



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Mesothelioma: Pleural

Version 2.2025 — January 14, 2025

**NCCN.org**

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available.  
Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at [www.nccn.org/patients](http://www.nccn.org/patients)

**Continue**



**\*Gregory J. Riely, MD, PhD/Chair † ‡**  
Memorial Sloan Kettering Cancer Center

**\*Douglas E. Wood, MD/Vice Chair ¶**  
Fred Hutchinson Cancer Center

**\*James Stevenson, MD/Lead †**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer Center  
and Cleveland Clinic Taussig Cancer Institute

**Dara L. Aisner, MD, PhD ≠**  
University of Colorado Cancer Center

**Wallace Akerley, MD †**  
Huntsman Cancer Institute at the University of Utah

**Jessica R. Bauman, MD ‡ †**  
Fox Chase Cancer Center

**Ankit Bharat, MD ¶ ≡**  
Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University

**Joe Y. Chang, MD, PhD §**  
The University of Texas  
MD Anderson Cancer Center

**Lucian R. Chirieac, MD ≠ ≡**  
Dana-Farber/Brigham and Women's  
Cancer Center

**Malcolm DeCamp, MD ¶**  
University of Wisconsin Carbone Cancer Center

**Aakash P. Desai, MD, MPH ‡**  
O'Neal Comprehensive Cancer Center at UAB

**Thomas J. Dilling, MD, MS §**  
Moffitt Cancer Center

**Jonathan Dowell, MD †**  
UT Southwestern Simmons  
Comprehensive Cancer Center

**Gregory A. Durm, MD, MS †**  
Indiana University Melvin and Bren Simon  
Comprehensive Cancer Center

**Scott Gettinger, MD † ‡**  
Yale Cancer Center/Smilow Cancer Hospital

**Travis E. Grotz, MD ¶**  
Mayo Clinic Comprehensive Cancer Center

**Matthew A. Gubens, MD, MS †**  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Aditya Juloori, MD §**  
The UChicago Medicine  
Comprehensive Cancer Center

**Rudy P. Lackner, MD ¶**  
Fred & Pamela Buffett Cancer Center

**Michael Lanuti, MD ¶**  
Mass General Cancer Center

**Jules Lin, MD ¶**  
University of Michigan Rogel Cancer Center

**Billy W. Loo, Jr., MD, PhD §**  
Stanford Cancer Institute

**Christine M. Lovly, MD, PhD †**  
Vanderbilt-Ingram Cancer Center

**Fabien Maldonado, MD ≡**  
Vanderbilt-Ingram Cancer Center

**Daniel Morgensztern, MD †**  
Siteman Cancer Center at Barnes-Jewish Hospital  
and Washington University School of Medicine

**Trey C. Mullikin, MD §**  
Duke Cancer Institute

**Thomas Ng, MD ¶**  
The University of Tennessee  
Health Science Center

**Dawn Owen, MD, PhD §**  
Mayo Clinic Comprehensive Cancer Center

**Dwight H. Owen, MD, MSc †**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Sandip P. Patel, MD ‡ † ‡**  
UC San Diego Moores Cancer Center

**Tejas Patil, MD †**  
University of Colorado Cancer Center

**Patricio M. Polanco, MD ¶**  
UT Southwestern Simmons  
Comprehensive Cancer Center

**Jonathan Riess, MD ‡**  
UC Davis Comprehensive Cancer Center

**Theresa A. Shapiro, MD, PhD ≠ ‡**  
Johns Hopkins Kimmel Cancer Center

**Aditi P. Singh, MD †**  
Abramson Cancer Center at the  
University of Pennsylvania

**Alda Tam, MD ϕ**  
The University of Texas  
MD Anderson Cancer Center

**Tawee Tanvetyanon, MD, MPH †**  
Moffitt Cancer Center

**Jane Yanagawa, MD ¶**  
UCLA Jonsson Comprehensive Cancer Center

**Stephen C. Yang, MD ¶**  
Johns Hopkins Kimmel Cancer Center

**Edwin Yau, MD, PhD †**  
Roswell Park Comprehensive Cancer Center

**NCCN**  
**Kristina Gregory, RN, MSN**  
**Lisa Hang, PhD**

**Continue**

ϕ Diagnostic/Interventional radiology  
‡ Hematology/Hematology oncology  
‡ Internal medicine  
† Medical oncology  
≠ Pathology  
¥ Patient advocacy

≡ Pulmonary medicine  
§ Radiation oncology/  
Radiotherapy  
¶ Surgery/Surgical oncology  
\* Discussion Section Writing  
Committee



[NCCN Mesothelioma: Pleural Panel Members](#)  
[Summary of the Guidelines Updates](#)

[Initial Evaluation \(PM-1\)](#)

[Pretreatment Evaluation \(PM-2\)](#)

[Clinical Stage I and Epithelioid Histology; Non-Surgical Treatment \(PM-2\)](#)

[Clinical Stage II–IV and Epithelioid Histology; Sarcomatoid or Biphasic Histology \(any stage\), or Medically Inoperable \(any stage\); Treatment \(PM-2\)](#)

[Clinical Stage I and Epithelioid Histology; Surgical Evaluation and Treatment \(PM-3\)](#)

[Principles of Pathologic Review \(PM-A\)](#)

[Principles of Supportive Care \(PM-B\)](#)

[Principles of Systemic Therapy \(PM-C\)](#)

[Principles of Radiation Therapy \(PM-D\)](#)

[Principles of Surgery \(PM-E\)](#)

[Staging \(ST-1\)](#)

[Abbreviations \(ABBR-1\)](#)

Find an NCCN Member Institution:  
<https://www.nccn.org/home/member-institutions>.

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

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2025.



### Updates in Version 2.2025 of the NCCN Guidelines for Mesothelioma: Pleural from Version 1.2025 include:

#### [PM-C 1 of 3](#)

- Footnote e added: Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

### 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.

[Continued](#)

**UPDATES**



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

#### **PM-D 1 of 3**

- 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.

#### **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:

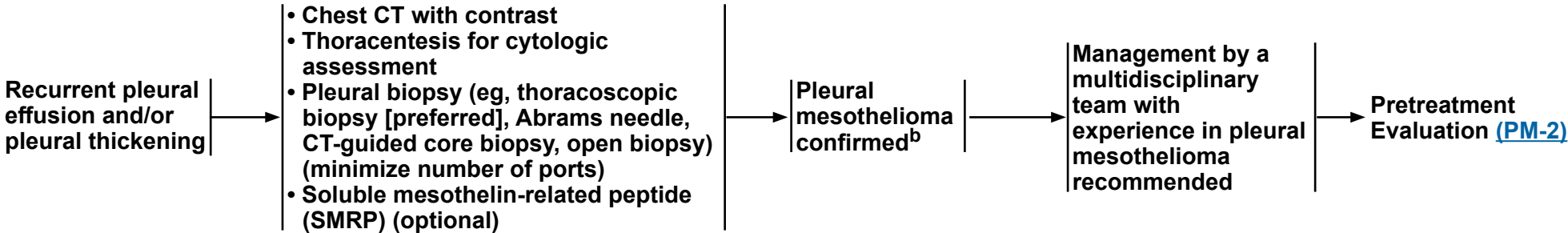
- ▶ Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2005;63:1045-1052.
- ▶ Gupta V, Krug LM, Laser B, et al. Patterns of local and nodal failure in malignant pleural mesothelioma after 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 options 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.*

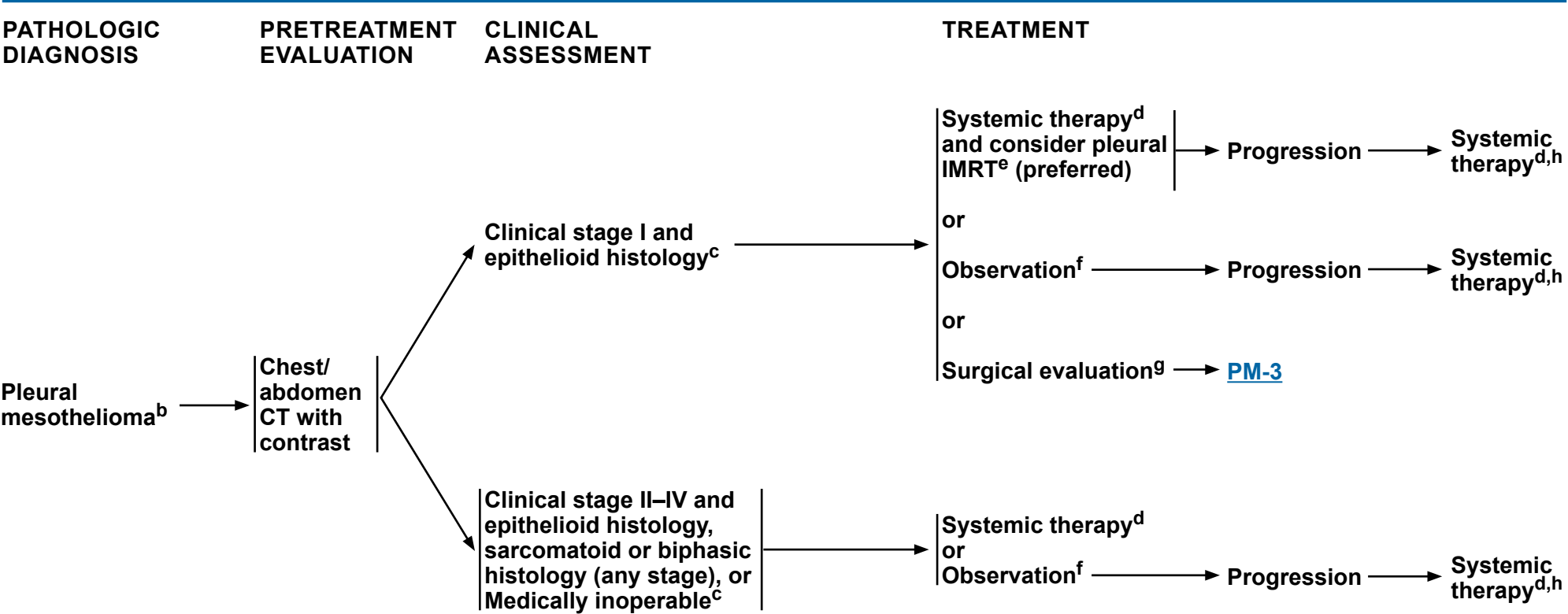


**INITIAL EVALUATION<sup>a</sup>**



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

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



<sup>b</sup> [Principles of Pathologic Review \(PM-A\)](#).

<sup>c</sup> Best supportive care is recommended for patients presenting with PS 3–4. See [Principles of Supportive Care \(PM-B\)](#).

<sup>d</sup> [Principles of Systemic Therapy \(PM-C\)](#).

<sup>e</sup> 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 \(PM-D\)](#).

<sup>f</sup> 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.

<sup>g</sup> 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.

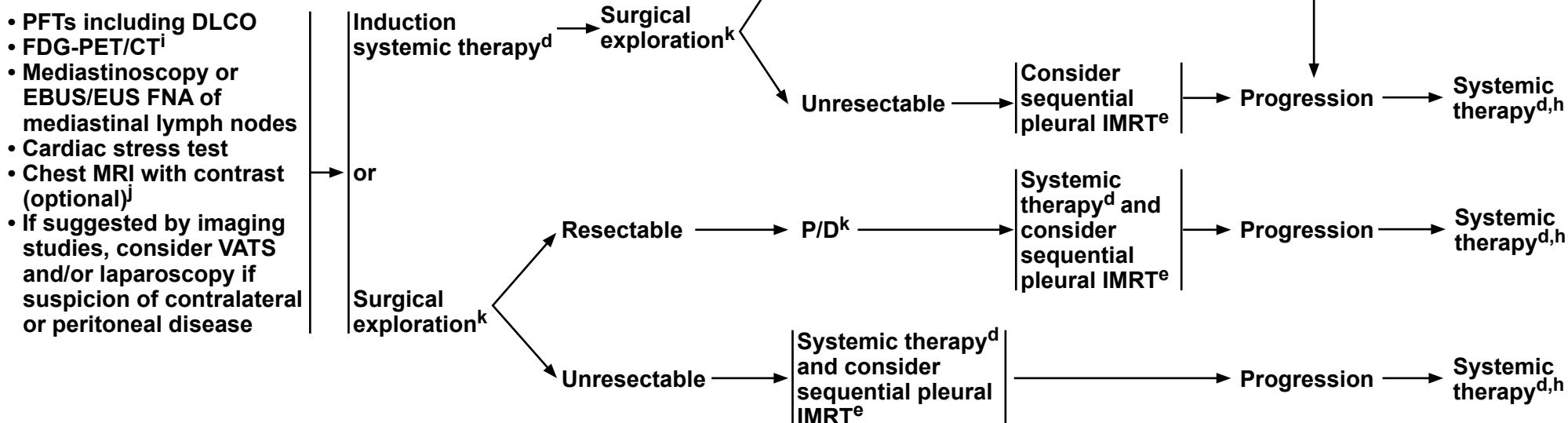
<sup>h</sup> [Principles of Supportive Care \(PM-B\)](#).

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



**CLINICAL STAGE I AND  
EPITHELIOID HISTOLOGY  
SURGICAL EVALUATION<sup>g</sup>**

**TREATMENT<sup>h</sup>**



<sup>d</sup> [Principles of Systemic Therapy \(PM-C\)](#).

<sup>e</sup> Pleural IMRT should only be performed in carefully selected patients at centers with experience in this technique. See [Principles of Radiation Therapy \(PM-D\)](#).

<sup>g</sup> 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.

<sup>h</sup> [Principles of Supportive Care \(PM-B\)](#).

<sup>i</sup> 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.

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

<sup>k</sup> [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.<sup>1</sup>
- In the United States, diffuse pleural mesothelioma affects ~3,000 patients each year, with an annual incidence of ~1 in 100,000.<sup>2,3</sup>
- 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:<sup>1,4</sup>
  - ▶ 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.<sup>1</sup>
- 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.

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

[Continued](#)  
[References](#)

PM-A  
1 OF 8

## 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.<sup>5</sup>
  - ▶ Other rare variants of epithelioid mesothelioma include clear cell, signet ring cell, rhabdoid, deciduoid, and small cell.<sup>6-8</sup> 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,<sup>9,10</sup> and lymphohistiocytoid.<sup>11-13</sup> A subset of sarcomatoid mesothelioma exhibits heterologous differentiation with osteosarcomatous, chondrosarcomatous, and/or rhabdomyosarcomatous elements.<sup>10</sup>
  - ▶ 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.<sup>14</sup> 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.<sup>14</sup>

**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.<sup>15-18</sup>
  - ▶ *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.<sup>19,20</sup> 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.<sup>19,21</sup> 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).<sup>22</sup>

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

[Continued](#)  
[References](#)

PM-A  
2 OF 8

## 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.<sup>23-25</sup> 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.<sup>26</sup>
- 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.<sup>27</sup>
- Recently, GATA3 has been explored as a potential diagnostic marker for sarcomatoid mesotheliomas since GATA3 is expressed in only ~10%–20% of sarcomatoid carcinoma<sup>28</sup> and strongly expressed in all sarcomatoid/desmoplastic mesotheliomas.<sup>29</sup>

**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.<sup>22</sup>
  - ▶ 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.<sup>30</sup> 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<sup>31-37</sup> but in <20% of sarcomatoid type.<sup>38</sup>
  - ▶ MTAP IHC has been used as a diagnostic marker for mesothelioma.<sup>39</sup> *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<sup>39</sup> and has been reported in ~40%–60% of mesothelioma but rarely in reactive proliferations.<sup>35-37</sup>
  - ▶ Although MTAP alone is not sensitive, combined use of BAP1 and MTAP IHC may improve sensitivity and specificity.<sup>35-37</sup> Since ~10%–20% of lung adenocarcinomas have MTAP loss,<sup>36</sup> 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.<sup>22</sup>

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

[Continued](#)  
[References](#)

PM-A  
3 OF 8



### 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.<sup>40</sup>
  - ▶ Patients with mesothelioma with germline *BAP1* mutations have a prolonged survival.<sup>41,42</sup>
  - ▶ *ALK* rearrangements by IHC found in rare patients with peritoneal mesothelioma<sup>43-46</sup> have shown dramatic response with *ALK* inhibitor therapies.<sup>47,48</sup>
- 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.<sup>49</sup>
- 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.<sup>50</sup>
- 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.<sup>51-53</sup>
  - ▶ 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.<sup>54</sup>
  - ▶ Hemizygous loss of *NF2* by FISH is present in ~50% of pleural mesotheliomas.<sup>55</sup>
- 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.<sup>56</sup>

#### Molecular Features

- Most mesotheliomas are characterized by recurrent mutations in tumor suppressors and epigenetic regulators, including *BAP1*, *NF2*, *TP53*, *SETD2*, and other genes.<sup>56-60</sup> 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.<sup>58</sup> *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.<sup>56-58,61-63</sup>
- 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*.<sup>56</sup>
- Peritoneal mesothelioma has distinct molecular features compared to pleural mesothelioma.<sup>64</sup>

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

[Continued](#)  
[References](#)

PM-A  
4 OF 8

### PRINCIPLES OF PATHOLOGIC REVIEW

#### Molecular Features (continued)

- Oncogenic *EWSR1::ATF1* fusion has been described in pleural and peritoneal mesotheliomas in young adults.<sup>64,65</sup>
  - ▶ *ALK* rearrangements have been identified in rare patients with peritoneal mesothelioma.<sup>43-45,48</sup>
- 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*.<sup>42,66,67</sup> 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.<sup>42,66,68</sup>

#### 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.<sup>1</sup>
  - ▶ *Localized pleural mesothelioma* is microscopically identical to mesothelioma, although it is radiographically and grossly solitary and circumscribed.<sup>15-17</sup> Genetically, localized pleural mesothelioma includes three groups (*BAP1*-mutant, *TRAF7*-mutant, and near-haploid), with similarities but also differences from pleural mesothelioma.<sup>18</sup>
  - ▶ *WDPMT*, often an incidental finding in the peritoneum of females, can occur in the pleura,<sup>69</sup> and is genetically characterized by recurrent mutations in *TRAF7* or *CDC42*.<sup>70</sup> Infrequently, WDPMT shows back-to-back papillae with foci of invasion,<sup>71</sup> 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.<sup>72</sup>
  - ▶ *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.

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

#### References





### PRINCIPLES OF PATHOLOGIC REVIEW — REFERENCES

- <sup>1</sup> WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Thoracic Tumours. 5th ed. Lyon, France: International Agency for Research on Cancer; 2021.
- <sup>2</sup> Moolgavkar SH, Meza R, Turim J. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973-2005. *Cancer Causes Control* 2009;20:935-944.
- <sup>3</sup> Beebe-Dimmer JL, Fryzek JP, Yee CL, et al. Mesothelioma in the United States: a surveillance, epidemiology, and end results (SEER)-Medicare investigation of treatment patterns and overall survival. *Clin Epidemiol* 2016;8:743-750.
- <sup>4</sup> Sauter JL, Dacic S, Galateau-Salle F, et al. The 2021 WHO classification of tumors of the pleura: advances since the 2015 classification. *J Thorac Oncol* 2022;17:608-622.
- <sup>5</sup> Husain AN, Colby T, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2013;137:647-667.
- <sup>6</sup> Ordonez NG. Mesothelioma with rhabdoid features: an ultrastructural and immunohistochemical study of 10 cases. *Mod Pathol* 2006;19:373-383.
- <sup>7</sup> Ordonez NG. Deciduoid mesothelioma: report of 21 cases with review of the literature. *Mod Pathol* 2012;25:1481-1495.
- <sup>8</sup> Ordonez NG. Mesotheliomas with small cell features: report of eight cases. *Mod Pathol* 2012;25:689-698.
- <sup>9</sup> Wilson GE, Hasleton PS, Chatterjee AK. Desmoplastic malignant mesothelioma: a review of 17 cases. *J Clin Pathol* 1992;45:295-298.
- <sup>10</sup> Klebe S, Brownlee NA, Mahar A, et al. Sarcomatoid mesothelioma: a clinical-pathologic correlation of 326 cases. *Mod Pathol* 2010;23:470-479.
- <sup>11</sup> Henderson DW, Attwood HD, Constance TJ, et al. Lymphohistiocytoid mesothelioma: a rare lymphomatoid variant of predominantly sarcomatoid mesothelioma. *Ultrastruct Pathol* 1988;12:367-384.
- <sup>12</sup> Yao DX, Shia J, Erlandson RA, et al. Lymphohistiocytoid mesothelioma: a clinical, immunohistochemical and ultrastructural study of four cases and literature review. *Ultrastruct Pathol* 2004;28:213-228.
- <sup>13</sup> Galateau-Salle F, Attanoos R, Gibbs AR, et al. Lymphohistiocytoid variant of malignant mesothelioma of the pleura: a series of 22 cases. *Am J Surg Pathol* 2007;31:711-716.
- <sup>14</sup> Chirieac LR, Hung YP, Foo WC, et al. Diagnostic value of biopsy sampling in predicting histology in patients with diffuse malignant pleural mesothelioma. *Cancer* 2019;125:4164-4171.
- <sup>15</sup> Okike N, Bernatz PE, Woolner LB. Localized mesothelioma of the pleura: benign and malignant variants. *J Thorac Cardiovasc Surg* 1978;75:363-372.
- <sup>16</sup> Allen TC, Cagle PT, Churg AM, et al. Localized malignant mesothelioma. *Am J Surg Pathol* 2005;29:866-873.
- <sup>17</sup> Marchevsky AM, Khoo A, Walts AE, et al. Localized malignant mesothelioma, an unusual and poorly characterized neoplasm of serosal origin: best current evidence from the literature and the International Mesothelioma Panel. *Mod Pathol* 2020;33:281-296.
- <sup>18</sup> Hung YP, Dong F, Dubuc AM, et al. Molecular characterization of localized pleural mesothelioma. *Mod Pathol* 2020;33:271-280.
- <sup>19</sup> Churg A, Colby TV, Cagle P, et al. The separation of benign and malignant mesothelial proliferations. *Am J Surg Pathol* 2000;24:1183-1200.
- <sup>20</sup> Churg A, Galateau-Salle F. The separation of benign and malignant mesothelial proliferations. *Arch Pathol Lab Med* 2012;136:1217-1226.
- <sup>21</sup> Churg A, Cagle P, Colby TV, et al. The fake fat phenomenon in organizing pleuritis: a source of confusion with desmoplastic malignant mesotheliomas. *Am J Surg Pathol* 2011;3:1823-1829.
- <sup>22</sup> Churg A, Naso JR. The separation of benign and malignant mesothelial proliferations: new markers and how to use them. *Am J Surg Pathol* 2020;44:e100-e112.
- <sup>23</sup> Ordonez NG. Immunohistochemical diagnosis of epithelioid mesothelioma: an update. *Arch Pathol Lab Med* 2005;129:1407-1414.
- <sup>24</sup> Facchetti F, Gentili F, Lonardi S, et al. Claudin-4 in mesothelioma diagnosis. *Histopathology* 2007;51:261-263.
- <sup>25</sup> Anttila S. Epithelioid lesions of the serosa. *Arch Pathol Lab Med* 2012;13:241-252.
- <sup>26</sup> Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 Update of the consensus statement from the international mesothelioma interest group. *Arch Pathol Lab Med* 2018;142:89-108.
- <sup>27</sup> Chirieac LR, Pinkus GS, Pinkus JL, et al. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. *Am J Cancer Res* 2011;1:14-24.
- <sup>28</sup> Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. *Am J Surg Pathol* 2014;38:13-22.
- <sup>29</sup> Berg KB, Churg A. GATA3 immunohistochemistry for distinguishing sarcomatoid and desmoplastic mesothelioma from sarcomatoid carcinoma of the lung. *Am J Surg Pathol* 2017;41:1221-1225.
- <sup>30</sup> Carbone M, Yang H, Pass HI, et al. BAP1 and cancer. *Nat Rev Cancer* 2013;13:153-159.

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

[Continued](#)

### PRINCIPLES OF PATHOLOGIC REVIEW — REFERENCES

- <sup>31</sup> Sheffield BS, Hwang HC, Lee AF, et al. BAP1 immunohistochemistry and p16 FISH to separate benign from malignant mesothelial proliferations. *Am J Surg Pathol* 2015;39:977-982.
- <sup>32</sup> Cigognetti M, Lonardi S, Fisogni S, et al. BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations. *Mod Pathol* 2015;28:1043-1057.
- <sup>33</sup> Andrici J, Jung J, Sheen A, et al. Loss of BAP1 expression is very rare in peritoneal and gynecologic serous adenocarcinomas and can be useful in the differential diagnosis with abdominal mesothelioma. *Hum Pathol* 2016;51:9-15.
- <sup>34</sup> Carbone M, Shimizu D, Napolitano A, et al. Positive nuclear BAP1 immunostaining helps differentiate non-small cell lung carcinomas from malignant mesothelioma. *Oncotarget* 2016;7:59314-59321.
- <sup>35</sup> Hida T, Hamasaki M, Matsumoto S, et al. Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: Comparison with 9p21 FISH and BAP1 immunohistochemistry. *Lung Cancer* 2017;104:98-105.
- <sup>36</sup> Berg KB, Dacic S, Miller C, et al. Utility of methylthioadenosine phosphorylase compared with BAP1 immunohistochemistry, and CDKN2A and NF2 fluorescence in situ hybridization in separating reactive mesothelial proliferations from epithelioid malignant mesotheliomas. *Arch Pathol Lab Med* 2018;142:1549-1553.
- <sup>37</sup> Kinoshita Y, Hamasaki M, Yoshimura M, et al. A combination of MTAP and BAP1 immunohistochemistry is effective for distinguishing sarcomatoid mesothelioma from fibrous pleuritis. *Lung Cancer* 2018;125:198-204.
- <sup>38</sup> Hwang HC, Sheffield BS, Rodriguez S, et al. Utility of BAP1 immunohistochemistry and p16 (CDKN2A) FISH in the diagnosis of malignant mesothelioma in effusion cytology specimens. *Am J Surg Pathol* 2016;40:120-126.
- <sup>39</sup> Chapel DB, Schulte JJ, Berg K, et al. MTAP immunohistochemistry is an accurate and reproducible surrogate for CDKN2A fluorescence in situ hybridization in diagnosis of malignant pleural mesothelioma. *Mod Pathol* 2020;33:245-254.
- <sup>40</sup> Chou A, Toon CW, Clarkson A, et al. The epithelioid BAP1-negative and p16-positive phenotype predicts prolonged survival in pleural mesothelioma. *Histopathology* 2018;72:509-515.
- <sup>41</sup> Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis* 2015;36:76-81.
- <sup>42</sup> Pastorino S, Yoshikawa Y, Pass HI, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. *J Clin Oncol* 2018;36:3485-3494.
- <sup>43</sup> Hung YP, Dong F, Watkins JC, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. *JAMA Oncol* 2018;4:235-238.
- <sup>44</sup> Loharamtaweethong K, Puripat N, Aoonjai N, et al. Anaplastic lymphoma kinase (ALK) translocation in paediatric malignant peritoneal mesothelioma: a case report of novel ALK-related tumour spectrum. *Histopathology* 2016;68:603-607.
- <sup>45</sup> Mian I, Abdullaev Z, Morrow B, et al. Anaplastic lymphoma kinase gene rearrangement in children and young adults with mesothelioma. *J Thorac Oncol* 2020;15:457-461.
- <sup>46</sup> Argani P, Lian DWQ, Agaimy A, et al. Pediatric mesothelioma with ALK fusions: a molecular and pathologic study of 5 cases. *Am J Surg Pathol* 2021;45:653-661.
- <sup>47</sup> Ruschoff JH, Gradhand E, Kahraman A, et al. STRN-ALK rearranged malignant peritoneal mesothelioma with dramatic response following ceritinib treatment. *JCO Precision Oncol* 2019;3:1-6.
- <sup>48</sup> Sakata S, Rees H, Parke S, et al. Complete pathological response after ceritinib for anaplastic lymphoma kinase-rearranged epithelioid peritoneal mesothelioma. *ANZ J Surg* 2021;91:475-476.
- <sup>49</sup> Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015;33:1974-1982.
- <sup>50</sup> Sandberg AA, Bridge JA. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors. *Mesothelioma. Cancer Genet Cytogenet* 2001;127:93-110.
- <sup>51</sup> Illei PB, Rusch VW, Zakowski MF, et al. Homozygous deletion of CDKN2A and codeletion of the methylthioadenosine phosphorylase gene in the majority of pleural mesotheliomas. *Clin Cancer Res* 2003;9:2108-2113.
- <sup>52</sup> Dacic S, Kothmaier H, Land S, et al. Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas. *Virchows Arch* 2008;453:627-635.
- <sup>53</sup> Chiosea S, Krasinskas A, Cagle PT, et al. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. *Mod Pathol* 2008;21:742-747.
- <sup>54</sup> Tochigi N, Attanoos R, Chirieac LR, et al. p16 Deletion in sarcomatoid tumors of the lung and pleura. *Arch Pathol Lab Med* 2013;137:632-636.
- <sup>55</sup> Kinoshita Y, Hamasaki M, Yoshimura M, et al. Hemizygous loss of NF2 detected by fluorescence in situ hybridization is useful for the diagnosis of malignant pleural mesothelioma. *Mod Pathol* 2020;33:235-244.
- <sup>56</sup> Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. *Cancer Discov* 2018;8:1548-1565.
- <sup>57</sup> Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. *Cancer Res* 2015;75:264-269.

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

[Continued](#)

**PM-A**  
**7 OF 8**





### PRINCIPLES OF PATHOLOGIC REVIEW — REFERENCES

- <sup>58</sup> Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016;48:407-416.
- <sup>59</sup> Blum Y, Meiller C, Quetel L, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. *Nat Commun* 2019;10:1333.
- <sup>60</sup> Quetel L, Meiller C, Assie JB, et al. Genetic alterations of malignant pleural mesothelioma: association to tumor heterogeneity and overall survival. *Mol Oncol* 2020;14:1207-1223.
- <sup>61</sup> Bott M, Brevet M, Taylor BS, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma. *Nat Genet* 2011;43:668-672.
- <sup>62</sup> Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. *J Thorac Oncol* 2015;10:492-499.
- <sup>63</sup> Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, et al. High-density array-CGH with targeted NGS unmask multiple noncontiguous minute deletions on chromosome 3p21 in mesothelioma. *Proc Natl Acad Sci U S A* 2016;113:13432-13437.
- <sup>64</sup> Offin M, Yang SR, Egger J, et al. Molecular characterization of peritoneal mesotheliomas. *J Thorac Oncol* 2022;17:455-460.
- <sup>65</sup> Desmeules P, Joubert P, Zhang L, et al. A subset of malignant mesotheliomas in young adults are associated with recurrent EWSR1/FUS-ATF1 fusions. *Am J Surg Pathol* 2017;41:980-988.
- <sup>66</sup> Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *J Clin Oncol* 2018;36:2863-2871.
- <sup>67</sup> Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. *Proc Natl Acad Sci U S A* 2019;116:9008-9013.
- <sup>68</sup> Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. *Cancer Res* 2016;76:206-215.
- <sup>69</sup> Galateau-Salle F, Vignaud JM, Burke L, et al. Well-differentiated papillary mesothelioma of the pleura: a series of 24 cases. *Am J Surg Pathol* 2004;28:534-540.
- <sup>70</sup> Stevers M, Rabban JT, Garg K, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42. *Mod Pathol* 2019;32:88-99.
- <sup>71</sup> Churg A, Allen T, Borczuk AC, et al. Well-differentiated papillary mesothelioma with invasive foci. *Am J Surg Pathol* 2014;38:990-998.
- <sup>72</sup> Goode B, Joseph NM, Stevers M, et al. Adenomatoid tumors of the male and female genital tract are defined by TRAF7 mutations that drive aberrant NF-κB pathway activation. *Mod Pathol* 2018;31:660-673.

**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.<sup>a</sup> 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<sup>1</sup>** are palliative options for symptomatic pleural disease.

<sup>a</sup> 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.

<sup>1</sup> Abtin F, Quirk MT, Suh RD, et al. Percutaneous cryoablation for the treatment of recurrent malignant pleural mesothelioma: safety, early-term efficacy, and predictors of local recurrence. J Vasc Interv Radiol 2017;28:213-221.

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

HISTOLOGY		PRINCIPLES OF SYSTEMIC THERAPY <sup>a,b</sup>	
	FIRST-LINE THERAPY		SUBSEQUENT THERAPY
Epithelioid	<p><b>Preferred</b></p> <ul style="list-style-type: none"> <li>• (Cisplatin or carboplatin) + pemetrexed<sup>1-4</sup> (category 1)</li> <li>• (Cisplatin or carboplatin) + pemetrexed + bevacizumab<sup>5-7,c</sup> (category 1)</li> <li>• (Cisplatin or carboplatin) + pemetrexed + pembrolizumab<sup>8</sup> (category 1)</li> <li>• Nivolumab/ipilimumab<sup>9</sup> (category 1)</li> </ul> <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• (Cisplatin or carboplatin) + gemcitabine<sup>10-12</sup></li> <li>• Pemetrexed<sup>13</sup></li> <li>• Vinorelbine<sup>14</sup></li> </ul>	Progression	<p><b>Preferred (if chemotherapy first line)<sup>d</sup></b></p> <ul style="list-style-type: none"> <li>• Nivolumab<sup>e</sup> ± ipilimumab<sup>15-17</sup></li> </ul> <p><b>Preferred (if nivolumab/ipilimumab first line)</b></p> <ul style="list-style-type: none"> <li>• (Cisplatin or carboplatin) + pemetrexed<sup>1-4</sup></li> <li>• (Cisplatin or carboplatin) + pemetrexed + bevacizumab<sup>5-7,c</sup></li> <li>• Pemetrexed (category 1)<sup>18,19</sup></li> </ul> <p><b>Other Recommended</b></p> <ul style="list-style-type: none"> <li>• Gemcitabine<sup>20,21</sup> ± ramucirumab<sup>22</sup></li> <li>• Vinorelbine<sup>23,24</sup></li> </ul>
Biphasic or Sarcomatoid	<p><b>Preferred</b></p> <ul style="list-style-type: none"> <li>• Nivolumab/ipilimumab<sup>9</sup> (category 1)</li> <li>• (Cisplatin or carboplatin) + pemetrexed + pembrolizumab<sup>8</sup> (category 1)</li> </ul> <p><b>Other Recommended</b></p> <ul style="list-style-type: none"> <li>• (Cisplatin or carboplatin) + pemetrexed<sup>1-4</sup> (category 1)</li> <li>• (Cisplatin or carboplatin) + pemetrexed + bevacizumab<sup>5-7,c</sup> (category 1)</li> </ul> <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• (Cisplatin or carboplatin) + gemcitabine<sup>10-12</sup></li> <li>• Pemetrexed<sup>13</sup></li> <li>• Vinorelbine<sup>14</sup></li> </ul>	Progression	<p><b>Preferred (if nivolumab/ipilimumab first-line)</b></p> <ul style="list-style-type: none"> <li>• (Cisplatin or carboplatin) + pemetrexed<sup>1-4</sup></li> <li>• (Cisplatin or carboplatin) + pemetrexed + bevacizumab<sup>5-7,c</sup></li> <li>• Pemetrexed (category 1)<sup>18,19</sup></li> </ul> <p><b>Preferred (if chemotherapy first-line)<sup>d</sup></b></p> <ul style="list-style-type: none"> <li>• Nivolumab<sup>e</sup> ± ipilimumab<sup>15-17</sup></li> </ul> <p><b>Other Recommended</b></p> <ul style="list-style-type: none"> <li>• Gemcitabine<sup>20,21</sup> ± ramucirumab<sup>22</sup></li> <li>• Vinorelbine<sup>23,24</sup></li> </ul>

[References PM-C \(2 of 3\)](#)

<sup>a</sup> All regimens may also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.

<sup>b</sup> 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.<sup>25</sup>

<sup>c</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>d</sup> Consider rechallenge with pemetrexed-based therapy, if good response to front-line pemetrexed-based treatment.<sup>26</sup>

<sup>e</sup> Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

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



### PRINCIPLES OF SYSTEMIC THERAPY — REFERENCES

- <sup>1</sup> Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636-2644.
- <sup>2</sup> Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma. *Ann Oncol* 2008;19:370-373.
- <sup>3</sup> Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol* 2006;24:1443-1448.
- <sup>4</sup> Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma. *J Thorac Oncol* 2008;3:756-763.
- <sup>5</sup> Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. *Br J Cancer* 2013;109:552-558.
- <sup>6</sup> Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, Phase 3 trial. *Lancet* 2016;387:1405-1414.
- <sup>7</sup> Popat S, Felip E, Dafni U, et al. BEAT-meso: A randomized phase III study of bevacizumab (B) and standard chemotherapy (C) with or without atezolizumab (A), as first-line treatment (TX) for advanced pleural mesothelioma (PM)—Results from the ETOP 13-18 trial. *J Clin Oncol* 2024;42(Suppl):Abstract LBA8002.
- <sup>8</sup> Chu Q, Perrone F, Greillier L, et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomised controlled trial. *Lancet* 2023; 16;402:2295-2306.
- <sup>9</sup> Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label phase 3 trial. *Lancet* 2021;397:375-386.
- <sup>10</sup> Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491-496.
- <sup>11</sup> Van Haarst JM, Baas J, Manegold CH, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002;86:342-345.
- <sup>12</sup> Favaretto AG, Aversa SM, Paccagnella A, et al. Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric phase II study. *Cancer* 2003;97:2791-2797.
- <sup>13</sup> Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol* 2008;3:764-771.
- <sup>14</sup> Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685-1694.
- <sup>15</sup> Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomized, non-comparative, phase 2 trial. *Lancet Oncol* 2019;20:239-253.
- <sup>16</sup> Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet Respir Med* 2019;7:260-270.
- <sup>17</sup> Fennell DA, Ewings S, Ottensmeier C, et al; CONFIRM trial investigators. Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. *Lancet Oncol* 2021;22:1530-1540.

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

[Continued](#)



### PRINCIPLES OF SYSTEMIC THERAPY — REFERENCES

- <sup>18</sup> Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008;26:1698-1704.
- <sup>19</sup> Zucal PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. *Lung Cancer* 2012;75:360-367.
- <sup>20</sup> Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005;16:923-927.
- <sup>21</sup> van Meerbeeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer* 1999;85:2577-2582.
- <sup>22</sup> Pinto C, Zucali PA, Pagano M, et al. Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma (RAMES): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2021;22:1438-1447.
- <sup>23</sup> Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009;63:94-97.
- <sup>24</sup> Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung Cancer* 2014;84:271-274.
- <sup>25</sup> Leal JL, Peters G, Szaumkessel M, et al. NTRK and ALK rearrangements in malignant pleural mesothelioma, pulmonary neuroendocrine tumors and non-small cell lung cancer. *Lung Cancer* 2020;146:154-159.
- <sup>26</sup> Bearz A, Talamini R, Rossoni G, et al. Re-challenge with pemetrexed in advanced mesothelioma: a multi-institutional experience. *BMC Res Notes* 2012;5:482.

**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.<sup>1</sup>
- 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.<sup>2</sup> 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.<sup>3-5</sup>
- 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).<sup>6</sup>

#### 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  $\geq 60$  Gy should be delivered to macroscopic residual tumors if the doses to adjacent normal structures are limited to their tolerances. In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall.<sup>7-9</sup>
- Daily doses of 4 Gy appear to be more efficacious than fractions of  $<4$  Gy in providing relief from chest pain associated with mesothelioma,<sup>8,10</sup> 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
<b><u>Palliative</u></b>			
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
<b><u>Post P/D</u></b>			
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.<sup>4,11</sup> 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,<sup>12</sup> as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup>
- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
- The clinical 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.**





### PRINCIPLES OF RADIATION THERAPY — REFERENCES

- <sup>1</sup> Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet Oncol* 2016;17:1094-1104.
- <sup>2</sup> Trovo M, Relevant A, Polesel J, et al. Radical hemithoracic radiotherapy versus palliative radiotherapy in non-metastatic malignant pleural mesothelioma: results from a phase 3 randomized trial. *In J Radiat Oncol Biol Phys* 2021;109:1368-1376.
- <sup>3</sup> Rimmer A, Zauderer MG, Gomez DR, et al. Phase II study of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) as part of lung-sparing multimodality therapy in patients with malignant pleural mesothelioma. *J Clin Oncol* 2016;34:2761-2768.
- <sup>4</sup> Shaikh F, Zauderer MG, von Reibnitz D, et al. Improved outcomes with modern lung-sparing trimodality therapy in patients with malignant pleural mesothelioma. *J Thorac Oncol* 2017;12:993-1000.
- <sup>5</sup> Minatel E, Trovo M, Bearz A, et al. Radical radiation therapy after lung-sparing surgery for malignant pleural mesothelioma: survival, pattern of failure, and prognostic factors. *Int J Radiat Oncol Biol Phys* 2015;93:606-613.
- <sup>6</sup> Zeng J, Badiyan SN, Garces YI, et al. Consensus statement on proton therapy in mesothelioma. *Pract Radiat Oncol* 2021;11:119-133.
- <sup>7</sup> Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. *Chest* 1995;108:754-758.
- <sup>8</sup> de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura—a single-institution experience with 189 patients. *Int J Radiat Oncol Biol Phys* 1999;43:511-516.
- <sup>9</sup> de Bree E, van Ruth S, Baas P, et al. Cyto-reductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. *Chest* 2002;121:480-487.
- <sup>10</sup> Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: review of a 5-year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990;13:4-9.
- <sup>11</sup> Chance WW, Rice DC, Allen PK, et al. Hemithoracic intensity modulated radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. *Int J Radiat Oncol Biol Phys* 2015;91:149-156.
- <sup>12</sup> Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2007;84:1685-1692; discussion 1692-1693.
- <sup>13</sup> Allen AM, Czerminska M, Jänne PA, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640-645.
- <sup>14</sup> Krayenbuehl J, Oertel S, Davis JB, Ciernik IF. Combined photon and electron three-dimensional conformal versus intensity-modulated radiotherapy with integrated boost for adjuvant treatment of malignant pleural mesothelioma after pleuropneumectomy. *Int J Radiat Oncol Biol Phys* 2007;69:1593-1599.
- <sup>15</sup> Patel R, Ludmir EB, Miccio JA, et al. Disease-related outcomes and toxicities of intensity modulated radiation therapy after lung-sparing pleurectomy for malignant pleural mesothelioma: a systematic review. *Pract Radiat Oncol* 2020;10:423-433.

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

### PRINCIPLES OF SURGERY<sup>1</sup>

- 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.<sup>2-5</sup>
- 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.

<sup>1</sup> Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: A consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol* 2011;6:1304-1312.

<sup>2</sup> Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008;135:620-626.

<sup>3</sup> 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.

<sup>4</sup> Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. *J Thorac Oncol* 2010;5:1649-1654.

<sup>5</sup> Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011;12:763-772.

**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
<b>Stage IA</b>	T1	N0	M0
<b>Stage IB</b>	T2-T3	N0	M0
<b>Stage II</b>	T1-T2	N1	M0
<b>Stage IIIA</b>	T3	N1	M0
<b>Stage IIIB</b>	T1-T3	N2	M0
	T4	Any N	M0
<b>Stage IV</b>	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

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



NCCN Categories of Evidence and Consensus	
<b>Category 1</b>	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.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	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	
<b>Preferred intervention</b>	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
<b>Other recommended intervention</b>	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
<b>Useful in certain circumstances</b>	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



### Discussion

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

### Table of Contents

Overview .....	MS-2
Literature Search Criteria and Guidelines Update Methodology .....	MS-3
Diagnosis .....	MS-3
Presentation and Evaluation .....	MS-3
Pathology .....	MS-3
Management .....	MS-4
Pretreatment Evaluation .....	MS-5
Staging .....	MS-5
Surgery .....	MS-5
Systemic Therapy .....	MS-7
Medically Operable PM .....	MS-7
Medically Inoperable PM .....	MS-8
Subsequent Systemic Therapy .....	MS-10
Radiation Therapy .....	MS-11
Summary .....	MS-13
References .....	MS-14



## 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.<sup>1-5</sup> 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.<sup>6-9</sup> 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.<sup>2,10-14</sup> 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]).<sup>14-17</sup>

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.<sup>1,18-21</sup> The mortality burden from asbestos-related diseases in the United States did not change from 1999 to 2015.<sup>10,22,23</sup> Although asbestos is no longer mined in the United States, it is still imported.<sup>21</sup> The incidence of PM is increasing in other countries such as Russia, Western Europe, China, and India.<sup>3,20,24-29</sup> 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.<sup>12,24,25,30</sup> Russia, China, Brazil, and Canada are the top producers of asbestos.<sup>31</sup>

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.<sup>32-42</sup> Two meta-analyses suggest that non-occupational exposure to asbestos is a risk factor for PM.<sup>43,44</sup> Data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma.<sup>45-48</sup> Genetic factors may also play a role in PM, with rare families carrying a germline mutation in the *BRCA1*-associated protein-1 (*BAP1*) gene.<sup>45,49-58</sup> Patients with germline *BAP1* mutations have prolonged survival.<sup>53,56</sup> *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).<sup>59-63</sup> Smoking is not a risk factor for mesothelioma.<sup>64</sup> However, patients who smoke and have been exposed to asbestos are at increased risk for lung cancer.<sup>65</sup> 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](http://www.NCCN.org)).<sup>66</sup> Some patients who have been exposed to asbestos only have benign pleural disease, although they may have significant chest pain.<sup>67,68</sup> 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).<sup>31,65,69-75</sup> 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.<sup>31,65,76-79</sup>

### 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](http://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](http://www.NCCN.org)).<sup>30,80,81</sup> 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.<sup>69</sup>

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).<sup>30,31,69,82-87</sup> However, cytologic samples are often negative even when patients have PM.<sup>88,89</sup> 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.<sup>30</sup>

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

### 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.<sup>4,63,114,115</sup> 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).<sup>63</sup>

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.<sup>26,116-123</sup> Almost all PMs are diffuse (>99%); however, rare cases of localized pleural mesothelioma have been diagnosed, which are less aggressive.<sup>124-128</sup> It is also difficult to distinguish localized PM from diffuse PM.<sup>124</sup> 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.<sup>69,88,89,129,130</sup> 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]).<sup>69,88,117,120,122,131,132</sup> A panel of two positive mesothelial markers and two negative markers is recommended for diagnosis of PM.<sup>117</sup> The presence or absence of *BAP1* nuclear expression assessed by immunohistochemistry can be used in the differential diagnosis of mesothelioma.<sup>133-135</sup>

Rare driver mutations have been identified in patients with PM, such as *EWSR1-ATF1* fusions, *TP53*, *NF2*, *SETDB1*, or *SETD2*.<sup>59-62,136,137</sup> 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.<sup>136,138-141</sup> *NTRK* and *ALK* fusions have been identified in patients with PM, although at very low frequencies (0.6%).<sup>138,142,143</sup> Targeted agents are available for *NTRK* and *ALK* fusions (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at [www.NCCN.org](http://www.NCCN.org)). Patients with PM have low tumor mutational burden.<sup>60,61</sup> 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.<sup>60,138</sup>

## 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.<sup>4</sup> 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.<sup>144-151</sup> Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.<sup>147,150</sup> Nodal status and response to systemic therapy can affect survival.<sup>150,152</sup> Appropriate patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists to assess if they are candidates for multimodality treatment. 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).<sup>148-154</sup> 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).<sup>155,156</sup> 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.<sup>69,90-95,99,157-159</sup> 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.<sup>30</sup>

### 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.<sup>83,84,160</sup> 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;<sup>161,162</sup> 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).<sup>163</sup> 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).<sup>164-166</sup> 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.<sup>166,167</sup> However, PET/CT is useful for determining whether metastatic disease is present.<sup>167,168</sup> 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.<sup>169-172</sup>

### Surgery

Surgery is recommended as a component of combined modality therapy for certain patients with stage I to IIIA PM who are medically operable.<sup>173</sup> The NCCN Panel recommends surgery for certain patients with clinical stage I to IIIA PM and epithelioid histology.<sup>174</sup> Surgery may be considered for certain patients with early-stage PM who have biphasic histology.<sup>147,175</sup> 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).<sup>176</sup> Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.<sup>176</sup> 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](http://www.NCCN.org)). The surgical goal for PM is cytoreductive surgery to achieve macroscopic complete resection by removing all visible or palpable tumors.<sup>177,178</sup> 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.<sup>4,30,69,173,179-187</sup> Neither EPP nor P/D will yield an R0 resection.<sup>4,188,189</sup> EPP would often be required to remove all gross tumor in patients with stages II to IIIA PM.<sup>81</sup> However, EPP is associated with higher morbidity and mortality.<sup>183,190</sup> P/D (ie, lung-preserving surgery) is safer than EPP.<sup>190-197</sup> 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.<sup>4,195</sup> Another retrospective analysis compared EPP (n = 187) versus P/D (n = 95) in patients with PM.<sup>198</sup> 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.<sup>15,183</sup> 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.<sup>180</sup> 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.<sup>188,199</sup>

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.<sup>200</sup> 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.<sup>201</sup> An Australian retrospective study (540 patients) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and treatment with pemetrexed.<sup>202</sup>

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.<sup>183,195,200,203,204</sup> 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.<sup>11,204</sup> 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.<sup>191</sup> P/D may also be useful for

symptom control (eg, patients with entrapped lung syndrome, recurrent pleural effusions).<sup>31</sup> 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.<sup>184,205-207</sup> All of the regimens recommended for PM can also be used for peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.<sup>7,208-210</sup>

#### Medically Operable PM

Trimodality therapy—using chemotherapy, surgery, and hemithoracic RT—has been studied in patients with medically operable PM.<sup>144-151</sup> Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.<sup>147,150</sup> Nodal status and response to chemotherapy can affect survival.<sup>150,152</sup> 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.<sup>211-220</sup>

A phase 2 trial assessed trimodality therapy in 77 eligible patients with resectable PM.<sup>150</sup> 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.<sup>147</sup> 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.<sup>151</sup> 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.<sup>195</sup> 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.<sup>147,150,151</sup> 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.<sup>221</sup> 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.<sup>222</sup> 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; 95% 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).<sup>222</sup> 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](http://www.NCCN.org)).<sup>223-225</sup> 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,  $P = .02$ ).<sup>226</sup> The



pemetrexed/carboplatin regimen was assessed in three large phase 2 studies (median survival = 12.7, 14, and 14 months, respectively).<sup>227-229</sup> 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.<sup>230</sup> The NCCN Panel recommends cisplatin/pemetrexed (category 1) for patients with PM based on clinical trial data and the FDA approval.<sup>222,226,231-234</sup> The panel also recommends pemetrexed/carboplatin (category 2A) based on clinical trial data.<sup>222,227-229</sup> Carboplatin regimens are recommended for patients who are not eligible for cisplatin.<sup>230</sup>

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.<sup>234</sup> 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).<sup>234</sup> Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity.<sup>69</sup> 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.<sup>235</sup> 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.<sup>235</sup> Gemcitabine/cisplatin was assessed in phase 2 studies (median survival, 9.6–14.1 months).<sup>236-238</sup> 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.<sup>236-238</sup> Other first-line options recommended by NCCN include pemetrexed or vinorelbine for patients who are not candidates for platinum-based combination therapy.<sup>239-241</sup>

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.<sup>222,226,228-230</sup> For the 2022 update (Version 1), the panel decided that the pemetrexed/platinum with or without bevacizumab regimens were preferred options.<sup>222,226-234</sup> 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.<sup>237,238,240,241</sup>

### Subsequent Systemic Therapy

Limited data are available to guide second-line and beyond (subsequent) chemotherapy in patients with PM.<sup>220,242-245</sup> 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.<sup>246-257</sup> Response rates have been low with subsequent chemotherapy (7%–20%), although they are slightly higher with the new immunotherapy regimens.<sup>247-249,258,259</sup>

### 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.<sup>246</sup> 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.<sup>247,252,253</sup> 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.<sup>247,253</sup> 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.<sup>247</sup> 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).<sup>247</sup> A phase 2 Dutch trial (INITIATE) assessed nivolumab/ipilimumab as subsequent therapy in patients with PM.<sup>248</sup> 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.<sup>248</sup> 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.<sup>260</sup> 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.<sup>261</sup> 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.<sup>242,259</sup> 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;  $P < .001$ ).<sup>259</sup>

### 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).<sup>69,250-253,261</sup> 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.<sup>240,242,259-266</sup> 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.<sup>260</sup> 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](http://www.NCCN.org)).<sup>223-225</sup>

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.<sup>69,250-253,259,261</sup> The panel voted that the following regimens are other recommended options: 1) vinorelbine; or 2) gemcitabine.<sup>260</sup>

### 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.<sup>267</sup> 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](http://www.NCCN.org)).<sup>30,155,268</sup> The dose of radiation should be based on the purpose of treatment.<sup>269</sup> 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.<sup>270-273</sup> 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.<sup>155,274</sup>

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.<sup>275</sup> 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.<sup>276</sup> 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.<sup>277</sup> 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.<sup>275-277</sup>

It has been controversial whether immediate (prophylactic) RT is useful for preventing instrument-tract recurrence after pleural intervention.<sup>278-283</sup> An older French trial reported that prophylactic RT was useful for preventing recurrence, but 2 other trials did not find any benefit.<sup>278,282,283</sup> 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.<sup>284</sup> 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).<sup>148,189,273,274,284-287</sup> Several prophylactic RT dose regimens are cited in the literature.<sup>278,282-284</sup>

CT simulation–guided planning using either IMRT or conventional photon/electron RT is acceptable.<sup>147,270,272,288</sup> 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](http://www.NCCN.org)).<sup>154</sup> The volume of postoperative radiation should cover the surgical bed within the thorax.<sup>148,189,273,274,286,287</sup> The optimal dose of RT for palliative purposes remains unclear.<sup>269,289</sup> For patients with chest pain from PM, total doses of 20 to 40 Gy appear to be effective in providing relief from pain.<sup>30,278,279</sup>

Hemithoracic pleural IMRT allows for a more conformal high-dose RT and improved coverage to the hemithorax at risk.<sup>154,155,270,271,275,276,290-293</sup>

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).<sup>267,294</sup> Intensity-modulated proton therapy (IMPT) may also be used.<sup>295</sup> RT to the contralateral uninvolved lung should be minimized,<sup>155,271,296</sup> because fatal pneumonitis may occur with IMRT if strict limits are not applied.<sup>297-299</sup> The contralateral uninvolved mean lung dose should be kept as low as possible, preferably less than 8.5 Gy.<sup>300</sup> The volume of contralateral lung receiving low-dose RT (eg, 5 Gy) should be minimized.<sup>301,302</sup> 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%.<sup>292</sup> 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.<sup>6-9</sup> 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](http://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.<sup>222,226-234</sup> The NCCN Panel deleted pembrolizumab as a subsequent therapy option for patients with relapsed PM based on updated clinical trial data.<sup>260</sup> 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).



### References

1. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Bethesda, MD: National Cancer Institute. Available at: [https://seer.cancer.gov/csr/1975\\_2015/](https://seer.cancer.gov/csr/1975_2015/).
2. Special Section – Rare Cancers in Adults. American Cancer Society. Cancer Facts & Figures 2017. Available at: <https://tinyurl.com/yb4joe3c>.
3. Price B, Ware A. Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005. *Crit Rev Toxicol* 2009;39:576-588. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19650718>.
4. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant pleural mesothelioma. *J Clin Oncol* 2009;27:2081-2090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19255316>.
5. SEER\*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program [Cited 2022 October 4] National Cancer Institute. Available at: <https://seer.cancer.gov/statistics-network/explorer/>.
6. Grogg JB, Fronzaroli JN, Oliveira P, et al. Clinicopathological characteristics and outcomes in men with mesothelioma of the tunica vaginalis testis: analysis of published case-series data. *J Cancer Res Clin Oncol* 2021;147:2671-2679. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33559739>.
7. Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. *Lung Cancer* 2009;64:211-218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19042053>.
8. Mirarabshahii P, Pillai K, Chua TC, et al. Diffuse malignant peritoneal mesothelioma--an update on treatment. *Cancer Treat Rev* 2012;38:605-612. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22104079>.
9. Chekol SS, Sun CC. Malignant mesothelioma of the tunica vaginalis testis: diagnostic studies and differential diagnosis. *Arch Pathol Lab Med* 2012;136:113-117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22208496>.
10. Mazurek JM, Syamlal G, Wood JM, et al. Malignant Mesothelioma Mortality - United States, 1999-2015. *MMWR Morb Mortal Wkly Rep* 2017;66:214-218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28253224>.
11. Meyerhoff RR, Yang CF, Speicher PJ, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. *J Surg Res* 2015;196:23-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25791825>.
12. Musk AW, Olsen N, Alfonso H, et al. Predicting survival in malignant mesothelioma. *Eur Respir J* 2011;38:1420-1424. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21737558>.
13. Linton A, Pavlakis N, O'Connell R, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. *Br J Cancer* 2014;111:1860-1869. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25188323>.
14. Mazurek JM, Blackley DJ, Weissman DN. Malignant Mesothelioma Mortality in Women - United States, 1999-2020. *MMWR Morb Mortal Wkly Rep* 2022;71:645-649. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35552365>.
15. Taioli E, Wolf AS, Camacho-Rivera M, et al. Determinants of Survival in Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients. *PLoS One* 2015;10:e0145039. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26660351>.



16. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. *J Occup Med* 1992;34:718-721. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1494965>.
17. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canada. *Cancer* 1980;46:2736-2740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7448712>.
18. Alpert N, van Gerwen M, Taioli E. Epidemiology of mesothelioma in the 21(st) century in Europe and the United States, 40 years after restricted/banned asbestos use. *Transl Lung Cancer Res* 2020;9:S28-S38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32206568>.
19. Delgermaa V, Takahashi K, Park EK, et al. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bull World Health Organ* 2011;89:716-724, 724A-724C. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22084509>.
20. Park EK, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect* 2011;119:514-518. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21463977>.
21. Centers for Disease C, Prevention. Malignant mesothelioma mortality--United States, 1999-2005. *MMWR Morb Mortal Wkly Rep* 2009;58:393-396. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19390506>.
22. Keshava HB, Tang A, Siddiqui HU, et al. Largely unchanged annual incidence and overall survival of pleural mesothelioma in the USA. *World J Surg* 2019;43:3239-3247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31428834>.
23. Bang KM, Mazurek JM, Wood JM, Hendricks SA. Diseases attributable to asbestos exposure: years of potential life lost, United States, 1999-2010. *Am J Ind Med* 2014;57:38-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24108494>.
24. Abdel-Rahman O. Global trends in mortality from malignant mesothelioma: Analysis of WHO mortality database (1994-2013). *Clin Respir J* 2018;12:2090-2100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29424961>.
25. Nishikawa K, Takahashi K, Karjalainen A, et al. Recent mortality from pleural mesothelioma, historical patterns of asbestos use, and adoption of bans: a global assessment. *Environ Health Perspect* 2008;116:1675-1680. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19079719>.
26. Larson T, Melnikova N, Davis SI, Jamison P. Incidence and descriptive epidemiology of mesothelioma in the United States, 1999-2002. *Int J Occup Environ Health* 2007;13:398-403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18085053>.
27. Price B, Ware A. Mesothelioma trends in the United States: an update based on Surveillance, Epidemiology, and End Results Program data for 1973 through 2003. *Am J Epidemiol* 2004;159:107-112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14718210>.
28. Peto J, Decarli A, La Vecchia C, et al. The European mesothelioma epidemic. *Br J Cancer* 1999;79:666-672. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10027347>.
29. Leigh J, Davidson P, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945-2000. *Am J Ind Med* 2002;41:188-201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11920963>.
30. van Zandwijk N, Clarke C, Henderson D, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. *J Thorac Dis* 2013;5:E254-307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24416529>.
31. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J* 2010;35:479-495. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19717482>.





32. Chang ET, Lau EC, Mowat FS, Teta MJ. Therapeutic radiation for lymphoma and risk of second primary malignant mesothelioma. *Cancer Causes Control* 2017;28:971-979. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28755241>.
33. Li X, Brownlee NA, Sporn TA, et al. Malignant (Diffuse) Mesothelioma in Patients With Hematologic Malignancies: A Clinicopathologic Study of 45 Cases. *Arch Pathol Lab Med* 2015;139:1129-1136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25844559>.
34. Goodman JE, Nascarella MA, Valberg PA. Ionizing radiation: a risk factor for mesothelioma. *Cancer Causes Control* 2009;20:1237-1254. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19444627>.
35. Chirieac LR, Barletta JA, Yeap BY, et al. Clinicopathologic characteristics of malignant mesotheliomas arising in patients with a history of radiation for Hodgkin and non-Hodgkin lymphoma. *J Clin Oncol* 2013;31:4544-4549. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24248693>.
36. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol* 2007;25:1489-1497. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17372278>.
37. Deutsch M, Land SR, Begovic M, et al. An association between postoperative radiotherapy for primary breast cancer in 11 National Surgical Adjuvant Breast and Bowel Project (NSABP) studies and the subsequent appearance of pleural mesothelioma. *Am J Clin Oncol* 2007;30:294-296. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17551308>.
38. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005;97:1354-1365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16174857>.
39. Teta MJ, Lau E, Scurman BK, Wagner ME. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. *Cancer* 2007;109:1432-1438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17315168>.
40. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. *Blood* 2009;113:3679-3681. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19234144>.
41. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. *Cancer* 1996;77:1379-1385. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8608519>.
42. Witherby SM, Butnor KJ, Grunberg SM. Malignant mesothelioma following thoracic radiotherapy for lung cancer. *Lung Cancer* 2007;57:410-413. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17475364>.
43. Xu R, Barg FK, Emmett EA, et al. Association between mesothelioma and non-occupational asbestos exposure: systematic review and meta-analysis. *Environ Health* 2018;17:90. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30567579>.
44. Marsh GM, Riordan AS, Keeton KA, Benson SM. Non-occupational exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Occup Environ Med* 2017;74:838-846. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28935666>.
45. Carbone M, Kanodia S, Chao A, et al. Consensus Report of the 2015 Weinman International Conference on Mesothelioma. *J Thorac Oncol* 2016;11:1246-1262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27453164>.
46. Baumann F, Buck BJ, Metcalf RV, et al. The Presence of Asbestos in the Natural Environment is Likely Related to Mesothelioma in Young Individuals and Women from Southern Nevada. *J Thorac Oncol* 2015;10:731-737. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25668121>.



47. Van Gosen BS, Blitz TA, Plumlee GS, et al. Geologic occurrences of erionite in the United States: an emerging national public health concern for respiratory disease. *Environ Geochem Health* 2013;35:419-430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23315055>.

48. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A* 2011;108:13618-13623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21788493>.

49. Carbone M, Pass HI, Ak G, et al. Medical and surgical care of patients with mesothelioma and their relatives carrying germline BAP1 mutations. *J Thorac Oncol* 2022;17:873-889. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35462085>.

50. Sculco M, La Vecchia M, Aspesi A, et al. Diagnostics of BAP1-tumor predisposition syndrome by a multitesting approach: A ten-year-long experience. *Diagnostics (Basel)* 2022;12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35885614>.

51. Pilarski R, Carlo MI, Cebulla C, Abdel-Rahman M. BAP1 tumor predisposition syndrome. 2016 Oct 13 [updated 2022 Mar 24]. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews*(®). Seattle (WA): University of Washington, Seattle

Copyright © 1993-2022, University of Washington, Seattle. *GeneReviews* is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.

52. Walpole S, Pritchard AL, Cebulla CM, et al. Comprehensive study of the clinical phenotype of germline BAP1 variant-carrying families worldwide. *J Natl Cancer Inst* 2018;110:1328-1341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30517737>.

53. Pastorino S, Yoshikawa Y, Pass HI, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. *J Clin Oncol* 2018;JCO2018790352. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30376426>.

54. Betti M, Casalone E, Ferrante D, et al. Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma. *Cancer Lett* 2017;405:38-45. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28687356>.

55. Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer. *Cancer Res* 2016;76:206-215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26719535>.

56. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis* 2015;36:76-81. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25380601>.

57. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. *J Transl Med* 2012;10:179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22935333>.

58. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet* 2011;43:1022-1025. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21874000>.

59. Quetel L, Meiller C, Assie JB, et al. Genetic alterations of malignant pleural mesothelioma: association with tumor heterogeneity and overall survival. *Mol Oncol* 2020;14:1207-1223. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32083805>.

60. Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. *Cancer Discov* 2018;8:1548-1565. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30322867>.

61. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016;48:407-416. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26928227>.



62. Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. *Cancer Res* 2015;75:264-269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25488749>.
63. Sauter JL, Dacic S, Galateau-Salle F, et al. The 2021 WHO classification of tumors of the pleura: Advances since the 2015 classification. *J Thorac Oncol* 2022;17:608-622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35026477>.
64. Mossman BT, Lippmann M, Hesterberg TW, et al. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. *J Toxicol Environ Health B Crit Rev* 2011;14:76-121. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21534086>.
65. Kato K, Gemba K, Ashizawa K, et al. Low-dose chest computed tomography screening of subjects exposed to asbestos. *Eur J Radiol* 2018;101:124-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29571785>.
66. Sorensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg* 2012;255:1069-1079. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22566015>.
67. Allen RK, Cramond T, Lennon D, Waterhouse M. A retrospective study of chest pain in benign asbestos pleural disease. *Pain Med* 2011;12:1303-1308. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21834915>.
68. Ameille J, Brochard P, Letourneux M, et al. Asbestos-related cancer risk in patients with asbestosis or pleural plaques. *Rev Mal Respir* 2011;28:e11-17. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21742228>.
69. Kindler HL, Ismaila N, Armato SG, 3rd, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018;36:1343-1373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29346042>.
70. Felten MK, Khatab K, Knoll L, et al. Changes of mesothelin and osteopontin levels over time in formerly asbestos-exposed power industry workers. *Int Arch Occup Environ Health* 2014;87:195-204. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23423281>.
71. Casjens S, Weber DG, Johnen G, et al. Assessment of potential predictors of calretinin and mesothelin to improve the diagnostic performance to detect malignant mesothelioma: results from a population-based cohort study. *BMJ Open* 2017;7:e017104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29025836>.
72. Johnen G, Gawrych K, Raiko I, et al. Calretinin as a blood-based biomarker for mesothelioma. *BMC Cancer* 2017;17:386. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28558669>.
73. van Meerbeeck JP, Hillerdal G. Screening for mesothelioma: more harm than good? *Am J Respir Crit Care Med* 2008;178:781-782. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18832552>.
74. Roberts HC, Patsios DA, Paul NS, et al. Screening for malignant pleural mesothelioma and lung cancer in individuals with a history of asbestos exposure. *J Thorac Oncol* 2009;4:620-628. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19357540>.
75. Pass HI, Carbone M. Current status of screening for malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 2009;21:97-104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19822280>.
76. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020;382:503-513. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31995683>.
77. National Lung Screening Trial Research T. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *J Thorac Oncol* 2019;14:1732-1742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31260833>.





78. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26 Suppl 5:v31-39. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26223247>.
79. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21714641>.
80. Dyer DS, Mohammed TL, Kirsch J, et al. ACR appropriateness Criteria(R) chronic dyspnea: suspected pulmonary origin. *J Thorac Imaging* 2013;28:W64-66. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23846109>.
81. Gadgeel S, Pass H. Malignant mesothelioma. *Commun Oncol* 2006;3:215-224. Available at:
82. Rossi G, Davoli F, Poletti V, et al. When the diagnosis of mesothelioma challenges textbooks and guidelines. *J Clin Med* 2021;10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34070888>.
83. Expert Panel on Thoracic I, Bacchus L, Shah RD, et al. ACR Appropriateness Criteria Review ACR Appropriateness Criteria(R) Occupational Lung Diseases. *J Thorac Imaging* 2016;31:W1-3. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26656194>.
84. Armato SG, 3rd, Coolen J, Nowak AK, et al. Imaging in pleural mesothelioma: A review of the 12th International Conference of the International Mesothelioma Interest Group. *Lung Cancer* 2015;90:148-154. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26298162>.
85. Armato SG, 3rd, Labby ZE, Coolen J, et al. Imaging in pleural mesothelioma: a review of the 11th International Conference of the International Mesothelioma Interest Group. *Lung Cancer* 2013;82:190-196. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24018024>.
86. Kao SC, Yan TD, Lee K, et al. Accuracy of diagnostic biopsy for the histological subtype of malignant pleural mesothelioma. *J Thorac Oncol* 2011;6:602-605. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21266919>.
87. Greillier L, Cavailles A, Fraticelli A, et al. Accuracy of pleural biopsy using thoracoscopy for the diagnosis of histologic subtype in patients with malignant pleural mesothelioma. *Cancer* 2007;110:2248-2252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17886249>.
88. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of mesothelioma: Part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. *J Clin Pathol* 2013;66:847-853. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23814259>.
89. Paintal A, Raparia K, Zakowski MF, Nayar R. The diagnosis of malignant mesothelioma in effusion cytology: a reappraisal and results of a multi-institution survey. *Cancer Cytopathol* 2013;121:703-707. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24039177>.
90. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018;198:839-849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30272503>.
91. Thomas R, Fysh ETH, Smith NA, et al. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. *JAMA* 2017;318:1903-1912. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29164255>.
92. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. *N Engl J Med* 2018;378:1313-1322. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29617585>.



93. Feller-Kopman D, Light R. Pleural Disease. N Engl J Med 2018;378:1754. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29719174>.

94. Boshuizen RC, Vd Noort V, Burgers JA, et al. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). Lung Cancer 2017;108:9-14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28625655>.

95. Hunt BM, Farivar AS, Vallieres E, et al. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. Ann Thorac Surg 2012;94:1053-1057; discussion 1057-1059. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22513274>.

96. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. Chest 2006;129:362-368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16478853>.

97. Schneider T, Reimer P, Storz K, et al. Recurrent pleural effusion: who benefits from a tunneled pleural catheter? Thorac Cardiovasc Surg 2009;57:42-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19169996>.

98. Zahid I, Routledge T, Bille A, Scarci M. What is the best treatment for malignant pleural effusions? Interact Cardiovasc Thorac Surg 2011;12:818-823. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21325469>.

99. Arapis K, Caliendo R, Stern JB, et al. Thoracoscopic palliative treatment of malignant pleural effusions: results in 273 patients. Surg Endosc 2006;20:919-923. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16738983>.

100. Hollevoet K, Reitsma JB, Creaney J, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. J Clin Oncol 2012;30:1541-1549. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22412141>.

101. Schneider J, Hoffmann H, Dienemann H, et al. Diagnostic and prognostic value of soluble mesothelin-related proteins in patients with malignant pleural mesothelioma in comparison with benign asbestosis and lung cancer. J Thorac Oncol 2008;3:1317-1324. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18978568>.

102. Luo L, Shi HZ, Liang QL, et al. Diagnostic value of soluble mesothelin-related peptides for malignant mesothelioma: a meta-analysis. Respir Med 2010;104:149-156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19945835>.

103. Hollevoet K, Nackaerts K, Thimpont J, et al. Diagnostic performance of soluble mesothelin and megakaryocyte potentiating factor in mesothelioma. Am J Respir Crit Care Med 2010;181:620-625. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20075387>.

104. Wheatley-Price P, Yang B, Patsios D, et al. Soluble mesothelin-related Peptide and osteopontin as markers of response in malignant mesothelioma. J Clin Oncol 2010;28:3316-3322. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20498407>.

105. Creaney J, Yeoman D, Demelker Y, et al. Comparison of osteopontin, megakaryocyte potentiating factor, and mesothelin proteins as markers in the serum of patients with malignant mesothelioma. J Thorac Oncol 2008;3:851-857. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18670302>.

106. Grigoriu BD, Scherpereel A, Devos P, et al. Utility of osteopontin and serum mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment. Clin Cancer Res 2007;13:2928-2935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17504993>.

107. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med 2005;353:1564-1573. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16221779>.

108. Cristaudo A, Foddìs R, Vivaldi A, et al. Clinical significance of serum mesothelin in patients with mesothelioma and lung cancer. Clin Cancer



Res 2007;13:5076-5081. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17785560>.

109. Panou V, Vyberg M, Weinreich UM, et al. The established and future biomarkers of malignant pleural mesothelioma. *Cancer Treat Rev* 2015;41:486-495. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25979846>.

110. Creaney J, Dick IM, Robinson BW. Comparison of mesothelin and fibulin-3 in pleural fluid and serum as markers in malignant mesothelioma. *Curr Opin Pulm Med* 2015;21:352-356. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26016578>.

111. Ostroff RM, Mehan MR, Stewart A, et al. Early detection of malignant pleural mesothelioma in asbestos-exposed individuals with a noninvasive proteomics-based surveillance tool. *PLoS One* 2012;7:e46091. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23056237>.

112. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. *N Engl J Med* 2012;367:1417-1427. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23050525>.

113. Brims FJ, Lee YC, Creaney J. The continual search for ideal biomarkers for mesothelioma: the hurdles. *J Thorac Dis* 2013;5:364-366. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23825777>.

114. Galateau-Salle F, Churg A, Roggli V, et al. The 2015 World Health Organization Classification of Tumors of the Pleura: Advances since the 2004 Classification. *J Thorac Oncol* 2016;11:142-154. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26811225>.

115. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of malignant mesothelioma: Part 2. Malignant mesothelioma subtypes, pleural synovial sarcoma, molecular and prognostic aspects of mesothelioma, BAP1, aquaporin-1 and microRNA. *J Clin Pathol* 2013;66:854-861. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23833051>.

116. Churg A, Attanoos R, Borczuk AC, et al. Dataset for Reporting of Malignant Mesothelioma of the Pleura or Peritoneum: Recommendations From the International Collaboration on Cancer Reporting (ICCR). *Arch Pathol Lab Med* 2016;140:1104-1110. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27031777>.

117. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2018;142:89-108. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28686500>.

118. Marchevsky AM, LeStang N, Hiroshima K, et al. The differential diagnosis between pleural sarcomatoid mesothelioma and spindle cell/pleomorphic (sarcomatoid) carcinomas of the lung: evidence-based guidelines from the International Mesothelioma Panel and the MESOPATH National Reference Center. *Hum Pathol* 2017;67:160-168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28782639>.

119. Arif Q, Husain AN. Malignant Mesothelioma Diagnosis. *Arch Pathol Lab Med* 2015;139:978-980. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26230591>.

120. Husain AN, Colby T, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2013;137:647-667. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22929121>.

121. Chirieac LR, Pinkus GS, Pinkus JL, et al. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. *Am J Cancer Res* 2011;1:14-24. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21969119>.

122. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2009;133:1317-1331. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19653732>.





123. Ordonez NG. What are the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma? A review and update. *Hum Pathol* 2007;38:1-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17056092>.

124. Marchevsky AM, Khoor A, Walts AE, et al. Localized malignant mesothelioma, an unusual and poorly characterized neoplasm of serosal origin: best current evidence from the literature and the International Mesothelioma Panel. *Mod Pathol* 2020;33:281-296. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31485011>.

125. Hung YP, Dong F, Torre M, et al. Molecular characterization of diffuse malignant peritoneal mesothelioma. *Mod Pathol* 2020;33:2269-2279. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32504035>.

126. Hung YP, Dong F, Dubuc AM, et al. Molecular characterization of localized pleural mesothelioma. *Mod Pathol* 2020;33:271-280. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31371807>.

127. Allen TC, Cagle PT, Churg AM, et al. Localized malignant mesothelioma. *Am J Surg Pathol* 2005;29:866-873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15958850>.

128. Okike N, Bernatz PE, Woolner LB. Localized mesothelioma of the pleura: benign and malignant variants. *J Thorac Cardiovasc Surg* 1978;75:363-372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/633933>.

129. Hjerpe A, Ascoli V, Bedrossian CW, et al. Guidelines for the cytopathologic diagnosis of epithelioid and mixed-type malignant mesothelioma. Complementary statement from the International Mesothelioma Interest Group, also endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology. *Acta Cytol* 2015;59:2-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25824655>.

130. Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. *Chest* 2009;136:888-896. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19736192>.

131. Chapel DB, Churg A, Santoni-Rugiu E, et al. Molecular pathways and diagnosis in malignant mesothelioma: A review of the 14th International Conference of the International Mesothelioma Interest Group. *Lung Cancer* 2019;127:69-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30642555>.

132. Schneider F, Roden AC, Dacic S, Baker TP. Protocol for the examination of specimens from patients with malignant pleural mesothelioma. Version 4.1.0.0. Based on AJCC/UICC TNM, 8th edition. Protocol web posting date: June 2021: Collage of American Pathologists; 2022. Available at: [https://documents.cap.org/protocols/PleuraPericard\\_4.1.0.0.REL\\_CAPCP.pdf](https://documents.cap.org/protocols/PleuraPericard_4.1.0.0.REL_CAPCP.pdf).

133. De Rienzo A, Chirieac LR, Hung YP, et al. Large-scale analysis of BAP1 expression reveals novel associations with clinical and molecular features of malignant pleural mesothelioma. *J Pathol* 2021;253:68-79. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32944962>.

134. Righi L, Duregon E, Vatrano S, et al. BRCA1-associated protein 1 (BAP1) immunohistochemical expression as a diagnostic tool in malignant pleural mesothelioma classification: a large retrospective study. *J Thorac Oncol* 2016;11:2006-2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27422796>.

135. Wang LM, Shi ZW, Wang JL, et al. Diagnostic accuracy of BRCA1-associated protein 1 in malignant mesothelioma: a meta-analysis. *Oncotarget* 2017;8:68863-68872. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28978163>.

136. Creaney J, Patch AM, Addala V, et al. Comprehensive genomic and tumour immune profiling reveals potential therapeutic targets in malignant pleural mesothelioma. *Genome Med* 2022;14:58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35637530>.



137. Desmeules P, Joubert P, Zhang L, et al. A subset of malignant mesotheliomas in young adults are associated with recurrent EWSR1/FUS-ATF1 fusions. *Am J Surg Pathol* 2017;41:980-988. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28505004>.

138. Leal JL, Peters G, Szaumkessel M, et al. NTRK and ALK rearrangements in malignant pleural mesothelioma, pulmonary neuroendocrine tumours and non-small cell lung cancer. *Lung Cancer* 2020;146:154-159. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32540558>.

139. Ghafoor A, Mian I, Wagner C, et al. Phase 2 study of olaparib in malignant mesothelioma and correlation of efficacy with germline or somatic mutations in BAP1 gene. *JTO Clin Res Rep* 2021;2:100231. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34661178>.

140. Fennell DA, King A, Mohammed S, et al. Rucaparib in patients with BAP1-deficient or BRCA1-deficient mesothelioma (MiST1): an open-label, single-arm, phase 2a clinical trial. *Lancet Respir Med* 2021;9:593-600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33515503>.

141. Fennell DA, King A, Mohammed S, et al. Abemaciclib in patients with p16ink4A-deficient mesothelioma (MiST2): a single-arm, open-label, phase 2 trial. *Lancet Oncol* 2022;23:374-381. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35157829>.

142. Cordier F, Van der Meulen J, van Roy N, et al. Malignant pleural mesothelioma with an EML4-ALK fusion: Expect the unexpected! *Pathol Res Pract* 2022;231:153772. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35074700>.

143. Bronte G, Delmonte A, Burgio MA, et al. Impressive clinical response to anti-PD-1 therapy in epithelioid mesothelioma with high clonal PD-L1 expression and EML4-ALK rearrangement. *Lung Cancer* 2020;142:47-50. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32088605>.

144. Kapeles M, Gensheimer MF, Mart DA, et al. Trimodality Treatment of Malignant Pleural Mesothelioma: An Institutional Review. *Am J Clin Oncol*

2018;41:30-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26353120>.

145. Nelson DB, Rice DC, Niu J, et al. Long-Term Survival Outcomes of Cancer-Directed Surgery for Malignant Pleural Mesothelioma: Propensity Score Matching Analysis. *J Clin Oncol* 2017;35:3354-3362. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28817374>.

146. Vogl SE. Guarantee-Time Bias and Benefits of Surgery for Pleural Mesothelioma. *J Clin Oncol* 2018;36:624-625. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29303626>.

147. Thieke C, Nicolay NH, Sterzing F, et al. Long-term results in malignant pleural mesothelioma treated with neoadjuvant chemotherapy, extrapleural pneumonectomy and intensity-modulated radiotherapy. *Radiat Oncol* 2015;10:267. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26715491>.

148. Bolukbas 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19765853>.

149. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009;27:1413-1418. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19224855>.

150. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009;27:3007-3013. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19364962>.

151. Weder W, Stahel RA, Bernhard J, et al. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in



malignant pleural mesothelioma. *Ann Oncol* 2007;18:1196-1202. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17429100>.

152. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg* 1999;117:54-63; discussion 63-55. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9869758>.

153. Frick AE, Nackaerts K, Moons J, et al. Combined modality treatment for malignant pleural mesothelioma: a single-centre long-term survival analysis using extrapleural pneumonectomy. *Eur J Cardiothorac Surg* 2019;55:934-941. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30535191>.

154. Shaikh F, Zauderer MG, von Reibnitz D, et al. Improved Outcomes with Modern Lung-Sparing Trimodality Therapy in Patients with Malignant Pleural Mesothelioma. *J Thorac Oncol* 2017;12:993-1000. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28341225>.

155. Baldini EH. Radiation therapy options for malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 2009;21:159-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19822288>.

156. Baldini EH. External beam radiation therapy for the treatment of pleural mesothelioma. *Thorac Surg Clin* 2004;14:543-548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15559061>.

157. Aelony Y, Yao JF. Prolonged survival after talc poudrage for malignant pleural mesothelioma: case series. *Respirology* 2005;10:649-655. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16268920>.

158. Schulze M, Boehle AS, Kurdow R, et al. Effective treatment of malignant pleural effusion by minimal invasive thoracic surgery: thoracoscopic talc pleurodesis and pleuroperitoneal shunts in 101 patients. *Ann Thorac Surg* 2001;71:1809-1812. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11426752>.

159. Petrou M, Kaplan D, Goldstraw P. Management of recurrent malignant pleural effusions. The complementary role talc pleurodesis and pleuroperitoneal shunting. *Cancer* 1995;75:801-805. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7530167>.

160. De Paoli L, Quaia E, Poillucci G, et al. Imaging characteristics of pleural tumours. *Insights Imaging* 2015;6:729-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26475741>.

161. Rice DC, Steliga MA, Stewart J, et al. Endoscopic ultrasound-guided fine needle aspiration for staging of malignant pleural mesothelioma. *Ann Thorac Surg* 2009;88:862-868; discussion 868-869. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19699913>.

162. Pilling JE, Stewart DJ, Martin-Ucar AE, et al. The case for routine cervical mediastinoscopy prior to radical surgery for malignant pleural mesothelioma. *Eur J Cardiothorac Surg* 2004;25:497-501. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15037261>.

163. Grossebner MW, Arifi AA, Goddard M, Ritchie AJ. Mesothelioma--VATS biopsy and lung mobilization improves diagnosis and palliation. *Eur J Cardiothorac Surg* 1999;16:619-623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10647830>.

164. Ahmadzadehfar H, Palmedo H, Strunk H, et al. False positive 18F-FDG-PET/CT in a patient after talc pleurodesis. *Lung Cancer* 2007;58:418-421. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17624474>.

165. Nguyen NC, Tran I, Hueser CN, et al. F-18 FDG PET/CT characterization of talc pleurodesis-induced pleural changes over time: a retrospective study. *Clin Nucl Med* 2009;34:886-890. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20139823>.

166. Pilling J, Dartnell JA, Lang-Lazdunski L. Integrated positron emission tomography-computed tomography does not accurately stage intrathoracic disease of patients undergoing trimodality therapy for malignant pleural mesothelioma. *Thorac Cardiovasc Surg* 2010;58:215-219. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20514576>.





167. Wilcox BE, Subramaniam RM, Peller PJ, et al. Utility of integrated computed tomography-positron emission tomography for selection of operable malignant pleural mesothelioma. Clin Lung Cancer 2009;10:244-248. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19632941>.

168. Flores RM, Akhurst T, Gonen M, et al. Positron emission tomography defines metastatic disease but not locoregional disease in patients with malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2003;126:11-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12878934>.

169. Amin MB, Greene FL, Byrd DR. AJCC Cancer Staging Manual, 8th edition: Springer International Publishing; 2017:1-1024.

170. Bonomi M, De Filippis C, Lopci E, et al. Clinical staging of malignant pleural mesothelioma: current perspectives. Lung Cancer (Auckl) 2017;8:127-139. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28860886>.

171. Rusch VW, Giroux D. Do we need a revised staging system for malignant pleural mesothelioma? Analysis of the IASLC database. Ann Cardiothorac Surg 2012;1:438-448. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23977534>.

172. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010.

173. Kaufman AJ, Flores RM. Surgical treatment of malignant pleural mesothelioma. Curr Treat Options Oncol 2011;12:201-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21465419>.

174. Kim S, Bull DA, Garland L, et al. Is There a Role for Cancer-Directed Surgery in Early-Stage Sarcomatoid or Biphasic Mesothelioma? Ann Thorac Surg 2019;107:194-201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30278171>.

175. Lococo F, Torricelli F, Lang-Lazdunski L, et al. Survival results in biphasic malignant pleural mesothelioma patients: A multicentric analysis.

J Thorac Cardiovasc Surg 2020;159:1584-1593 e1582. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31590954>.

176. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. J Thorac Oncol 2011;6:1304-1312. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847060>.

177. Bolukbas S, Eberlein M, Fisseler-Eckhoff A, Schirren J. Radical pleurectomy and chemoradiation for malignant pleural mesothelioma: the outcome of incomplete resections. Lung Cancer 2013;81:241-246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23688589>.

178. Sugarbaker DJ, Wolf AS, Chirieac LR, et al. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. Eur J Cardiothorac Surg 2011;40:298-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21310625>.

179. Abdel-Rahman O, Elsayed Z, Mohamed H, Eltobgy M. Radical multimodality therapy for malignant pleural mesothelioma. Cochrane Database Syst Rev 2018;1:CD012605. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29309720>.

180. van Gerwen M, Wolf A, Liu B, et al. Short-term outcomes of pleurectomy decortication and extrapleural pneumonectomy in mesothelioma. J Surg Oncol 2018;118:1178-1187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30293239>.

181. Taioli E, van Gerwen M, Mihalopoulos M, et al. Review of malignant pleural mesothelioma survival after talc pleurodesis or surgery. J Thorac Dis 2017;9:5423-5433. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29312753>.

182. Teh E, Fiorentino F, Tan C, Treasure T. A systematic review of lung-sparing extirpative surgery for pleural mesothelioma. J R Soc Med



2011;104:69-80. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21282797>.

183. Cao C, Tian D, Park J, et al. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. *Lung Cancer* 2014;83:240-245. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24360321>.

184. Bovolato P, Casadio C, Bille A, et al. Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients. *J Thorac Oncol* 2014;9:390-396. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24518090>.

185. Kindler HL. Surgery for mesothelioma? The debate continues. *Lancet Oncol* 2011;12:713-714. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21723780>.

186. Rice D. Surgical therapy of mesothelioma. *Recent Results Cancer Res* 2011;189:97-125. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21479898>.

187. Maziak DE, Gagliardi A, Haynes AE, et al. Surgical management of malignant pleural mesothelioma: a systematic review and evidence summary. *Lung Cancer* 2005;48:157-169. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15829316>.

188. Friedberg JS. The state of the art in the technical performance of lung-sparing operations for malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 2013;25:125-143. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24216529>.

189. 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. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19546819>.

190. Schipper PH, Nichols FC, Thomse KM, et al. Malignant pleural mesothelioma: surgical management in 285 patients. *Ann Thorac Surg*

2008;85:257-264; discussion 264. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18154820>.

191. Nakas A, von Meyenfeldt E, Lau K, et al. Long-term survival after lung-sparing total pleurectomy for locally advanced (International Mesothelioma Interest Group Stage T3-T4) non-sarcomatoid malignant pleural mesothelioma. *Eur J Cardiothorac Surg* 2012;41:1031-1036. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22219469>.

192. Bille A, Belcher E, Raubenheimer H, et al. Induction chemotherapy, extrapleural pneumonectomy, and adjuvant radiotherapy for malignant pleural mesothelioma: experience of Guy's and St Thomas' hospitals. *Gen Thorac Cardiovasc Surg* 2012;60:289-296. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22453539>.

193. Zahid I, Sharif S, Routledge T, Scarci M. Is pleurectomy and decortication superior to palliative care in the treatment of malignant pleural mesothelioma? *Interact Cardiovasc Thorac Surg* 2011;12:812-817. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21345818>.

194. Shatin Y, Wellham J, Jappie R, et al. How successful is lung-preserving radical surgery in the mesothelioma and radical surgery-trial environment? A case-controlled analysis. *Eur J Cardiothorac Surg* 2011;39:360-363. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20692844>.

195. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008;135:620-626, 626 e621-623. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18329481>.

196. Sugarbaker DJ, Jaklitsch MT, Bueno R, et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. *J Thorac Cardiovasc Surg* 2004;128:138-146. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15224033>.



197. Yan TD, Boyer M, Tin MM, et al. Extrapleural pneumonectomy for malignant pleural mesothelioma: outcomes of treatment and prognostic factors. *J Thorac Cardiovasc Surg* 2009;138:619-624. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19698846>.
198. Zhou N, Rice DC, Tsao AS, et al. Extrapleural pneumonectomy versus pleurectomy/decortication for malignant pleural mesothelioma. *Ann Thorac Surg* 2022;113:200-208. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33971174>.
199. Halstead JC, Lim E, Venkateswaran RM, et al. Improved survival with VATS pleurectomy-decortication in advanced malignant mesothelioma. *Eur J Surg Oncol* 2005;31:314-320. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15780570>.
200. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011;12:763-772. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21723781>.
201. Weder W, Stahel RA, Baas P, et al. The MARS feasibility trial: conclusions not supported by data. *Lancet Oncol* 2011;12:1093-1094; author reply 1094-1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22041539>.
202. Yan TD, Cao CQ, Boyer M, et al. Improving survival results after surgical management of malignant pleural mesothelioma: an Australian institution experience. *Ann Thorac Cardiovasc Surg* 2011;17:243-249. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21697784>.
203. Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. *J Thorac Oncol* 2010;5:1649-1654. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20871264>.
204. Spaggiari L, Marulli G, Bovolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. *Ann Thorac Surg* 2014;97:1859-1865. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24726598>.
205. Blomberg C, Nilsson J, Holgersson G, et al. Randomized Trials of Systemic Medically-treated Malignant Mesothelioma: A Systematic Review. *Anticancer Res* 2015;35:2493-2501. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25964522>.
206. Kelly RJ, Sharon E, Hassan R. Chemotherapy and targeted therapies for unresectable malignant mesothelioma. *Lung Cancer* 2011;73:256-263. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21620512>.
207. Ellis P, Davies AM, Evans WK, et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. *J Thorac Oncol* 2006;1:591-601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17409924>.
208. Kim ST, Park JY, Lee J, et al. The efficacy of the frontline platinum-based combination chemotherapy in malignant peritoneal mesothelioma. *Jpn J Clin Oncol* 2010;40:1031-1036. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20534685>.
209. Recabal P, Rosenzweig B, Bazzi WM, et al. Malignant Mesothelioma of the Tunica Vaginalis Testis: Outcomes Following Surgical Management Beyond Radical Orchiectomy. *Urology* 2017;107:166-170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28416299>.
210. Kim JS, Lim SY, Hwang J, et al. A Case Report of Primary Pericardial Malignant Mesothelioma Treated with Pemetrexed and Cisplatin. *J Korean Med Sci* 2017;32:1879-1884. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28960045>.
211. Srinivasan G, Sidhu GS, Williamson EA, et al. Synthetic lethality in malignant pleural mesothelioma with PARP1 inhibition. *Cancer Chemother Pharmacol* 2017;80:861-867. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28756516>.





212. Lang-Lazdunski L, Bille A, Papa S, et al. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy, and systemic chemotherapy in patients with malignant pleural mesothelioma: a 10-year experience. *J Thorac Cardiovasc Surg* 2015;149:558-565; discussion 565-556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25726878>.

213. Lang-Lazdunski L, Bille A, Belcher E, et al. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine followed by adjuvant chemotherapy in patients with malignant pleural mesothelioma. *J Thorac Oncol* 2011;6:1746-1752. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21876457>.

214. Friedberg JS, Culligan MJ, Mick R, et al. Radical pleurectomy and intraoperative photodynamic therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2012;93:1658-1665; discussion 1665-1657. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22541196>.

215. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. *J Thorac Cardiovasc Surg* 2013;145:955-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23434448>.

216. Simone CB, 2nd, Cengel KA. Photodynamic therapy for lung cancer and malignant pleural mesothelioma. *Semin Oncol* 2014;41:820-830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25499640>.

217. Du KL, Both S, Friedberg JS, et al. Extrapleural pneumonectomy, photodynamic therapy and intensity modulated radiation therapy for the treatment of malignant pleural mesothelioma. *Cancer Biol Ther* 2010;10:425-429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20699634>.

218. Ried M, Potzger T, Braune N, et al. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience. *Eur J*

*Cardiothorac Surg* 2013;43:801-807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22885228>.

219. de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. *Chest* 2002;121:480-487. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11834661>.

220. Kotova S, Wong RM, Cameron RB. New and emerging therapeutic options for malignant pleural mesothelioma: review of early clinical trials. *Cancer Manag Res* 2015;7:51-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25670913>.

221. Horn L, Spigel DR, Vokes EE, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017;35:3924-3933. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29023213>.

222. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2021;397:375-386. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33485464>.

223. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2016;2:1607-1616. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27540850>.

224. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* 2017;35:709-717. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27646942>.

225. Sgambato A, Casaluce F, Sacco PC, et al. Anti PD-1 and PDL-1 Immunotherapy in the Treatment of Advanced Non- Small Cell Lung



Cancer (NSCLC): A Review on Toxicity Profile and its Management. Curr Drug Saf 2016;11:62-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26412670>.

226. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-2644. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12860938>.

227. Katirtzoglou N, Gkiozos I, Makrilia N, et al. Carboplatin plus pemetrexed as first-line treatment of patients with malignant pleural mesothelioma: a phase II study. Clin Lung Cancer 2010;11:30-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20085865>.

228. Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol 2006;24:1443-1448. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16549838>.

229. Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann Oncol 2008;19:370-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18156144>.

230. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol 2008;3:756-763. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18594322>.

231. Kondola S, Manners D, Nowak AK. Malignant pleural mesothelioma: an update on diagnosis and treatment options. Ther Adv Respir Dis 2016;10:275-288. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26873306>.

232. Raynaud C, Greillier L, Mazieres J, et al. Management of malignant pleural mesothelioma: a French multicenter retrospective study (GFPC 0802 study). BMC Cancer 2015;15:857. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26546402>.

233. Krug LM. An overview of chemotherapy for mesothelioma. Hematol Oncol Clin North Am 2005;19:1117-1136, vii. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16325127>.

234. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:1405-1414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26719230>.

235. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer 2013;109:552-558. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23860535>.

236. Arrieta O, Lopez-Macias D, Mendoza-Garcia VO, et al. A phase II trial of prolonged, continuous infusion of low-dose gemcitabine plus cisplatin in patients with advanced malignant pleural mesothelioma. Cancer Chemother Pharmacol 2014;73:975-982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24687408>.

237. van Haarst JM, Baas P, Manegold C, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer 2002;86:342-345. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11875695>.

238. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 2002;87:491-496. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12189542>.

239. Scagliotti GV, Shin D-M, Kindler HL, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. J Clin Oncol 2003;21:1556-1561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12697881>.

240. Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma:



results of an International Expanded Access Program. *J Thorac Oncol* 2008;3:764-771. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18594323>.

241. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685-1694. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18486741>.

242. Abdel-Rahman O, Kelany M. Systemic therapy options for malignant pleural mesothelioma beyond first-line therapy: a systematic review. *Expert Rev Respir Med* 2015;9:533-549. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26366804>.

243. Zauderer MG, Krug LM. Novel therapies in phase II and III trials for malignant pleural mesothelioma. *J Natl Compr Canc Netw* 2012;10:42-47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22223868>.

244. Thomas A, Hassan R. Immunotherapies for non-small-cell lung cancer and mesothelioma. *Lancet Oncol* 2012;13:e301-310. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22748269>.

245. Ceresoli GL, Zucali PA, Gianoncelli L, et al. Second-line treatment for malignant pleural mesothelioma. *Cancer Treat Rev* 2010;36:24-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19879055>.

246. Fennell DA, Ewings S, Ottensmeier C, et al. Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. *Lancet Oncol* 2021;22:1530-1540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34656227>.

247. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol* 2019;20:239-253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30660609>.

248. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet Respir Med* 2019;7:260-270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30660511>.

249. Metaxas Y, Rivalland G, Mauti LA, et al. Pembrolizumab as Palliative Immunotherapy in Malignant Pleural Mesothelioma. *J Thorac Oncol* 2018;13:1784-1791. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30142389>.

250. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol* 2017;18:623-630. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28291584>.

251. Alley EW, Lopez J, Santoro A, et al. OA13.03 Long-term overall survival for patients with malignant pleural mesothelioma on pembrolizumab enrolled in KEYNOTE-028 [abstract]. *J Thorac Oncol* 2017;12:S294. Available at: [http://www.jto.org/article/S1556-0864\(16\)31543-X/fulltext](http://www.jto.org/article/S1556-0864(16)31543-X/fulltext).

252. Scherpereel A, Mazieres J, Greiller L, et al. Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase 2 trial [abstract]. *J Clin Oncol* 2017;35:Abstract LBA8507. Available at: [http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18\\_suppl.LBA8507](http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA8507).

253. Zalcmán G, Mazieres J, Greillier L, et al. Second or 3rd line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Updated results of the IFCT-1501 MAPS2 randomized phase 2 trial [abstract]. *Ann Oncol* 2017;28:Abstract LBA58\_PR. Available at: <https://tinyurl.com/ych67u3c>.

254. Alley EW, Molife LR, Santoro A, et al. Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma: Preliminary results from KEYNOTE-028 [abstract]. *Cancer*



Research 2015;75:Abstract CT103. Available at:  
<https://tinyurl.com/y9xqndc4>.

255. Alley EW, Schellens JH, Santoro A, et al. Single-agent pembrolizumab for patients with malignant pleural mesothelioma (MPM) [abstract]. World Conference on Lung Cancer. Denver, Colorado: IASCL; 2015:Abstract 3011. Available at: <https://tinyurl.com/ybrdtp2c>.

256. Marcq E, Pauwels P, van Meerbeeck JP, Smits EL. Targeting immune checkpoints: New opportunity for mesothelioma treatment? Cancer Treat Rev 2015;41:914-924. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26433514>.

257. Calabro L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 2015;3:301-309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25819643>.

258. Buikhuisen WA, Hiddinga BI, Baas P, van Meerbeeck JP. Second line therapy in malignant pleural mesothelioma: A systematic review. Lung Cancer 2015;89:223-231. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26162564>.

259. Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung Cancer 2012;75:360-367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21937142>.

260. Popat S, Curioni-Fontecedro A, Dafni U, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol 2020;31:1734-1745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32976938>.

261. Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin

Oncol 2008;26:1698-1704. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18375898>.

262. Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-274. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24690410>.

263. Janne PA, Wozniak AJ, Belani CP, et al. Pemetrexed alone or in combination with cisplatin in previously treated malignant pleural mesothelioma: outcomes from a phase IIIB expanded access program. J Thorac Oncol 2006;1:506-512. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17409909>.

264. van Meerbeeck JP, Baas P, Debruyne C, et al. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999;85:2577-2582. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10375105>.

265. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer 2009;63:94-97. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18486273>.

266. Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. Ann Oncol 2005;16:923-927. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15824080>.

267. Ashton M, O'Rourke N, Currie S, et al. The role of radical radiotherapy in the management of malignant pleural mesothelioma: A systematic review. Radiother Oncol 2017;125:1-12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28859932>.

268. Price A. What is the role of radiotherapy in malignant pleural mesothelioma? Oncologist 2011;16:359-365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21346022>.



269. van Thiel ER, Surmont VF, van Meerbeeck JP. Malignant pleural mesothelioma: when is radiation therapy indicated? *Expert Rev Anticancer Ther* 2011;11:551-560. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21504322>.

270. Gomez DR, Hong DS, Allen PK, et al. Patterns of failure, toxicity, and survival after extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy for malignant pleural mesothelioma. *J Thorac Oncol* 2013;8:238-245. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23247629>.

271. Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2007;84:1685-1692; discussion 1692-1683. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17954086>.

272. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12873676>.

273. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11581615>.

274. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16054774>.

275. Trovo M, Relevant A, Polesel J, et al. Radical hemithoracic radiotherapy versus palliative radiotherapy in non-metastatic malignant pleural mesothelioma: Results from a phase 3 randomized clinical trial. *Int J Radiat Oncol Biol Phys* 2021;109:1368-1376. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33259933>.

276. Rimner A, Zauderer MG, Gomez DR, et al. Phase II study of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) as part of lung-sparing multimodality therapy in patients with malignant pleural mesothelioma. *J Clin Oncol* 2016;34:2761-2768. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27325859>.

277. Minatel E, Trovo M, Bearz A, et al. Radical radiation therapy after lung-sparing surgery for malignant pleural mesothelioma: Survival, pattern of failure, and prognostic factors. *Int J Radiat Oncol Biol Phys* 2015;93:606-613. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26281826>.

278. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. *Chest* 1995;108:754-758. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7656629>.

279. de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura--a single-institution experience with 189 patients. *Int J Radiat Oncol Biol Phys* 1999;43:511-516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10078630>.

280. Di Salvo M, Gambaro G, Pagella S, et al. Prevention of malignant seeding at drain sites after invasive procedures (surgery and/or thoracoscopy) by hypofractionated radiotherapy in patients with pleural mesothelioma. *Acta Oncol* 2008;47:1094-1098. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18770063>.

281. Davies HE, Musk AW, Lee YC. Prophylactic radiotherapy for pleural puncture sites in mesothelioma: the controversy continues. *Curr Opin Pulm Med* 2008;14:326-330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18520267>.

282. O'Rourke N, Garcia JC, Paul J, et al. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. *Radiother Oncol* 2007;84:18-22. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17588698>.





283. Bydder S, Phillips M, Joseph DJ, et al. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. *Br J Cancer* 2004;91:9-10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15199394>.

284. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet Oncol* 2016;17:1094-1104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27345639>.

285. Stewart SA, Clive AO, Maskell NA, Penz E. Evaluating quality of life and cost implications of prophylactic radiotherapy in mesothelioma: Health economic analysis of the SMART trial. *PLoS One* 2018;13:e0190257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29401495>.

286. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19404212>.

287. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9033296>.

288. Chance WW, Rice DC, Allen PK, et al. Hemithoracic intensity modulated radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. *Int J Radiat Oncol Biol Phys* 2015;91:149-156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25442335>.

289. Waite K, Gilligan D. The role of radiotherapy in the treatment of malignant pleural mesothelioma. *Clin Oncol (R Coll Radiol)* 2007;19:182-187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17359904>.

290. Jhavar S, Pruszynski J, Gowan A, et al. Intensity modulated radiation therapy after extra-pleural pneumonectomy for malignant pleural mesothelioma is feasible without fatal pulmonary toxicity and provides good survival. *Asia Pac J Clin Oncol* 2018;14:e88-e94. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28371288>.

291. Krayenbuehl J, Dimmerling P, Ciernik IF, Riesterer O. Clinical outcome of postoperative highly conformal versus 3D conformal radiotherapy in patients with malignant pleural mesothelioma. *Radiat Oncol* 2014;9:32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24456714>.

292. Cho BC, Feld R, Leigh N, et al. A feasibility study evaluating Surgery for Mesothelioma After Radiation Therapy: the "SMART" approach for resectable malignant pleural mesothelioma. *J Thorac Oncol* 2014;9:397-402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24445595>.

293. Rosenzweig KE, Zauderer MG, Laser B, et al. Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2012;83:1278-1283. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22607910>.

294. Miller AC, Miettinen M, Schrupp DS, Hassan R. Malignant mesothelioma and central nervous system metastases. Report of two cases, pooled analysis, and systematic review. *Ann Am Thorac Soc* 2014;11:1075-1081. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25079105>.

295. Zeng J, Badiyan SN, Garces YI, et al. Consensus statement on proton therapy in mesothelioma. *Pract Radiat Oncol* 2021;11:119-133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32461036>.

296. Rice DC, Smythe WR, Liao Z, et al. Dose-dependent pulmonary toxicity after postoperative intensity-modulated radiotherapy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2007;69:350-357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17467922>.



297. Allen AM, Czerminska M, Janne PA, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640-645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16751058>.

298. Kristensen CA, Notttrup TJ, Berthelsen AK, et al. Pulmonary toxicity following IMRT after extrapleural pneumonectomy for malignant pleural mesothelioma. *Radiother Oncol* 2009;92:96-99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19364621>.

299. Miles EF, Larrier NA, Kelsey CR, et al. Intensity-modulated radiotherapy for resected mesothelioma: the Duke experience. *Int J Radiat Oncol Biol Phys* 2008;71:1143-1150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18262369>.

300. Patel PR, Yoo S, Broadwater G, et al. Effect of increasing experience on dosimetric and clinical outcomes in the management of malignant pleural mesothelioma with intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2012;83:362-368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22516382>.

301. Stahel RA, Weder W, Lievens Y, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v126-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20555061>.

302. Kraysenbuehl J, Oertel S, Davis JB, Ciernik IF. Combined photon and electron three-dimensional conformal versus intensity-modulated radiotherapy with integrated boost for adjuvant treatment of malignant pleural mesothelioma after pleuropneumectomy. *Int J Radiat Oncol Biol Phys* 2007;69:1593-1599. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17931793>.

Discussion  
update in  
progress