been described in pleural and peritoneal mesotheliomas in young adults.[64,65]
  - *ALK* rearrangements have been identified in rare patients with peritoneal mesothelioma.[43-45,48]
- Germline mutations are overall present in 12%–16% of patients with pleural and peritoneal mesotheliomas and primarily involved genes in the DNA repair and cell cycle regulation, such as *BAP1, BRCA2, CDKN2A, TMEM127, VHL, WT1, MRE11A, and MSH6*.[42,66,67] Germline mutations appear to be more common in patients who are young, have a family history of mesothelioma, or have a clinical history of other synchronous malignancies.[42,66,68]

Differential Diagnosis

- The differential diagnosis of mesothelioma depends on the histologic type (epithelioid, biphasic, or sarcomatoid) under consideration. Mesothelioma can resemble reactive pleuritis or diverse tumor types, including carcinoma, melanoma, and sarcomas.
- In addition to diffuse mesothelioma, WHO recognizes additional types of mesothelial lesions: 1) localized mesothelioma, 2) WDPMT, and 3) adenomatoid tumor.[1]
  - *Localized pleural mesothelioma* is microscopically identical to mesothelioma, although it is radiographically and grossly solitary and circumscribed.[15-17] Genetically, localized pleural mesothelioma includes three groups (*BAP1*-mutant, *TRAF7*-mutant, and near-haploid), with similarities but also differences from pleural mesothelioma.[18]
  - *WDPMT*, often an incidental finding in the peritoneum of females, can occur in the pleura,[69] and is genetically characterized by recurrent mutations in *TRAF7* or *CDC42*.[70] Infrequently, WDPMT shows back-to-back papillae with foci of invasion,[71] morphologically mimicking mesothelioma. Furthermore, distinction between a mesothelioma with prominent papillary surface projections and WDPMT can be challenging, particularly in small superficial biopsies.
  - *Adenomatoid tumor* primarily affects the genital tracts but rarely can involve the pleura; recurrent mutations in *TRAF7* have been described in adenomatoid tumors of genital type.[72]
  - *Peritoneal inclusion cyst* is a benign, rare tumor that displays multiple mesothelial-lined cysts that may be distinguished from mesothelial neoplasia. This lesion is almost always located in the peritoneum, although uncommon cases have been described in the pleura. These cystic proliferations are lined by bland mesothelial cells and lack significant stratification, papillary structures, or atypia.
  - *Mesothelioma in situ* is a preinvasive, single-layer surface proliferation of neoplastic mesothelial cells. Since the diagnosis of mesothelioma in situ cannot be simply made on conventional hematoxylin and eosin (H&E) stains, the diagnosis requires either 1) loss of BAP1 nuclear expression by IHC; and/or 2) *CDKN2A* homozygous deletion identified either by FISH or by MTAP IHC (cytoplasmic staining). Furthermore, no mass lesions should be identified on imaging or thoracoscopy.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW — REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

- **Pleural effusions: Talc pleurodesis or pleural catheter, if required for management of pleural effusion.[a] Drainage is preferred for candidates with potentially operable disease; drainage or pleurodesis are both options for patients with inoperable disease.**
- **Smoking cessation counseling and intervention: NCCN Guidelines for Smoking Cessation; NCCN Guidelines for Lung Cancer Screening**
- **Pain management: NCCN Guidelines for Adult Cancer Pain**
- **Nausea/vomiting: NCCN Guidelines for Antiemesis**
- **Psychosocial distress: NCCN Guidelines for Distress Management**
- **NCCN Guidelines for Palliative Care as indicated**
- **Radiotherapy and image-guided thermal ablation[1] are palliative options for symptomatic pleural disease.**

[a] If FDG-PET/CT is to be done, recommend obtaining FDG-PET/CT before pleurodesis. Confirm diagnosis of pleural mesothelioma prior to pleurodesis. If pleural mesothelioma is suspected, consider evaluation by a multidisciplinary team with expertise in pleural mesothelioma.

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Note: All recommendations are category 2A unless otherwise indicated.

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Discussion

PRINCIPLES OF SYSTEMATIC THERAPY[a,b]

HISTOLOGY	FIRST-LINE THERAPY		SUBSEQUENT THERAPY
Epithelioid	**Preferred** • (Cisplatin or carboplatin) + pemetrexed[1-4] (category 1) • (Cisplatin or carboplatin) + pemetrexed + bevacizumab[5-7,c] (category 1) • (Cisplatin or carboplatin) + pemetrexed + pembrolizumab[8] (category 1) • Nivolumab/ipilimumab[9] (category 1) **Useful in Certain Circumstances** • (Cisplatin or carboplatin) + gemcitabine[10-12] • Pemetrexed[13] • Vinorelbine[14]	Progression	**Preferred** (if chemotherapy first line)[d] • Nivolumab ± ipilimumab[15-17] **Preferred** (if nivolumab/ipilimumab first line) • (Cisplatin or carboplatin) + pemetrexed[1-4] • (Cisplatin or carboplatin) + pemetrexed + bevacizumab[5-7,c] • Pemetrexed (category 1)[18,19] **Other Recommended** • Gemcitabine[20,21] ± ramucirumab[22] • Vinorelbine[23,24]
Biphasic or Sarcomatoid	**Preferred** • Nivolumab/ipilimumab[9] (category 1) • (Cisplatin or carboplatin) + pemetrexed + pembrolizumab[8] (category 1) **Other Recommended** • (Cisplatin or carboplatin) + pemetrexed[1-4] (category 1) • (Cisplatin or carboplatin) + pemetrexed + bevacizumab[5-7,c] (category 1) **Useful in Certain Circumstances** • (Cisplatin or carboplatin) + gemcitabine[10-12] • Pemetrexed[13] • Vinorelbine[14]	Progression	**Preferred** (if nivolumab/ipilimumab first-line) • (Cisplatin or carboplatin) + pemetrexed[1-4] • (Cisplatin or carboplatin) + pemetrexed + bevacizumab[5-7,c] • Pemetrexed (category 1)[18,19] **Preferred** (if chemotherapy first-line)[d] • Nivolumab ± ipilimumab[15-17] **Other Recommended** • Gemcitabine[20,21] ± ramucirumab[22] • Vinorelbine[23,24]

References PM-C (2 of 3)

[a] All regimens may also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.
[b] Broad molecular tumor profiling is recommended with the goal of identifying rare driver alterations (eg, *NTRK* or *ALK*) for which effective drugs may be available or to appropriately counsel patients regarding the availability of clinical trials.[25]
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[d] Consider rechallenge with pemetrexed-based therapy, if good response to front-line pemetrexed-based treatment.[26]

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY — REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

General Principles

- Recommendations regarding RT should be made by radiation oncologists with experience in managing pleural mesothelioma.
- The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed by a multidisciplinary team including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- PET scanning for treatment planning can be used as indicated.
- Prophylactic RT is not routinely recommended to prevent instrument-tract recurrence after pleural intervention.[1]
- RT is an effective palliative treatment for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with mesothelioma.
- A randomized phase III trial in patients with non-metastatic pleural mesothelioma who underwent non-radical lung-sparing surgery found substantially greater overall survival with sequential pleural intensity-modulated RT (IMRT) compared to palliative RT.[2] Sequential pleural IMRT after P/D in the presence of an intact lung may be considered in centers with experience and expertise in these methods, given the technical difficulty of this treatment.[3-5]
- Advanced technologies may be used, such as image-guided RT (IGRT) for treatment involving IMRT/stereotactic radiosurgery (SRS)/ stereotactic body RT (SBRT), and intensity-modulated proton therapy (IMPT).[6]

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment. See Recommended Doses for Radiation Therapy (PM-D 2 of 3).
- 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 <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 remains unclear.
- For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam RT (EBRT) in combination with surgery.

Radiation Techniques (PM-D 2 of 3)
References (PM-D 3 of 3)

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

Recommended Doses for Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
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 metastases	30 Gy	3 Gy	2 weeks
Post P/D Higher dose to higher risk areas	45–60 Gy	1.8–2 Gy	5–6 weeks

Radiation Techniques

- Use of highly conformal radiation technology (IMRT) is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.[4,11] Advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/volumetric modulated arc therapy (VMAT), IGRT, motion management, and proton therapy.
- 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 contralateral uninvolved mean lung dose (MLD) should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.[14] For postoperative RT for patients who have P/D, other recommended specific lung-preserving techniques are advised. Limit the ipsilateral lung dose to decrease risk of pneumonitis and keep total MLD <21 Gy and V20 <40% and contralateral lung V20 <7% and MLD <8 Gy.[15]
- 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 P/D should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
- Extensive elective nodal irradiation (ENI) (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
- The planning target volume (PTV) should consider the target motion and daily setup errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

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

References (PM-D 3 of 3)

Note: All recommendations are category 2A unless otherwise indicated.

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGERY[1]

- **Surgical resection should be performed on carefully evaluated patients by thoracic surgeons with experience in managing pleural mesothelioma.**
- **Decisions regarding surgical options for treatment are highly dependent on accurate histology. Pleural biopsy for diagnosis should provide enough tissue for differentiation of epithelioid, sarcomatoid, or mixed histology and clearly exclude metastatic pleural involvement of another primary. Cytology is generally not considered adequate for important histologic differentiation required for treatment decisions.**
- **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) P/D with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor ± en-bloc resection of pericardium and/or diaphragm with reconstruction; and 2) 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.**
- **For early-stage disease (confined to the pleural envelope, no clinical evidence for lymph node involvement) with favorable histology (epithelioid), P/D may be considered but it is unclear whether there is benefit over systemic therapy alone. There is controversy regarding a decision for surgical resection that needs to be weighed, taking into account tumor histology, distribution, the patient's pulmonary reserve, and availability of adjuvant and intraoperative strategies. P/D is the preferred surgical treatment option and can be considered in select patients for complete gross cytoreduction. EPP may be selected in certain cases that require careful consideration of the total treatment plan that includes the patient and multidisciplinary team.[2-5]**
- **If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in pleural mesothelioma.**
- **If technically appropriate for even more advanced disease, lung-sparing operations like P/D reduce the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection. P/D can provide excellent symptomatic control of recurrent pleural effusions.**
- **Intraoperative adjuvant therapy 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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Note: All recommendations are category 2A unless otherwise indicated.

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura with or without involvement of: -visceral pleura -mediastinal pleura -diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: -Involvement of diaphragmatic muscle -Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but **potentially resectable** tumor. Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least one of the following features: -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 ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: -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 tumor to mediastinal organs -Direct extension of tumor into the spine -Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis present

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1	N0	M0
Stage IB	T2-T3	N0	M0
Stage II	T1-T2	N1	M0
Stage IIIA	T3	N1	M0
Stage IIIB	T1-T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy
4D-CT	four-dimensional computed tomography
CEA	carcinoembryonic antigen
CTV	clinical target volume
DLCO	diffusing capacity of the lung for carbon monoxide
EBRT	external beam radiation therapy
EBUS/ EUS	endobronchial ultrasound/ endoscopic ultrasound
ENI	elective nodal irradiation
EPP	extrapleural pneumonectomy
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
GTV	gross tumor volume
H&E	hematoxylin and eosin
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMPT	intensity-modulated proton therapy
IMRT	intensity-modulated radiation therapy
MLD	mean lung dose
NGS	next-generation sequencing
P/D	pleurectomy/decortication
PD-L1	programmed death ligand 1
PFT	pulmonary function test
PS	performance status
PTV	planning target volume
SBRT	stereotactic body radiation therapy
SMRP	soluble mesothelin-related peptide
SRS	stereotactic radiosurgery
TTF-1	thyroid transcription factor-1
VATS	video-assisted thoracic surgery
VMAT	volumetric modulated arc therapy
WDPMT	well-differentiated papillary mesothelial tumor

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 1.2025
Mesothelioma: Pleural

Discussion

This discussion corresponds to the NCCN Guidelines for Mesothelioma: Pleural. Last updated: October 17, 2022

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NCCN Guidelines Version 1.2025
Mesothelioma: Pleural

Overview

Mesothelioma is a rare cancer originating in mesothelial surfaces of the pleura and other sites that is estimated to occur in approximately 3500 people in the United States every year.[1-5] These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) focus on pleural mesothelioma (PM), which is the most common type (approximately 85%). Mesothelioma can also occur in the lining of other sites, such as the peritoneum (approximately 15%), pericardium, and tunica vaginalis testis.[6-9] PM is difficult to treat, because most patients have advanced disease at presentation. Median overall survival is approximately 1 year after diagnosis of PM, and 5-year overall survival is about 10%; cure is rare.[2,10-14] PM occurs mainly in older males (median age at diagnosis, 72 years) who have been exposed to asbestos, although death occurs decades after exposure (approximately 32 years later [range, 13–70 years]).[14-17]

These NCCN Guidelines® for Mesothelioma: Pleural were first published in 2010 and have been subsequently updated every year. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2022, which are described in greater detail in this revised Discussion text; recent references have been added. For example, a new section on pathology was added for the 2022 update (see *Principles of Pathologic Review* in the algorithm). Additional supplementary material in the NCCN Guidelines for Mesothelioma: Pleural includes the *Principles of Systemic Therapy*, *Principles of Supportive Care, Principles of Surgery*, and *Principles of Radiation Therapy*. These NCCN Guidelines for Mesothelioma: Pleural were developed and are updated by panel members who also update the NCCN Guidelines for Mesothelioma: Peritoneal and the NCCN Guidelines for Non-Small Cell Lung Cancer.

Asbestos use has decreased since the 1970s; however, the United States still has more reported cases and deaths from PM than anywhere else in the world because of the long latency period before the disease occurs.[1,18-21] The mortality burden from asbestos-related diseases in the United States did not change from 1999 to 2015.[10,22,23] Although asbestos is no longer mined in the United States, it is still imported.[21] The incidence of PM is increasing in other countries such as Russia, Western Europe, China, and India.[3,20,24-29] Mortality rates from PM are highest in the United Kingdom, Netherlands, and Australia; mortality rates are increasing in Poland, Spain, China, Japan, Argentina, Republic of Korea, and Brazil.[12,24,25,30] Russia, China, Brazil, and Canada are the top producers of asbestos.[31]

Although most mesothelioma is linked to asbestos exposure, reports suggest that ionizing radiation may also cause mesothelioma, such as in patients previously treated with mantle radiation for Hodgkin lymphoma.[32-42] Two meta-analyses suggest that non-occupational exposure to asbestos is a risk factor for PM.[43,44] Data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma.[45-48] Genetic factors may also play a role in PM, with rare families carrying a germline mutation in the *BRCA1*-associated protein-1 (*BAP1*) gene.[45,49-58] Patients with germline *BAP1* mutations have prolonged survival.[53,56] *BAP1* is one of the most frequently altered genes in patients with mesotheliomas; however, other genes may also be altered such as *NF2*, *TP53*, and *SETD2* (see *Principles of Pathologic Review* in the algorithm).[59-63] Smoking is not a risk factor for mesothelioma.[64] However, patients who smoke and have been exposed to asbestos are at increased risk for lung cancer.[65] Patients who smoke should be encouraged to quit because smoking impedes treatment (eg, delays wound healing after surgery) (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[66] Some patients who have been exposed to asbestos only have benign pleural disease, although they may have significant chest pain.[67,68] Although screening for mesothelioma has been studied in patients at high risk (ie, those with asbestos exposure),

these NCCN Guidelines do not recommend screening for PM because it has not been shown to decrease mortality (see *Initial Evaluation* in the algorithm).[31,65,69-75] Note that data and guidelines about screening for lung cancer with low-dose CT do not apply to PM; there are no data to suggest that screening with low-dose CT improves survival for patients with PM.[31,65,76-79]

Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature on mesothelioma using the following search term: malignant pleural mesothelioma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, then recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

Presentation and Evaluation

Patients with suspected PM often have dyspnea and chest pain; they may also have pleural effusion, fatigue, insomnia, cough, chest wall mass, loss of appetite, and weight loss (see the NCCN Guidelines for Adult Cancer Pain, available at www.NCCN.org).[30,80,81] Patients with PM often have a high symptom burden when compared with patients who have other types of cancer (see *Principles of Supportive Care* in the algorithm). Symptoms such as chest pain and/or dyspnea are associated with local disease. Patients often present without distant metastases; CNS metastases are uncommon.[69]

In patients with recurrent pleural effusion and/or pleural thickening, the recommended initial evaluation for suspected PM includes: 1) CT with contrast of the chest; 2) pleural biopsy (eg, thoracoscopic biopsy [preferred]); and 3) thoracentesis for cytologic assessment of the effusion (see *Initial Evaluation* in the algorithm).[30,31,69,82-87] However, cytologic samples are often negative even when patients have PM.[88,89] Fine-needle aspiration (FNA) is not recommended for diagnosis, although endobronchial ultrasound (EBUS)/endoscopic ultrasound (EUS) FNA may be used to assess mediastinal lymph nodes.[30]

Talc pleurodesis or pleural catheter may be needed for management of pleural effusion (see *Principles of Supportive Care* in the algorithm).[69,90-99] Drainage is preferred for patients with potentially operable disease, whereas either drainage or pleurodesis are options for patients who are medically inoperable.[90] Soluble mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status;[100-103] osteopontin does not appear to be as useful for diagnosis.[69,104-108] Other potential diagnostic biomarkers are being assessed.[70-72,109-113]

Pathology

The NCCN Guidelines include an extensive section on pathologic evaluation of tumor tissue to diagnose PM (see *Principles of Pathologic Review* in the algorithm). The goals of assessment are to confirm the pathologic diagnosis of PM and to determine the histology. The histologic

subtypes of mesothelioma include epithelioid (most common), sarcomatoid, and biphasic (mixed), which includes epithelioid and sarcomatoid.[4,63,114,115] Patients with epithelioid histology have better outcomes than those with either mixed or sarcomatoid histologies. It is essential to determine the histology, which is used to direct treatment. The WHO introduced several changes in 2021 for mesothelioma including new terminology: 1) diffuse pleural mesothelioma; 2) localized pleural mesothelioma; and 3) well-differentiated papillary mesothelioma (see *Principles of Pathologic Review* in the algorithm).[63]

It can be difficult to distinguish malignant from benign pleural disease (such as reactive pleuritis) and also to distinguish PM from other malignancies such as metastatic adenocarcinoma, melanoma, sarcoma, or other metastases to the pleura.[26,116-123] Almost all PMs are diffuse (>99%); however, rare cases of localized pleural mesothelioma have been diagnosed, which are less aggressive.[124-128] It is also difficult to distinguish localized PM from diffuse PM.[124] On CT, thymoma metastatic to the pleura can mimic PM; however, pleural effusion does not typically occur with thymoma. Cytologic samples of pleural fluid are often negative or inconclusive, but diagnosis can sometimes be made using cytology.[69,88,89,129,130] Immunohistochemical markers are used to diagnose PM, including markers specific for PM (eg, WT1, calretinin, D2-40) and markers that typically are positive in carcinoma and negative in mesothelioma (eg, thyroid transcription factor 1 [TTF-1], polyclonal carcinoembryonic antigen [CEA], claudin-4) (see *Principles of Pathologic Review* in the algorithm and *Protocol for the Examination of Specimens From Patients With Malignant Pleural Mesothelioma* from the College of American Pathologists [CAP]).[69,88,117,120,122,131,132] A panel of two positive mesothelial markers and two negative markers is recommended for diagnosis of PM.[117] The presence or absence of *BAP1* nuclear expression assessed by immunohistochemistry can be used in the differential diagnosis of mesothelioma.[133-135]

Rare driver mutations have been identified in patients with PM, such as *EWSR1-ATF1* fusions, *TP53, NF2*, *SETDB1,* or *SETD2.*[59-62,136,137] A recent analysis in 229 patients with PM identified seven somatic driver mutations including *BAP1, NF2, TP53, SETD2, LATS2, DDX3X*, and *SETDB1;* targeted agents are being assessed.[136,138-141] *NTRK* and *ALK* fusions have been identified in patients with PM, although at very low frequencies (0.6%).[138,142,143] Targeted agents are available for *NTRK* and *ALK* fusions (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). Patients with PM have low tumor mutational burden.[60,61] For the 2022 update, the NCCN Panel now recommends broad molecular profiling for patients with PM to identify rare driver alterations (eg, *ALK* or *NTRK* fusions) for which effective drugs may be available or to counsel patients about clinical trials.[60,138]

Management

The NCCN Guidelines recommend that patients with PM be managed by a multidisciplinary team with experience in PM. A general overview of management is provided here; specific details are provided in the following sections (see *Surgery*, *Systemic Therapy*, and *Radiation Therapy* in this Discussion). Treatment options for patients with PM include surgery, radiation therapy (RT), and/or systemic therapy.[4] Most patients have advanced disease at presentation, and surgery is not recommended for these patients. Trimodality therapy—using chemotherapy, surgery, and hemithoracic RT—has been assessed in patients with medically operable PM.[144-151] Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.[147,150] Nodal status and response to systemic therapy can affect survival.[150,152] 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. Select patients with medically operable disease are candidates for multimodality therapy, including those with clinical stages I to IIIA PM and epithelioid histology

and good performance status (PS).[148-154] Surgical resection is recommended for certain patients with clinical stage I to IIIA PM who are medically operable and can tolerate the surgery. Patients who are candidates for surgery may have preoperative or postoperative chemotherapy followed by postoperative RT. Systemic therapy alone is recommended for patients with PS 0 to 2 and medically inoperable PM (see *Systemic Therapy* in this Discussion and *Treatment* in the algorithm).[155,156] Definitive RT alone is not recommended in any setting for patients with PM.

Observation for progression may be considered for patients with PS 0 to 2 who are not eligible for surgery and are asymptomatic with minimal burden of disease if systemic therapy is planned when progression occurs (either radiologic or symptomatic progression). Best supportive care is recommended for patients with PS 3 to 4 (see *Chemotherapy* in this Discussion and *Principles of Systemic Therapy* and *Principles of Supportive Care* in the algorithm). Pleural effusion can be managed using thoracoscopic talc pleurodesis or placement of a drainage catheter.[69,90-95,99,157-159] Therapeutic/palliative thoracentesis can also be used to remove pleural fluid and thus decrease dyspnea either before treatment or for patients who are not candidates for more aggressive treatment.[30]

Pretreatment Evaluation

For patients diagnosed with PM, pretreatment evaluation, using chest and abdominal CT with contrast, is recommended to stage patients and to assess whether patients are candidates for surgery.[83,84,160] For patients with a clinical diagnosis of stages I to IIIA PM with epithelioid histology who are being considered for surgery, additional testing may be done to rule out metastatic disease, including 1) FDG PET/CT; 2) mediastinoscopy or EBUS/EUS FNA of the mediastinal lymph nodes;[161,162] 3) optional chest MRI with contrast to evaluate possible chest wall, spinal, diaphragmatic, or vascular involvement; and 4) video-assisted thoracoscopic surgery (VATS) or laparoscopy can be considered if contralateral or peritoneal disease is suspected to rule out transdiaphragmatic extension (eg, extension to the peritoneum is indicative of stage IV [unresectable] disease).[163] PET/CT scans should be obtained before pleurodesis if practical, because talc produces pleural inflammation, which can affect the fluorodeoxyglucose (FDG) avidity (ie, false-positive result).[164-166] Patients with clinical stage I to IIIA epithelioid PM are evaluated to assess whether they can tolerate surgery using 1) pulmonary function tests (PFTs), including diffusing capacity for carbon dioxide (DLCO); 2) perfusion scanning (if forced expiratory volume in 1 second [FEV1] <80%); and 3) cardiac stress tests (see *Surgical Evaluation* in the algorithm).

Staging

Patients who are not candidates for surgery only have clinical staging. It is difficult to clinically stage patients using CT, MRI, or PET/CT; therefore, patients who have surgery may be upstaged. Understaging is common with PET/CT.[166,167] However, PET/CT is useful for determining whether metastatic disease is present.[167,168] Surgical staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system (see *Staging* in the algorithm), which was approved by the AJCC.[169-172]

Surgery

Surgery is recommended as a component of combined modality therapy for certain patients with stage I to IIIA PM who are medically operable.[173] The NCCN Panel recommends surgery for certain patients with clinical stage I to IIIA PM and epithelioid histology.[174] Surgery may be considered for certain patients with early-stage PM who have biphasic histology.[147,175] However, surgery is generally not an option for those with stage IIIB or IV PM regardless of histology. It is essential that patients receive a careful assessment before surgery is performed.

Surgical resection for patients with PM can include either 1) pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor with or without en-bloc resection of the pericardium and/or diaphragm; or 2) extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium (see *Principles of Surgery* in the algorithm).[176] Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[176] Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). The surgical goal for PM is cytoreductive surgery to achieve macroscopic complete resection by removing all visible or palpable tumors.[177,178] If macroscopic complete resection is not possible—such as patients with multiple sites of chest wall invasion—then surgery should be aborted. However, surgery should be continued—if most of the gross disease can be removed—to help with postoperative management and if there will be a minimal impact on morbidity.

The choice of surgery for PM is controversial, because data from randomized controlled trials are not available.[4,30,69,173,179-187] Neither EPP nor P/D will yield an R0 resection.[4,188,189] EPP would often be required to remove all gross tumor in patients with stages II to IIIA PM.[81] However, EPP is associated with higher morbidity and mortality.[183,190] P/D (ie, lung-preserving surgery) is safer than EPP.[190-197] A retrospective analysis (n = 663) suggested that survival was greater after P/D than after EPP, but this analysis may have been confounded by patient selection.[4,195] Another retrospective analysis compared EPP (n = 187) versus P/D (n = 95) in patients with PM.[198] Median overall survival was 15 months for patients receiving EPP versus 22 months for P/D (*P* = .276). Perioperative mortality was 11% for those receiving EPP versus 0% for P/D (*P* = .031).

A large meta-analysis (n = 2903) suggests that 30-day mortality is improved with P/D versus EPP; 2-year mortality was similar between the arms.[15,183] Another meta-analysis (n = 500) suggests that P/D is associated with decreased 30-day mortality and complications (especially supraventricular arrhythmia) when compared with EPP.[180] Lung-sparing options, such as P/D, reduce the risk for perioperative mortality when compared with EPP and yield either equal or better long-term survival than non-surgical therapy in patients with more advanced disease.[188,199]

A feasibility trial (Mesothelioma and Radical Surgery [MARS]) assessed whether patients treated with induction chemotherapy would accept randomization to EPP or no surgery; 112 patients were enrolled in the trial, and 50 patients were randomized.[200] The authors concluded that due to the observed high rate of surgical mortality, EPP was not beneficial when compared with chemotherapy treatment alone. However, these results were controversial because survival was not the primary outcome of the study, the sample size was small, and the surgical mortality was higher than expected.[201] An Australian retrospective study (540 patients) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and treatment with pemetrexed.[202]

The NCCN Panel feels that P/D and EPP are reasonable surgical options that should be considered in select patients to achieve complete gross cytoreduction.[183,195,200,203,204] Although P/D may be safer than EPP, it is not clear which operation is oncologically better. When surgery is indicated, the choice between P/D and EPP should be made based on several factors, including tumor histology and distribution, stage, pulmonary reserve, surgical experience and expertise, and availability of adjuvant and intraoperative strategies.[11,204] In patients who are medically operable, the decision about whether to do a P/D or an EPP may not be made until surgical exploration. P/D may be more appropriate for patients with advanced PM who cannot tolerate an EPP.[191] P/D may also be useful for

symptom control (eg, patients with entrapped lung syndrome, recurrent pleural effusions).[31] The NCCN Panel does not generally recommend surgery for patients with stage IIIB to IV PM regardless of histology; systemic therapy is recommended for these patients who have PS 0 to 2 (see *Systemic Therapy* in this Discussion and *Treatment* in the algorithm). Prognosis with surgery (and other therapy) is substantially diminished in patients with N2 disease. Surgical resection should only be considered for patients with N2 disease at a center of expertise in PM or in a clinical trial.

Systemic Therapy

Chemotherapy is recommended as part of a multimodality regimen for patients with medically operable PM (see *Treatment* and *Principles of Systemic Therapy* in the algorithm). Patients with medically operable stage I to IIIA PM can receive chemotherapy either before or after surgery. Systemic therapy alone is recommended for patients with 1) stage IIIB or IV PM (PS 0–2) regardless of histology; 2) those with sarcomatoid or biphasic histology, regardless of clinical stage; or 3) medically inoperable stages I to IV PM, or those who refuse surgery.[184,205-207] All of the regimens recommended for PM can also be used for peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[7,208-210]

Medically Operable PM

Trimodality therapy—using chemotherapy, surgery, and hemithoracic RT—has been studied in patients with medically operable PM.[144-151] Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.[147,150] Nodal status and response to chemotherapy can affect survival.[150,152] In patients who do not receive induction chemotherapy before EPP, postoperative sequential chemotherapy with hemithoracic RT is recommended; hemithoracic pleural IMRT may be considered at centers that have expertise with this therapy for patients who have had P/D. Intraoperative adjuvant therapies—such as hyperthermic pleural lavage, photodynamic therapy, or heated chemotherapy—have also been studied, however, they are of unclear benefit.[211-220]

A phase 2 trial assessed trimodality therapy in 77 eligible patients with resectable PM.[150] Patients received preoperative chemotherapy with cisplatin/pemetrexed followed by EPP in 54 patients and then hemithoracic RT. In the overall population, median survival was 16.8 months (95% CI, 13.6–23.2). For patients who completed all of the trimodality therapy, median overall survival was 29.1 months with a 2-year survival of 61.2%.

Another phase 2 trial assessed trimodality therapy in eligible patients with resectable PM.[147] Patients received preoperative chemotherapy with cisplatin/pemetrexed, carboplatin/pemetrexed, or cisplatin/gemcitabine followed by EPP and intensity-modulated RT (IMRT) in 62 patients. The median overall survival was 20.4 months. The 1-year overall survival rate was 63%; the 2-year overall survival rate was 42%. Patients with biphasic histology had a worse outcome compared with those who had epithelioid histology.

A phase 2 trial assessed trimodality therapy in 61 eligible patients with resectable PM.[151] Patients received neoadjuvant therapy with cisplatin/gemcitabine; 45 patients had EPP and 36 patients had postoperative RT. In the overall population, median survival was 19.8 months (95% CI, 14.6–24.5). For patients who EPP, median overall survival was 23 months (95% CI, 16.6–32.9).

A retrospective analysis assessed EPP versus P/D in 663 patients with resectable PM who received trimodality therapy.[195] Patients (28%) received chemotherapy; 14% of patients received chemotherapy and RT. Approximately 60% of patients received EPP. At 5 years, overall survival was 12%. The analysis suggested that survival was greater after P/D than

after EPP, but this analysis may have been confounded by patient selection.

The NCCN Panel recommends preoperative (induction) chemotherapy with pemetrexed plus (cisplatin or carboplatin) for eligible patients with resectable PM based on clinical trial results.[147,150,151] The panel also recommends postoperative chemotherapy if patients have not received induction chemotherapy.

Medically Inoperable PM

First-Line Therapy

Human immune checkpoint inhibitor antibodies, such as nivolumab, inhibit the programmed death-1 (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.[221] Ipilimumab is a monoclonal antibody that inhibits cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which is another immune checkpoint; inhibition of CTLA-4 improves T-cell activity, thus increasing the anti-tumor immune response. CheckMate 743, a phase 3 randomized trial, assessed first-line therapy with nivolumab plus ipilimumab versus platinum/pemetrexed chemotherapy in 605 patients with unresectable PM.[222] Many patients had epithelioid histology (75%). Most of the patients were males (77%), and the median age was 69 years. The median overall survival in the entire population was 18.1 months (95% CI, 16.8–21.4) in patients receiving nivolumab plus ipilimumab versus 14.1 months (95% CI, 12.4–16.2) in those receiving chemotherapy (HR, 0.74; 96.6% CI, 0.60–0.91). The 2-year overall survival rate was 41% (95% CI, 35.1%–46.5%) in the nivolumab plus ipilimumab group versus 27% (95% CI, 21.9%–32.4%) in the chemotherapy group in the entire population. Although the trial was not powered to assess superiority within the subgroups, the data are interesting. In patients with epithelioid histology, the median overall survival was 18.7 months (95% CI, 16.9–22.0) in patients receiving nivolumab plus ipilimumab versus 16.5 months (95% CI, 14.9–20.5) in those receiving chemotherapy (HR, 0.86; 95% CI, 0.69–1.08). In patients with nonepithelioid histology, the median overall survival was 18.1 months (95% CI, 12.2–22.8) in patients receiving nivolumab plus ipilimumab versus 8.8 months (95% CI, 7.4–10.2) in those receiving chemotherapy (HR, 0.46; 95% CI, 0.31–0.68). Grade 3 to 4 treatment-related adverse events were similar in both groups: 30% (91/300) of patients receiving nivolumab plus ipilimumab and 32% (91/284) of those receiving chemotherapy. Three treatment-related deaths (1%) occurred in the nivolumab plus ipilimumab group, which were due to pneumonitis, encephalitis, and heart failure; one death (<1%) occurred in the chemotherapy group, which was due to myelosuppression.

The NCCN Panel recommends (category 1) nivolumab plus ipilimumab for eligible patients with unresectable PM based on clinical trial data and the FDA approval (see *Principles of Systemic Therapy* in the algorithm).[222] Testing for PD-L1 is not required for prescribing nivolumab for therapy for patients with PM. Immune-related adverse events, such as pneumonitis, may occur with nivolumab plus ipilimumab (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[223-225] Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events. Nivolumab plus ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). Ipilimumab can also cause immune-mediated adverse events such as hepatitis and endocrinopathies.

A phase 3 randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients with PM who were not candidates for surgery; the combined regimen increased survival by 2.8 months when compared with cisplatin alone (12.1 vs. 9.3 months, $P = .02$).[226] The

pemetrexed/carboplatin regimen was assessed in three large phase 2 studies (median survival = 12.7, 14, and 14 months, respectively).[227-229] A comparison of 1704 patients with medically inoperable PM treated with cisplatin/pemetrexed or carboplatin/pemetrexed as part of an expanded access trial found that outcomes with the regimens were similar.[230] The NCCN Panel recommends cisplatin/pemetrexed (category 1) for patients with PM based on clinical trial data and the FDA approval.[222,226,231-234] The panel also recommends pemetrexed/carboplatin (category 2A) based on clinical trial data.[222,227-229] Carboplatin regimens are recommended for patients who are not eligible for cisplatin.[230]

A multicenter phase 3 randomized trial (IFCT-GFPC-0701 MAPS) compared adding bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) versus cisplatin/pemetrexed alone for patients with unresectable PM and PS 0 to 2 who did not have bleeding or thrombosis.[234] Overall survival was increased in the bevacizumab plus chemotherapy arm by 2.7 months when compared with chemotherapy alone (18.8 vs. 16.1 months; HR, 0.77; *P* = .0167). Grade 3 to 4 adverse events were reported in 71% (158/222) of patients receiving the bevacizumab regimen when compared with 62% (139/224) of those receiving cisplatin/pemetrexed alone. More grade 3 or higher hypertension (23% vs. 0%), grade 3 proteinuria (3.1% vs. 0%), and grade 3 to 4 thrombotic events (6% vs. 1%) were observed in patients receiving the triplet arm. The NCCN Panel recommends (category 1) bevacizumab, cisplatin, and pemetrexed followed by maintenance bevacizumab for bevacizumab-eligible patients with unresectable PM regardless of histology based on this trial (see *Principles of Systemic Therapy* in the algorithm).[234] Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity.[69] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

A phase 2 trial assessed adding bevacizumab to carboplatin/pemetrexed with or without maintenance bevacizumab as first-line therapy for patients with unresectable PM.[235] Overall survival was 15.3 months; 34% (26/76) of patients had a partial response and 58% (44/76) had stable disease. Bowel perforation occurred in 4% of patients, and grade 3 to 4 fatigue occurred in 8%; there were 3 toxic deaths. Maintenance bevacizumab (maximum, 1 year) was administered to patients without progression and/or severe toxicities. The NCCN Panel recommends (category 2A) adding bevacizumab to carboplatin/pemetrexed with or without maintenance bevacizumab as a first-line therapy option for patients with unresectable PM based on this trial.[235] Gemcitabine/cisplatin was assessed in phase 2 studies (median survival, 9.6–14.1 months).[236-238] Gemcitabine/cisplatin may be useful for patients who cannot take pemetrexed. The NCCN Panel recommends gemcitabine/cisplatin for eligible patients with unresectable PM based on clinical trial data.[236-238] Other first-line options recommended by NCCN include pemetrexed or vinorelbine for patients who are not candidates for platinum-based combination therapy.[239-241]

The NCCN Panel recommends systemic therapy alone for patients with PM and PS 0 to 2, including 1) those who are medically inoperable or refuse surgery; 2) those with clinical stage IIIB to IV PM, regardless of histology; or 3) those with sarcomatoid or biphasic histology, regardless of clinical stage. The NCCN Panel has preference stratified the systemic therapy regimens and voted that the following regimens are preferred first-line therapy options for certain patients with unresectable PM: 1) pemetrexed plus (cisplatin or carboplatin) with or without bevacizumab; or 2) nivolumab plus ipilimumab.[222,226,228-230] For the 2022 update (Version 1), the panel decided that the pemetrexed/platinum with or without bevacizumab regimens were preferred options.[222,226-234] The panel voted that nivolumab plus ipilimumab is a preferred option for patients with biphasic or sarcomatoid histology and is also an option for patients with

epithelioid histology. The panel voted that the following regimens are useful in certain circumstances: 1) gemcitabine/cisplatin; 2) pemetrexed; or 3) vinorelbine.[237,238,240,241]

Subsequent Systemic Therapy

Limited data are available to guide second-line and beyond (subsequent) chemotherapy in patients with PM.[220,242-245] Data suggest that nivolumab with (or without) ipilimumab may be useful as subsequent systemic therapy for patients with PM who have not received prior immunotherapy.[246-257] Response rates have been low with subsequent chemotherapy (7%–20%), although they are slightly higher with the new immunotherapy regimens.[247-249,258,259]

Trial Data

CONFIRM, a phase 3 randomized trial, assessed nivolumab (67%) versus placebo (33%) in 332 patients with PM who had progressed after platinum-based chemotherapy.[246] Most patients had pleural mesothelioma (95%) and epithelioid histology (88%). Many patients had received third-line therapy (56%). Median overall survival was 10.2 months (95% CI, 8.5–12.1) in patients receiving nivolumab versus 6.9 months (95% CI, 5.0–8.0) in those receiving placebo (HR, 0.69; 95% CI, 0.52–0.91). Grade 3 or worse adverse events were reported in 3% of patients receiving nivolumab (diarrhea and infusion-related reaction, 6/221). Serious adverse events were similar between the groups (41% for nivolumab vs. 44% for placebo).

A phase 2 randomized trial (IFCT-1501 MAPS2; n = 125) assessed nivolumab with (or without) ipilimumab as subsequent therapy for patients with PM.[247,252,253] Updated results from this trial indicate that median overall survival was 15.9 months (95% CI, 10.7–not reached) in the nivolumab/ipilimumab arm and 11.9 months (95% CI, 6.7–17.7) with nivolumab alone.[247,253] The 12-month overall survival rates were 58% with the nivolumab/ipilimumab arm and 49% with nivolumab alone. The overall response rate was 28% (95% CI, 16%–40%) with nivolumab/ipilimumab versus 19% (95% CI, 8%–29%) with nivolumab alone. The disease control rate at 12 weeks was 52% (32/62) for nivolumab/ipilimumab versus 40% (25/63) for nivolumab alone.[247] Positive PD-L1 levels were associated with overall response rate, especially high PD-L1 levels of 25% or more. However, only a few patients had very high PD-L1 expression levels of 50% or more. There were more grade 3 to 4 adverse events in the nivolumab/ipilimumab arm when compared with the nivolumab alone arm (26% vs. 14%) based on updated data; 3 treatment-related deaths were reported in the nivolumab/ipilimumab arm (one each: metabolic encephalopathy, fulminant hepatitis, and acute renal failure).[247] A phase 2 Dutch trial (INITIATE) assessed nivolumab/ipilimumab as subsequent therapy in patients with PM.[248] Results showed a disease control rate of 68% at 12 weeks (23/34; 95% CI, 50%–83%); 29% (10/34) had a partial response and 38% (13/34) of patients had stable disease.[248] Grade 3 treatment-related adverse events were reported in 34% (12/35) of patients; 94% (33/34) of patients had treatment-related adverse events.

PROMISE-meso, a multicenter phase 3 randomized trial, assessed subsequent therapy with pembrolizumab versus either gemcitabine or vinorelbine in 144 patients with relapsed PM after progression on platinum-based chemotherapy.[260] There was no difference in overall survival between the groups (HR, 1.12; 95% CI, 0.74–1.69; *P* = .59).

A phase 3 randomized trial assessed subsequent therapy with pemetrexed plus best supportive care versus best supportive care alone in 243 patients with PM who had progressed on systemic therapy.[261] Median overall survival was not statistically significant between the arms (8.4 months for pemetrexed vs. 9.7 months for supportive care only; *P*=.74), probably because patients could cross over to pemetrexed. Data suggest that rechallenging with pemetrexed-based regimens is effective if patients had a good response to first-line pemetrexed.[242,259] A retrospective

multicenter survey reported that rechallenging with a pemetrexed/platinum regimen reduced the risk of death when compared with rechallenging with pemetrexed alone (HR, 0.11; $P < .001$).[259]

NCCN Recommendations

Based on these trials, the NCCN Panel recommends the following subsequent therapy options for patients with PM if not administered first line: 1) pemetrexed (category 1); or 2) nivolumab with (or without) ipilimumab (category 2A).[69,250-253,261] The panel decided that if immunotherapy was administered as first-line treatment, then combination pemetrexed/platinum regimens are subsequent therapy options (eg, pemetrexed plus either cisplatin or carboplatin). The NCCN Panel also recommends other subsequent chemotherapy options based on clinical trial data, including 1) rechallenging with pemetrexed-based regimens if patients had a good sustained response to first-line therapy; 2) vinorelbine; or 3) gemcitabine.[240,242,259-266] For the 2022 update (Version 1), the NCCN Panel deleted pembrolizumab as a subsequent therapy option for patient with relapsed PM based on updated clinical trial data.[260] As previously mentioned, immune-related adverse events, such as pneumonitis, may occur with nivolumab with (or without) ipilimumab (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[223-225]

The NCCN Panel has preference stratified the systemic therapy regimens and voted that the following regimens are preferred subsequent therapy options for certain patients with PM who have progressed on systemic therapy, including 1) pemetrexed if not given first line (category 1); 2) rechallenging with pemetrexed-based regimens if good response with first-line therapy; or 3) nivolumab with (or without) ipilimumab.[69,250-253,259,261] The panel voted that the following regimens are other recommended options: 1) vinorelbine; or 2) gemcitabine.[260]

Radiation Therapy

It is very challenging to accurately and safely deliver RT to the entire pleural surface without damaging radiosensitive sites, such as the lung and heart, especially when the lungs are intact.[267] The *Principles of Radiation Therapy* for PM are described in the algorithm and are summarized in this Discussion. The NCCN Guidelines for Non-Small Cell Lung Cancer are also a useful resource (see *Principles of Radiation Therapy*). In patients with PM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended for treatment. RT can also be used as palliative therapy for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with PM, such as metastases in bone or in the brain (see the algorithm and NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[30,155,268] The dose of radiation should be based on the purpose of treatment.[269] The most appropriate timing of delivering RT (ie, after surgical intervention, with [or without] chemotherapy) should be discussed with a multidisciplinary team. After EPP, adjuvant hemithoracic RT may reduce the local recurrence rate.[270-273] Patients are candidates for RT if they have good PS, pulmonary function, and kidney function (see *Principles of Radiation Therapy* in the algorithm). In patients with limited or no resection of disease (ie, in the setting of an intact lung), high-dose conventional RT to the entire hemithorax has not been shown to improve survival and is associated with significant toxicity.[155,274]

A phase 3 randomized trial assessed postoperative radical hemithoracic IMRT versus palliative RT given after lung-sparing surgery and chemotherapy in 108 patients with PM.[275] The 2-year overall survival rate was 58% in the IMRT arm versus 28% in the palliative RT arm (HR, 0.54; 95% CI, 0.31–0.95; $P = .031$). In the IMRT arm, 11 patients had grade 3 or greater acute toxicity; 17 patients had grade 3 to 4 late toxicity. One patient died. A phase 2 trial (IMPRINT) (n = 27) evaluated the safety of hemithoracic IMRT in patients with PM, given after induction

chemotherapy and surgery.[276] Radiation pneumonitis, which was reversible with corticosteroids, was reported in 30% (95% CI, 14%–50%) of patients (grade 2 in 6 patients, grade 3 in 2 patients). Most patients had stage III or IV PM; most evaluable patients had a partial P/D. In patients with resectable tumors, 2-year overall survival was 59%. Mediastinal nodal failure occurred in 22% (6/27) of patients; distant progression occurred in 48% (13/27) of patients. Another trial assessed postoperative hemithoracic IMRT given after lung-sparing surgery and cisplatin/pemetrexed in 69 patients with PM.[277] Patients received either extended P/D (35) or partial pleurectomy (34); the 2-year overall survival was 65% and 64%, respectively. Grade 2 to 3 pneumonitis occurred in 20% of patients; one patient died from pneumonitis. Based on these trials, the NCCN Panel recommends that hemithoracic pleural IMRT can be considered following induction chemotherapy and P/D in certain patients with PM if done in centers with expertise in this technique.[275-277]

It has been controversial whether immediate (prophylactic) RT is useful for preventing instrument-tract recurrence after pleural intervention.[278-283] An older French trial reported that prophylactic RT was useful for preventing recurrence, but 2 other trials did not find any benefit.[278,282,283] A phase 3 randomized trial (SMART trial) compared prophylactic radiotherapy with deferred radiotherapy to assess the rate of recurrences in patients who had had procedures for PM.[284] Patients in the deferred RT arm did not receive RT until procedure-tract metastases were evident. Data showed no difference in procedure-tract recurrence in the prophylactic RT arm (9% [9/102]) versus the deferred RT arm (16% [16/101]) (odds ratio [OR], 0.51; 95% CI, 0.19–1.32). In addition, prophylactic RT did not improve the quality of life, decrease chest pain, or decrease the need for analgesic drugs. However, if patients did not receive chemotherapy, prophylactic RT did decrease the risk for procedure-tract metastases (OR, 0.16; 95% CI, 0.02–0.93; P = .021). The NCCN Panel does not routinely recommend prophylactic RT to prevent instrument-tract recurrence after pleural intervention based on the SMART trial (see *Principles of Radiation Therapy* in the algorithm).[148,189,273,274,284-287] Several prophylactic RT dose regimens are cited in the literature.[278,282-284]

CT simulation–guided planning using either IMRT or conventional photon/electron RT is acceptable.[147,270,272,288] For treatment planning, PET scans can be used as indicated. The clinical target volumes should be reviewed with the thoracic surgeon to ensure coverage of all the volumes at risk. The total doses of radiation are described in the algorithm (see *Principles of Radiation Therapy*). The postoperative RT doses after EPP are 45 to 60 Gy in 1.8 to 2 Gy, with a higher dose to higher risk areas. A dose of 60 Gy or more is recommended for macroscopic residual tumors, if the doses to normal adjacent structures are limited to their tolerances (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).[154] The volume of postoperative radiation should cover the surgical bed within the thorax.[148,189,273,274,286,287] The optimal dose of RT for palliative purposes remains unclear.[269,289] For patients with chest pain from PM, total doses of 20 to 40 Gy appear to be effective in providing relief from pain.[30,278,279]

Hemithoracic pleural IMRT allows for a more conformal high-dose RT and improved coverage to the hemithorax at risk.[154,155,270,271,275,276,290-293] Advanced technologies, such as image-guided RT (IGRT), may be used for treatments involving IMRT or helical tomotherapy (HT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT).[267,294] Intensity-modulated proton therapy (IMPT) may also be used.[295] RT to the contralateral uninvolved lung should be minimized,[155,271,296] because fatal pneumonitis may occur with IMRT if strict limits are not applied.[297-299] The contralateral uninvolved mean lung dose should be kept as low as possible, preferably less than 8.5 Gy.[300] The volume of contralateral lung receiving low-dose RT (eg, 5 Gy) should be minimized.[301,302] Hemithoracic IMRT immediately followed by EPP was assessed in 25 patients with

stage III or IV PM on final pathologic review; for patients with epithelial subtypes of PM, 3-year survival reached 84%.[292] However, 13 patients had grade 3+ surgical complications and one patient died from treatment. The NCCN Panel does not recommend hemithoracic pleural IMRT after EPP.

Summary

These NCCN Guidelines focus on PM, which is the most common type of mesothelioma (approximately 85%). Mesothelioma can also occur in the lining of other sites, such as the peritoneum (approximately 15%), pericardium, and tunica vaginalis testis.[6-9] The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2022. This Discussion text for PM describes the recommendations in the algorithm in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithm. The Version 2 update reflects the addition of the updated Discussion. The NCCN Pleural Mesothelioma Panel has also developed a guideline for peritoneal mesothelioma (see the NCCN Guidelines for Mesothelioma: Peritoneal, available at www.NCCN.org).

For the 2022 update (Version 1), the NCCN Pleural Mesothelioma Panel decided that the pemetrexed/platinum with or without bevacizumab regimens were preferred first-line therapy options.[222,226-234] The NCCN Panel deleted pembrolizumab as a subsequent therapy option for patients with relapsed PM based on updated clinical trial data.[260] The panel also clarified that if immunotherapy is administered as first-line therapy then pemetrexed combination regimens are options for subsequent therapy (eg, pemetrexed plus either cisplatin or carboplatin). The panel added a new section on pathology for the 2022 update (see *Principles of Pathologic Review* in the algorithm).

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