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Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Mesothelioma: Peritoneal

Version 2.2024 — September 23, 2024

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

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

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

Travis E. Grotz, MD/Co-Lead ¶
Mayo Clinic Comprehensive Cancer Center

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
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

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

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

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

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

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 ¥ ‡
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

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

Alda Tam, MD ¶
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 ¶
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

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

NCCN
Kristina Gregory, RN, MSN
Lisa Hang, PhD

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 2.2024 of the NCCN Guidelines for Mesothelioma: Peritoneal from Version 1.2024 include:

[PEM-C 1 of 2](#)

- Footnote f added: Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for intravenous infusion.

Updates in Version 1.2024 of the NCCN Guidelines for Mesothelioma: Peritoneal from Version 2.2023 include:

[PEM-1](#)

- Initial Evaluation
 - ▶ Bullet 2 added: Consider FDG-PET/CT scan

[PEM-2 \(previous version\) removed](#)

- Pathologic subtype removed: Peritoneal inclusion cyst or well-differentiated papillary mesothelial tumor (includes removal of PEM-5 [previous version])
- Diffuse peritoneal mesothelioma changed to Peritoneal mesothelioma

[PEM-2](#)

- Footnote removed: Adjuvant intraperitoneal (IP) chemotherapy may be considered for patients who do not receive HIPEC.

[PEM-3](#)

- Biphasic/sarcomatoid histology
 - ▶ Treatment options expanded after initial systemic therapy
 - ◊ Medically operable and complete cytoreduction achievable
 - CRS + HIPEC
 - Imaging Surveillance

[PEM-A 3 of 8](#)

- Markers to confirm a mesothelial malignant proliferation
 - ▶ Bullet 2; sub-bullet 5 added: *CDKN2A* FISH and MTAP IHC are less useful for the diagnosis of peritoneal mesotheliomas because the prevalence of *CDKN2A* deletions is 8%–26% and MTAP loss is 14%–16% in peritoneal mesotheliomas.

[PEM-A 7 of 8](#)

- References 40-44 added.
 - ▶ 40 Dagogo-Jack I, Madison RW, Lennerz JK, et al. Molecular characterization of mesothelioma: Impact of histologic type and site of origin on molecular landscape. *JCO Precis Oncol* 2022;6:e2100422.
 - ▶ 41 Hiltbrunner S, Fleischmann Z, Sokol E, et al. Genomic landscape of pleural and peritoneal mesothelioma tumors. *Br J Cancer* 2022;127:1997-2005.
 - ▶ 42 Joseph NM, Chen Y-Y, Nasr A, et al. Genomic profiling of malignant peritoneal mesothelioma reveals recurrent alterations in epigenetic regulatory genes BAP1, SETD2 and DDX3X. *Mod Pathol* 2017;30:246-254.
 - ▶ 43 Hung YP, Dong F, Torre M, et al. Molecular characterization of diffuse malignant peritoneal mesothelioma. *Mod Pathol* 2020;33:2269-2279.
 - ▶ 44 Offin M, Yang S-R, Egger J, et al. Molecular characterization of peritoneal mesotheliomas. *J Thorac Oncol* 2022;17:455-460.

[Continued](#)

UPDATES

**Updates in Version 1.2024 of the NCCN Guidelines for Mesothelioma: Peritoneal from Version 2.2023 include:****PEM-B 1 of 3**

- Bullet 7 added: Resectable epithelioid mesothelioma should undergo upfront CRS and HIPEC. If there are no high-risk features identified (positive lymph node [LN], incomplete cytoreduction, or high Ki-67 >9%) then surveillance is sufficient. If high-risk features are identified then consideration for adjuvant therapy is recommended.
- Bullet 8 added: For patients with biphasic, sarcomatoid, clinically positive LN, or high PCI >17; neoadjuvant therapy is strongly encouraged followed by re-evaluation for complete CRS and HIPEC.
- Bullet 9 added: For patients with bicavitary disease and minimal disease burden in the thorax, systemic therapy is recommended. Surgery can be considered in select cases.
- Bullet 10 added: If a bevacizumab-containing regimen is administered, there should be at least a 6-week interval between the last dose and CRS.
- Bullet 12 added: Early postoperative or prolonged adjuvant IP therapy have been investigated with some success and limited toxicity, but there remains insufficient evidence to recommend their use outside of a clinical trial.
- Bullet 13 added: Patients who recur in the peritoneum after CRS and HIPEC should be re-evaluated for repeat CRS and HIPEC, as studies show this can be done safely and with good outcomes in appropriately selected patients
- Bullets removed
 - ▶ The presence of bicavitary mesothelioma is a relative contraindication to surgery. In selected situations, bicavitary surgery with resection of the diaphragm and bicavitary chemoperfusion or staged approaches may be considered. Neoadjuvant chemotherapy is also a strong consideration in this borderline group.
 - ▶ Long-term survival is achievable in select patients with low-volume biphasic mesothelioma if complete cytoreduction (CC-0) can be achieved. Neoadjuvant systemic chemotherapy is a strong consideration in this histologic subtype.
 - ▶ Perioperative systemic therapy should be considered for high-risk features such as: Ki-67 >9%, nodal metastasis, high tumor burden (PCI >17), CC score >1, biphasic disease, or bicavitary disease. Patients with favorable prognostic profile (ie, complete cytoreduction, epithelioid subtype, no lymph node involvement, Ki-67 ≤9%, PCI ≤17) could be followed in surveillance as the benefit of adjuvant therapy is unknown.

PEM-B 3 of 3

- References 6–8, 11–14 added.
 - ▶ 6 Ripley RT, Holmes HM, Whitlock RS, et al. Pleurectomy and decortication are associated with better survival for bicavitary cytoreductive surgery for mesothelioma compared with extrapleural pneumonectomy. *J Thorac Cardiovasc Surg.* 2023;165:1722-1730.
 - ▶ 7 Petrillo M, Nero C, Carbone V, et al. Systematic review of cytoreductive surgery and bevacizumab-containing chemotherapy in advanced ovarian cancer: focus on safety. *Ann Surg Oncol.* 2018;25:247-254.
 - ▶ 8 King BH, Baumgartner JM, Kelly KJ, et al. Preoperative bevacizumab does not increase complications following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *PLoS One.* 2020;15:e0243252.
 - ▶ 11 Sugarbaker PH, Chang D. Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival. *Eur J Surg Oncol* 2017;43:1228-1235.
 - ▶ 12 Bijelic L, Stuart OA, Sugarbaker PH. Adjuvant bidirectional chemotherapy with intraperitoneal pemetrexed combined with intravenous Cisplatin for diffuse malignant peritoneal mesothelioma. *Gastroenterol Res Pract* 2012;2012:890450.
 - ▶ 13 Pasqual EM, Londero AP, Robella M, et al. Repeated cytoreduction combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in selected patients affected by peritoneal metastases: Italian PSM Oncoteam Evidence. *Cancers (Basel)* 2023;15:607.
 - ▶ 14 Wong J, Koch AL, Deneve JL, et al. Repeat cytoreductive surgery and heated intraperitoneal chemotherapy may offer survival benefit for intraperitoneal mesothelioma: a single institution experience. *Ann Surg Oncol* 2014;21:1480-1486.

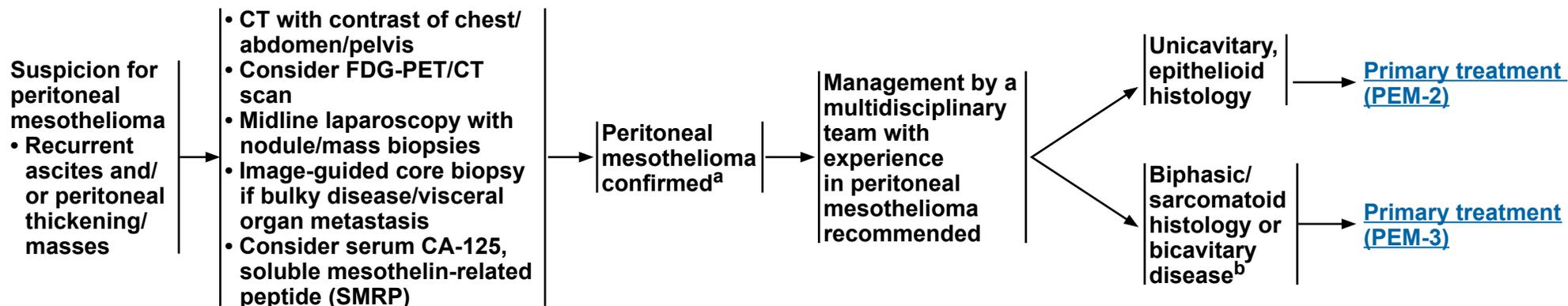
PEM-C 1 of 2

- Footnote removed: The combination regimens of pemetrexed/cisplatin/bevacizumab, pemetrexed/carboplatin/bevacizumab, and nivolumab/ipilimumab are only for unresectable disease.



INITIAL EVALUATION

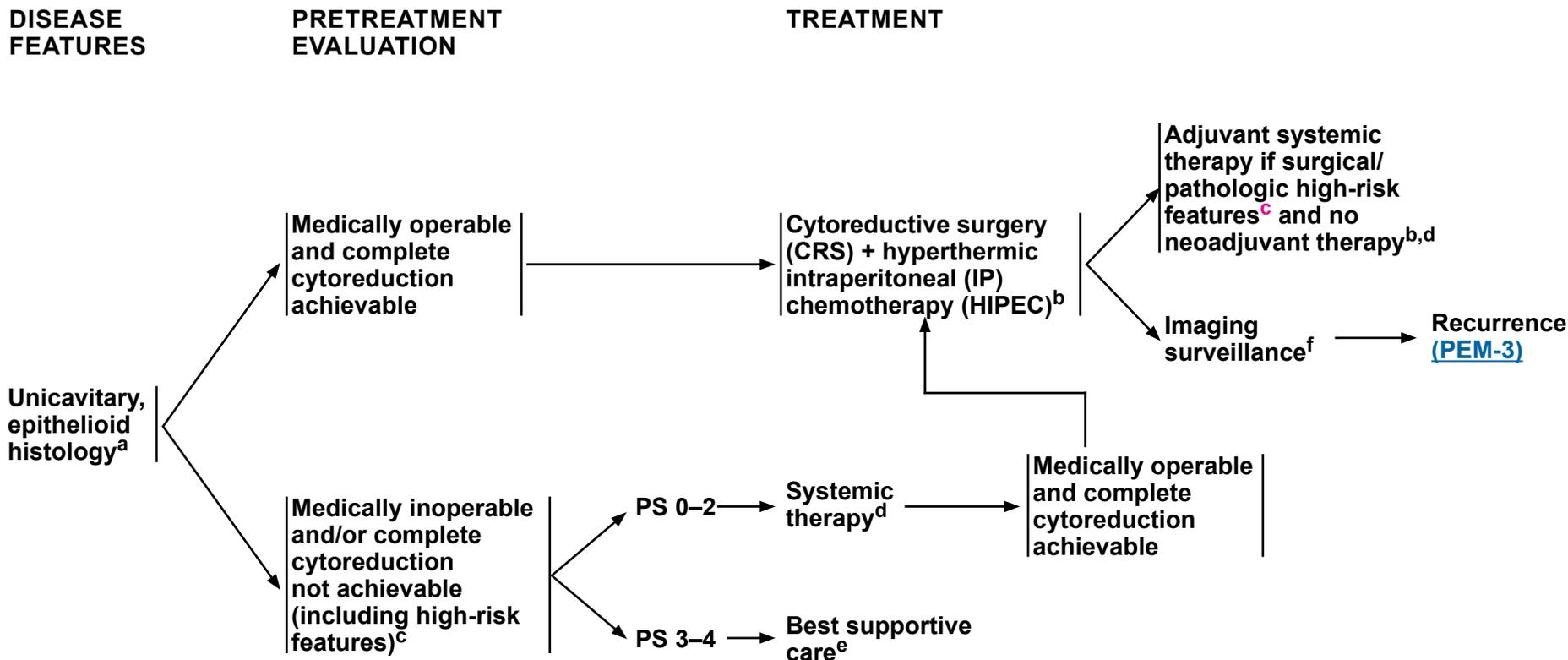
PATHOLOGIC DIAGNOSIS



^a [Principles of Pathologic Review \(PEM-A\)](#).

^b [Principles of Surgery \(PEM-B\)](#).

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



^a [Principles of Pathologic Review \(PEM-A\)](#).

^b [Principles of Surgery \(PEM-B\)](#).

^c Perioperative systemic therapy should be considered for high-risk features such as: Ki-67 >9%, nodal metastasis, high tumor burden (Peritoneal Cancer Index [PCI] >17), completeness of cytoreduction (CC) score >1, biphasic disease, or bicavitary disease. Patients with favorable prognostic profile (ie, complete cytoreduction, epithelioid subtype, no lymph node (LN) involvement, Ki-67 ≤9%, PCI ≤17) could be followed in surveillance as the benefit of adjuvant therapy is unknown.

^d [Principles of Systemic Therapy \(PEM-C\)](#).

^e [Principles of Supportive Care \(PEM-D\)](#).

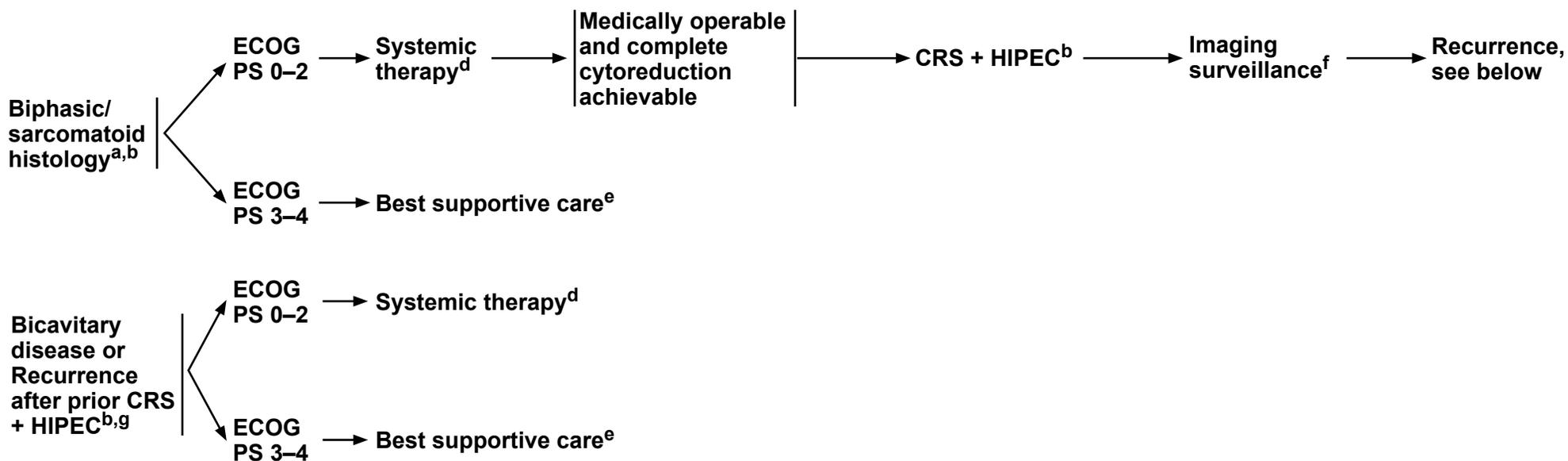
^f Recommended surveillance: CT chest/abdomen/pelvis every 3–6 mo x 5 y then yearly until 10 y.

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



DISEASE FEATURES

TREATMENT



^a [Principles of Pathologic Review \(PEM-A\)](#).

^b [Principles of Surgery \(PEM-B\)](#).

^d [Principles of Systemic Therapy \(PEM-C\)](#).

^e [Principles of Supportive Care \(PEM-D\)](#).

^f Recommended surveillance: CT chest/abdomen/pelvis every 3–6 mo x 5 y then yearly until 10 y.

^g Repeat CRS + HIPEC can be considered in patients who are >12 mo from prior CRS and are otherwise considered to have operable disease.

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



PRINCIPLES OF PATHOLOGIC REVIEW

Pathologic Evaluation

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

Mesothelioma Classification

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

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**PRINCIPLES OF PATHOLOGIC REVIEW****Mesothelioma Classification (continued)**

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

Histologic Criteria for Mesothelioma

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

Note: All recommendations are category 2A unless otherwise indicated.
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**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 calretinin and D2-40; and 2) negative markers to exclude mimics, such as polyclonal carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), and claudin-4.²³⁻²⁵ One of the caveats is that no individual IHC marker is entirely sensitive and specific. Therefore, it is recommended that a panel including at least two mesothelial markers (eg, calretinin, D2-40) and two carcinoma markers (eg, claudin-4, TTF-1, polyclonal CEA, PAX8) should be used to establish the diagnosis.²⁶
- Broad-spectrum keratins (eg, AE1/AE3, pancytokeratin, MNF116) are not specific and are expressed in both mesothelioma and carcinomas.
- Sarcomatoid mesothelioma often shows focal to absent expression for most mesothelial markers, with the most sensitive marker being D2-40/podoplanin.²⁷
- Recently, GATA3 has been explored as a potential diagnostic marker for sarcomatoid mesotheliomas since GATA3 is expressed in only ~10%–20% of sarcomatoid carcinoma²⁸ and strongly expressed in all sarcomatoid/desmoplastic mesotheliomas.²⁹

Markers to confirm a mesothelial malignant proliferation

- Although the distinction between mesothelioma and reactive mesothelial proliferations primarily relies on histologic assessment, this can be challenging in some cases.
- BAP1, MTAP IHC, and *CDKN2A* (p16) FISH are established markers for diagnosing mesothelioma.²²
 - ▶ BAP1 IHC is a specific (though not sensitive) marker to distinguish mesothelioma from reactive mesothelial proliferations.
 - ▶ *BAP1* is a tumor suppressor implicated in the pathogenesis of mesothelioma, uveal melanoma, cholangiocarcinoma, and clear-cell renal cell carcinoma.³⁰ Recurrent somatic and/or germline mutations in *BAP1* are present in mesothelioma. As a surrogate for *BAP1* genomic status, BAP1 IHC is used as a diagnostic marker for mesothelioma, whereas reactive proliferations have intact BAP1 nuclear staining. Complete absence of expression or cytoplasmic staining is considered a loss of BAP1 expression. Aberrant BAP1 protein expression, defined as absence of nuclear BAP1 staining, is present in ~50%–70% of mesothelioma epithelioid type³¹⁻³⁷ but in less than 20% of sarcomatoid type.³⁸
 - ▶ MTAP IHC has been used as a diagnostic marker for mesothelioma.³⁹ *MTAP* is located near *CDKN2A* on the chromosomal region 9p21. Loss of cytoplasmic MTAP staining is considered a surrogate for chromosomal 9p loss as determined by concurrent *CDKN2A* FISH testing³⁹ and has been reported in ~40%–60% of mesothelioma but rarely in reactive proliferations.³⁵⁻³⁷
 - ▶ Although MTAP alone is not sensitive, combined use of BAP1 and MTAP IHC may improve sensitivity and specificity.³⁵⁻³⁷ Since ~10%–20% of lung adenocarcinomas have MTAP loss,³⁶ MTAP IHC is not useful for distinction between mesothelioma and lung carcinoma.
 - ▶ *CDKN2A* FISH and MTAP IHC are less useful for the diagnosis of peritoneal mesotheliomas because the prevalence of *CDKN2A* deletions is 8%–26% and MTAP loss is 14%–16% in peritoneal mesotheliomas.⁴⁰⁻⁴⁴
- Additional IHC markers such as 5-hydroxymethyl cytosine (5-HMC), enhancer of zeste homolog 2 (EZH2), cyclin D1, and programmed death ligand 1 (PD-L1), and *NF2* by FISH are all potentially useful to distinguish mesothelioma from reactive mesothelial proliferations, but need further study since their utility in clinical practice remains unclear.²²

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

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**PRINCIPLES OF PATHOLOGIC REVIEW*****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.⁴⁵
 - ▶ Patients with mesothelioma with germline *BAP1* mutations have a prolonged survival.^{46,47}
 - ▶ *ALK* rearrangements by IHC found in rare patients with peritoneal mesothelioma⁴⁸⁻⁵¹ have shown dramatic response with ALK inhibitor therapies.^{52,53}
- 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.⁵⁴
- 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.⁵⁵
- 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.⁵⁶⁻⁵⁸
 - ▶ 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.⁵⁹
 - ▶ Hemizygous loss of *NF2* by FISH is present in ~50% of pleural mesotheliomas.⁶⁰
- 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 7.⁶¹

Molecular Features

- Most mesotheliomas are characterized by recurrent mutations in tumor suppressors and epigenetic regulators, including *BAP1*, *NF2*, *TP53*, *SETD2*, and other genes.⁶¹⁻⁶⁵ 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.⁶³ *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.^{61-63,66-68}
- 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*.⁶¹
- Peritoneal mesothelioma has distinct molecular features compared to pleural mesothelioma.⁶⁹

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

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**PRINCIPLES OF PATHOLOGIC REVIEW****Molecular Features** (continued)

- Oncogenic *EWSR1::ATF1* fusion has been described in pleural and peritoneal mesotheliomas from young adults.^{69,70}
 - ▶ *ALK* rearrangements have been identified in rare patients with peritoneal mesothelioma.^{48-50,53}
- Germline mutations are overall present in 12%–16% of patients with pleural and peritoneal mesothelioma and primarily involved genes in the DNA repair and cell cycle regulation, such as *BAP1*, *BRCA2*, *CDKN2A*, *TMEM127*, *VHL*, *WT1*, *MRE11A*, and *MSH6*.^{47,71,72} 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.^{47,71,73}

Differential Diagnosis

- The differential diagnosis of mesothelioma depends on the histologic type (epithelioid, biphasic, or sarcomatoid) under consideration. Mesothelioma can resemble reactive pleuritis or diverse tumor types, including carcinoma, melanoma, and sarcomas.
- In addition to diffuse mesothelioma, WHO recognizes additional types of mesothelial lesions: 1) localized mesothelioma, 2) WDPMT, and 3) adenomatoid tumor.¹
 - ▶ *Localized pleural mesothelioma* is microscopically identical to mesothelioma, although it is radiographically and grossly solitary and circumscribed.¹⁵⁻¹⁷ Genetically, localized pleural mesothelioma includes three groups (*BAP1*-mutant, *TRAF7*-mutant, and near-haploid), with similarities but also differences from pleural mesothelioma.¹⁸
 - ▶ *WDPMT*, often an incidental finding in the peritoneum of females, can occur in the pleura,⁷⁴ and is genetically characterized by recurrent mutations in *TRAF7* or *CDC42*.⁷⁵ Infrequently, WDPMT shows back-to-back papillae with foci of invasion,⁷⁶ 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.⁷⁷
 - ▶ *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**

- 1 WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Thoracic Tumours. 5th ed. Lyon, France: International Agency for Research on Cancer; 2021.
- 2 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.
- 3 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.
- 4 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.
- 5 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.
- 6 Ordonez NG. Mesothelioma with rhabdoid features: an ultrastructural and immunohistochemical study of 10 cases. *Mod Pathol* 2006;19:373-383.
- 7 Ordonez NG. Deciduoid mesothelioma: report of 21 cases with review of the literature. *Mod Pathol* 2012;25:1481-1495.
- 8 Ordonez NG. Mesotheliomas with small cell features: report of eight cases. *Mod Pathol* 2012;25:689-698.
- 9 Wilson GE, Hasleton PS, Chatterjee AK. Desmoplastic malignant mesothelioma: a review of 17 cases. *J Clin Pathol* 1992;45:295-298.
- 10 Klebe S, Brownlee NA, Mahar A, et al. Sarcomatoid mesothelioma: a clinical-pathologic correlation of 326 cases. *Mod Pathol* 2010;23:470-479.
- 11 Henderson DW, Attwood HD, Constance TJ, et al. Lymphohistiocytoid mesothelioma: a rare lymphomatoid variant of predominantly sarcomatoid mesothelioma. *Ultrastruct Pathol* 1988;12:367-384.
- 12 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.
- 13 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.
- 14 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.
- 15 Okike N, Bernatz PE, Woolner LB. Localized mesothelioma of the pleura: benign and malignant variants. *J Thorac Cardiovasc Surg* 1978;75:363-372.
- 16 Allen TC, Cagle PT, Churg AM, et al. Localized malignant mesothelioma. *Am J Surg Pathol* 2005;29:866-873.
- 17 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.
- 18 Hung YP, Dong F, Dubuc AM, et al. Molecular characterization of localized pleural mesothelioma. *Mod Pathol* 2020;33:271-280.
- 19 Churg A, Colby TV, Cagle P, et al. The separation of benign and malignant mesothelial proliferations. *Am J Surg Pathol* 2000;24:1183-1200.
- 20 Churg A, Galateau-Salle F. The separation of benign and malignant mesothelial proliferations. *Arch Pathol Lab Med* 2012;136:1217-1226.
- 21 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.
- 22 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.
- 23 Ordonez NG. Immunohistochemical diagnosis of epithelioid mesothelioma: an update. *Arch Pathol Lab Med* 2005;129:1407-1414.
- 24 Facchetti F, Gentili F, Lonardi S, et al. Claudin-4 in mesothelioma diagnosis. *Histopathology* 2007;51:261-263.
- 25 Anttila S. Epithelioid lesions of the serosa. *Arch Pathol Lab Med* 2012;13:241-252.
- 26 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.
- 27 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.
- 28 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.
- 29 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.
- 30 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.

**PRINCIPLES OF PATHOLOGIC REVIEW — REFERENCES**

- ³¹ 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.
- ³² 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.
- ³³ 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.
- ³⁴ 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.
- ³⁵ 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.
- ³⁶ 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.
- ³⁷ 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.
- ³⁸ 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.
- ³⁹ 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.
- ⁴⁰ Dagogo-Jack I, Madison RW, Lennerz JK, et al. Molecular characterization of mesothelioma: Impact of histologic type and site of origin on molecular landscape. *JCO Precis Oncol* 2022;6:e2100422.
- ⁴¹ Hiltbrunner S, Fleischmann Z, Sokol E, et al. Genomic landscape of pleural and peritoneal mesothelioma tumors. *Br J Cancer* 2022;127:1997-2005.
- ⁴² Joseph NM, Chen Y-Y, Nasr A, et al. Genomic profiling of malignant peritoneal mesothelioma reveals recurrent alterations in epigenetic regulatory genes BAP1, SETD2 and DDX3X. *Mod Pathol* 2017;30:246-254.
- ⁴³ Hung YP, Dong F, Torre M, et al. Molecular characterization of diffuse malignant peritoneal mesothelioma. *Mod Pathol* 2020;33:2269-2279.
- ⁴⁴ Offin M, Yang S-R, Egger J, et al. Molecular characterization of peritoneal mesotheliomas. *J Thorac Oncol* 2022;17:455-460.
- ⁴⁵ 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.
- ⁴⁶ 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.
- ⁴⁷ 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.
- ⁴⁸ Hung YP, Dong F, Watkins JC, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. *JAMA Oncol* 2018;4:235-238.
- ⁴⁹ 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.
- ⁵⁰ 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.
- ⁵¹ 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.
- ⁵² Ruschoff JH, Gradhand E, Kahraman A, et al. STRN-ALK rearranged malignant peritoneal mesothelioma with dramatic response following ceritinib treatment. *JCO Precis Oncol* 2019;3:1-6.
- ⁵³ 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.
- ⁵⁴ Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015;33:1974-1982.

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

**PRINCIPLES OF PATHOLOGIC REVIEW — REFERENCES**

- ⁵⁵ 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.
- ⁵⁶ 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.
- ⁵⁷ Dacic S, Kothmaier H, Land S, et al. Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas. *Virchows Arch* 2008;453:627-635.
- ⁵⁸ Chiosea S, Krasinskas A, Cagle PT, et al. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. *Mod Pathol* 2008;21:742-747.
- ⁵⁹ 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.
- ⁶⁰ 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.
- ⁶¹ Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. *Cancer Discov* 2018;8:1548-1565.
- 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.
- ⁶³ 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.
- ⁶⁴ 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.
- ⁶⁵ 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.
- ⁶⁶ 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.
- ⁶⁷ 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.
- ⁶⁸ 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.
- ⁶⁹ Offin M, Yang SR, Egger J, et al. Molecular characterization of peritoneal mesotheliomas. *J Thorac Oncol* 2022;17:455-460.
- ⁷⁰ 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.
- ⁷¹ 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.
- ⁷² 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.
- ⁷³ 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.
- ⁷⁴ 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.
- ⁷⁵ 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.
- ⁷⁶ Churg A, Allen T, Borczuk AC, et al. Well-differentiated papillary mesothelioma with invasive foci. *Am J Surg Pathol* 2014;38:990-998.
- ⁷⁷ 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 SURGERY**

- All recommendations are from well-designed retrospective case-control or cohort studies.
- Surgical resection should be performed on carefully evaluated patients by surgical oncologists with experience in managing peritoneal mesothelioma.
- Decisions regarding surgical options for treatment are highly dependent on accurate histology. Peritoneal biopsy for diagnosis should provide enough tissue for differentiation between peritoneal inclusion cyst, WDPMT, and subtypes of diffuse mesothelioma such as epithelioid, biphasic, and sarcomatoid. Cytology is generally not considered adequate for important histologic differentiation required for treatment decisions.
- For patients being considered for surgery, a laparoscopy is recommended to determine candidacy for complete cytoreduction.¹
- The goal of surgery is complete gross cytoreduction of the tumor. The goal of CRS is “macroscopic complete resection”—in other words, removal of ALL visible or palpable tumors (CC-0). A near complete cytoreduction with <2.5 mm visible residual disease (CC-1) is also acceptable for epithelioid mesothelioma subtype, as a large multi-institutional study suggests <2% change in 5-year overall survival (OS) and unchanged median OS for epithelioid peritoneal mesothelioma undergoing CC-1 compared to CC-0.² In cases where this is not possible, palliative surgery and/or HIPEC can be considered if associated with minimal morbidity. Otherwise, surgery should be aborted/not offered.³
- Complete cytoreduction frequently requires a total parietal peritonectomy, including visceral resections when necessary to achieve complete cytoreduction.⁴
- Resectable epithelioid mesothelioma should undergo upfront CRS and HIPEC. If there are no high-risk features identified (positive lymph node [LN], incomplete cytoreduction, or high Ki-67 >9%)⁵ then surveillance is sufficient. If high-risk features are identified then consideration for adjuvant therapy is recommended.
- For patients with biphasic, sarcomatoid, clinically positive LN, or high PCI >17, neoadjuvant therapy is strongly encouraged followed by re-evaluation for complete CRS and HIPEC.
- For patients with bicavitary disease and minimal disease burden in the thorax, systemic therapy is recommended. Surgery can be considered in select cases.⁶
- If a bevacizumab-containing regimen is administered, there should be at least a 6-week interval between the last dose and CRS.^{7,8}
- [Intraperitoneal \(IP\) chemotherapy regimens](#) typically consist of cisplatin, carboplatin, or mitomycin C. Platinum agents (both cisplatin and carboplatin) have been associated with improved outcomes over mitomycin C in retrospective comparisons.^{9,10}
- Early postoperative or prolonged adjuvant IP therapy have been investigated with some success and limited toxicity, but there remains insufficient evidence to recommend their use outside of a clinical trial.^{11,12}
- Patients who recur in the peritoneum after CRS and HIPEC should be re-evaluated for repeat CRS and HIPEC, as studies show this can be done safely and with good outcomes in appropriately selected patients.^{13,14}

[IP Chemotherapy Regimens \(PEM-B 2 of 3\)](#)
[Completeness of Cytoreduction Score \(PEM-B 2 of 3\)](#)
[Peritoneal Cancer Index Scoring System \(PEM-B 2 of 3\)](#)

[References \(PEM-B 3 of 3\)](#)

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

PRINCIPLES OF SURGERY

IP Chemotherapy Regimens

Preferred

- Cisplatin 50 mg/L + doxorubicin 15 mg/L of perfusate for 90 minutes¹⁵
- Cisplatin 50 mg/m² + doxorubicin 15 mg/m² for 90 minutes¹⁵
- Cisplatin 100–240 mg/m² for 90–110 minutes^{16,17}
- Carboplatin 600–800 mg/m² for 90 minutes¹⁸
- Cisplatin 25 mg/m²/L + mitomycin C 3.3 mg/m²/L for 60–90 minutes^{19,20}

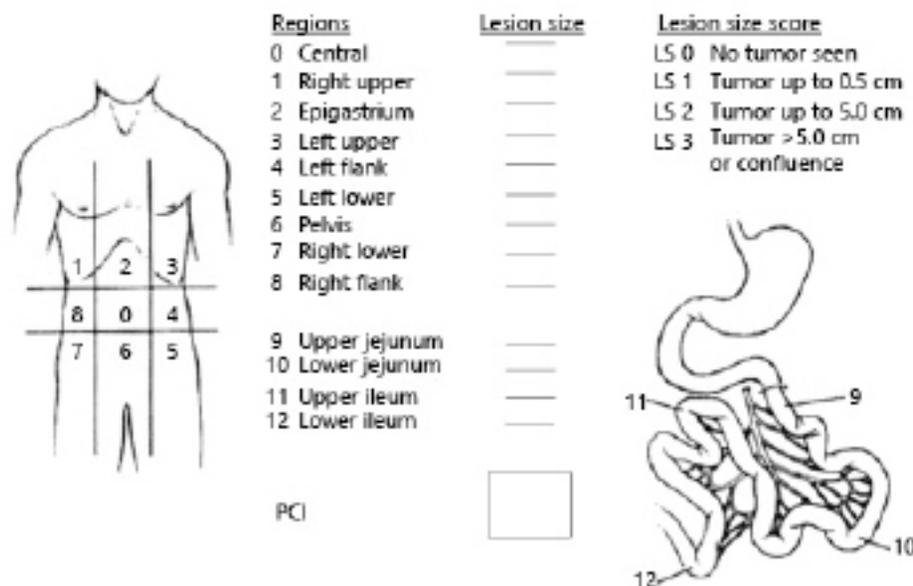
Useful in Certain Circumstances

- Mitomycin C 30 mg/m² for 90–110 minutes¹⁵
- Mitomycin C 30 mg at time 0 followed by mitomycin C 10 mg beginning at 60 minutes and continuing for 90–110 minutes¹⁵

Completeness of Cytoreduction (CC) Score²¹

Score	Definition
CC-0	No residual tumor
CC-1	Residual tumor <2.5 mm
CC-2	Residual tumor 2.5–25 mm
CC-3	Residual tumor >25 mm

Peritoneal Cancer Index (PCI) Scoring System²¹



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

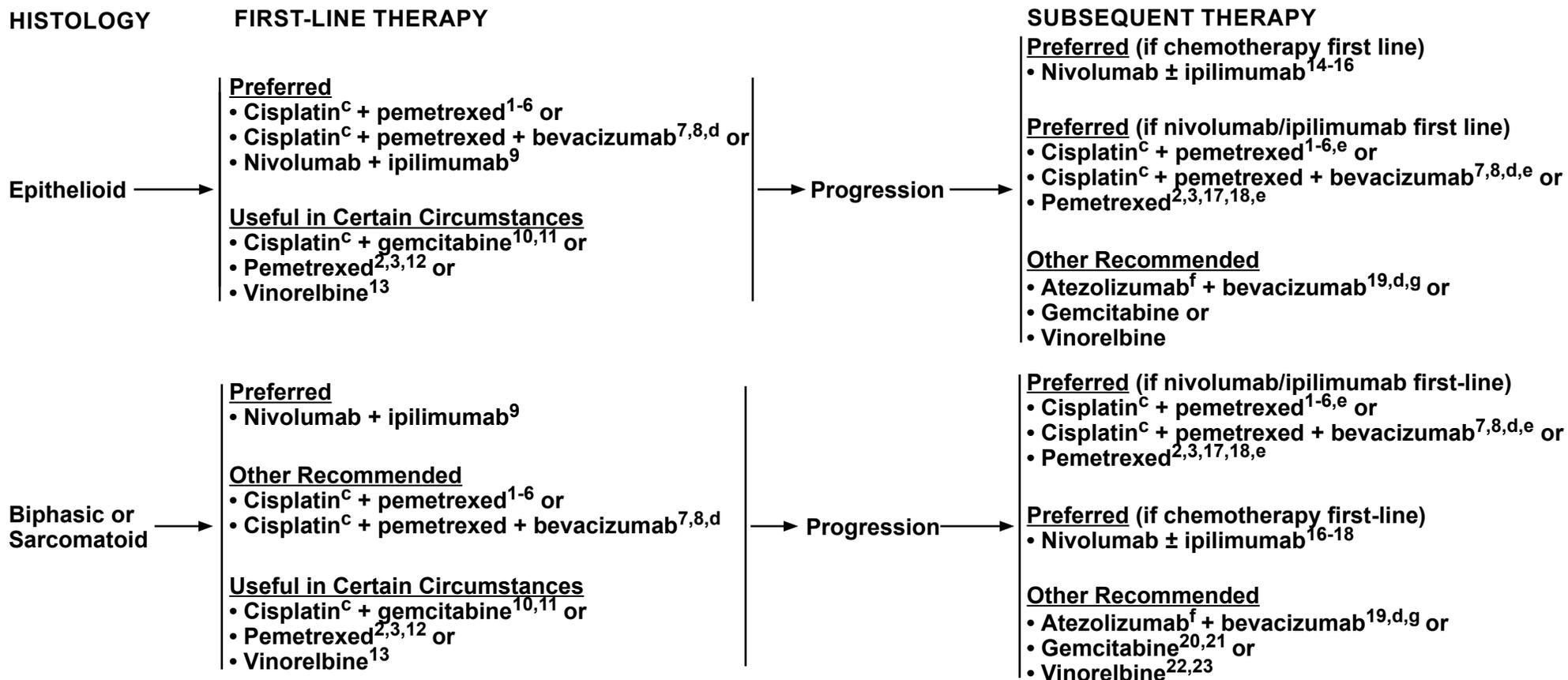
**PRINCIPLES OF SURGERY — REFERENCES**

- 1 Laterza B, Kusamura S, Baratti D, et al. Role of explorative laparoscopy to evaluate optimal candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal mesothelioma. *In Vivo* 2009;23:187-190.
- 2 Votanopoulos KI, Sugarbaker P, Deraco M, et al. Is cytoreductive surgery with hyperthermic intraperitoneal chemotherapy justified for biphasic variants of peritoneal mesothelioma? Outcomes from the Peritoneal Surface Oncology Group International Registry. *Ann Surg Oncol* 2018;25:667-673.
- 3 Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol* 2009;27:6237-6242.
- 4 Baratti D, Kusamura S, Cabras AD, Deraco M. Cytoreductive surgery with selective versus complete parietal peritonectomy followed by hyperthermic intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma: a controlled study. *Ann Surg Oncol* 2012;19:1416-1424.
- 5 Gilly FN, Cotte E, Brigand C, et al. Quantitative prognostic indices in peritoneal carcinomatosis. *Eur J Surg Oncol* 2006;32:597-601.
- 6 Ripley RT, Holmes HM, Whitlock RS, et al. Pleurectomy and decortication are associated with better survival for bicavitary cytoreductive surgery for mesothelioma compared with extrapleural pneumonectomy. *J Thorac Cardiovasc Surg* 2023;165:1722-1730.
- 7 Petrillo M, Nero C, Carbone V, et al. Systematic review of cytoreductive surgery and bevacizumab-containing chemotherapy in advanced ovarian cancer: focus on safety. *Ann Surg Oncol* 2018;25:247-254.
- 8 King BH, Baumgartner JM, Kelly KJ, et al. Preoperative bevacizumab does not increase complications following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *PLoS One* 2020;15:e0243252.
- 9 Helm JH, Miura JT, Glenn JA, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. *Ann Surg Oncol* 2015;22:1686-1693.
- 10 Shetty SJ, Bathla L, Govindarajan V, et al. Comparison of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin or carboplatin for diffuse malignant peritoneal mesothelioma. *Am Surg* 2014;80:348-352.
- 11 Sugarbaker PH, Chang D. Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival. *Eur J Surg Oncol* 2017;43:1228-1235.
- 12 Bijelic L, Stuart OA, Sugarbaker PH. Adjuvant bidirectional chemotherapy with intraperitoneal pemetrexed combined with intravenous Cisplatin for diffuse malignant peritoneal mesothelioma. *Gastroenterol Res Pract* 2012;2012:890450.
- 13 Pasqual EM, Londero AP, Robella M, et al. Repeated cytoreduction combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in selected patients affected by peritoneal metastases: Italian PSM Oncoteam Evidence. *Cancers (Basel)* 2023;15:607.
- 14 Wong J, Koch AL, Deneve JL, et al. Repeat cytoreductive surgery and heated intraperitoneal chemotherapy may offer survival benefit for intraperitoneal mesothelioma: a single institution experience. *Ann Surg Oncol* 2014;21:1480-1486.
- 15 Chicago Consensus Working Group. The Chicago Consensus on peritoneal surface malignancies: Management of peritoneal mesothelioma. *Cancer*. 2020;126:2547-2552.
- 16 Kusamura S, Baratti D, Younan R, et al. Impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on systemic toxicity. *Ann Surg Oncol* 2007;14:2550-2558.
- 17 Baratti D, Kusamura S, Laterza B, et al. Early and long-term postoperative management following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Gastrointest Oncol* 2010;2:36-43.
- 18 Shetty SJ, Bathla L, Govindarajan V, et al. Comparison of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin or carboplatin for diffuse malignant peritoneal mesothelioma. *Am Surg* 2014;80:348-52.
- 19 Baratti D, Kusamura S, Cabras AD, et al. Diffuse malignant peritoneal mesothelioma: Long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Cancer*. 2013;49:3140-3148.
- 20 Kepenekian V, Elias D, Passot G, et al. Diffuse malignant peritoneal mesothelioma: Evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE database. *Eur J Cancer* 2016;69-79.
- 21 Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol* 1999;43:S15-S25.

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



PRINCIPLES OF SYSTEMIC THERAPY^{a,b}



[References on PEM-C \(2 of 2\)](#)

^a All regimens may also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.

^b Broad molecular tumor profiling is recommended with the goal of identifying rare driver alterations (eg, *NTRK* or *ALK*) for which effective drugs may be available or to appropriately counsel patients regarding the availability of clinical trials.^{24,25}

^c Carboplatin is recommended for patients who are not candidates for cisplatin.

^d An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

^e Consider rechallenge if good response to front-line pemetrexed-based treatment.²⁶

^f Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for intravenous infusion.

^g Atezolizumab/bevacizumab should only be considered if patients have not been previously treated with immune checkpoint inhibitors.

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

**PRINCIPLES OF SYSTEMIC THERAPY — REFERENCES**

- ¹ 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.
- ² Janne PA, Wozniak AJ, Belani CP, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer* 2005;7:40-46.
- ³ 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.
- ⁴ 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.
- ⁵ 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.
- ⁶ Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma. *J Thorac Oncol* 2008;3:756-763.
- ⁷ 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.
- ⁸ 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.
- ⁹ 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.
- ¹⁰ Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491-496.
- ¹¹ 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.
- ¹² Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol* 2008;3:764-771.
- ¹³ 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.
- ¹⁴ 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.
- ¹⁵ 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.
- ¹⁶ 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.
- ¹⁷ 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.
- ¹⁸ 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.
- ¹⁹ Raghav K, Liu S, Overman MJ, et al. Efficacy, safety, and biomarker analysis of combined PD-L1 (atezolizumab) and VEGF (bevacizumab) blockade in advanced malignant peritoneal mesothelioma. *Cancer Discov* 2021;11:2738-2747.
- ²⁰ 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.
- ²¹ 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.
- ²² 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.
- ²³ 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.
- ²⁴ Hung YP, Dong F, Watkins JC, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. *Jama Oncol* 2018;4:235-238.
- ²⁵ Rüschoff JH, Gradhand E, Kahraman A, et al. *STRN-ALK* rearranged malignant peritoneal mesothelioma with dramatic response following ceritinib treatment. *JCO Precis Oncol* 2019;3:1-6.
- ²⁶ 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 SUPPORTIVE CARE

- **Peritoneal effusions:** paracentesis or peritoneal catheter, if required for management of ascites
- **Smoking cessation counseling and intervention:** [NCCN Guidelines for Smoking Cessation](#)
- **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

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



ABBREVIATIONS

CC	completeness of cytoreduction
CRS	cytoreductive surgery
ECOG	Eastern Cooperative Oncology Group
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
H&E	hematoxylin and eosin
HIPEC	hyperthermic intraperitoneal chemotherapy
IHC	immunohistochemistry
IP	intraperitoneal
LN	lymph node
NGS	next-generation sequencing
OS	overall survival
PCI	Peritoneal Cancer Index
PD-L1	programmed death ligand 1
PS	performance status
WDPMT	well-differentiated papillary mesothelial tumor



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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.



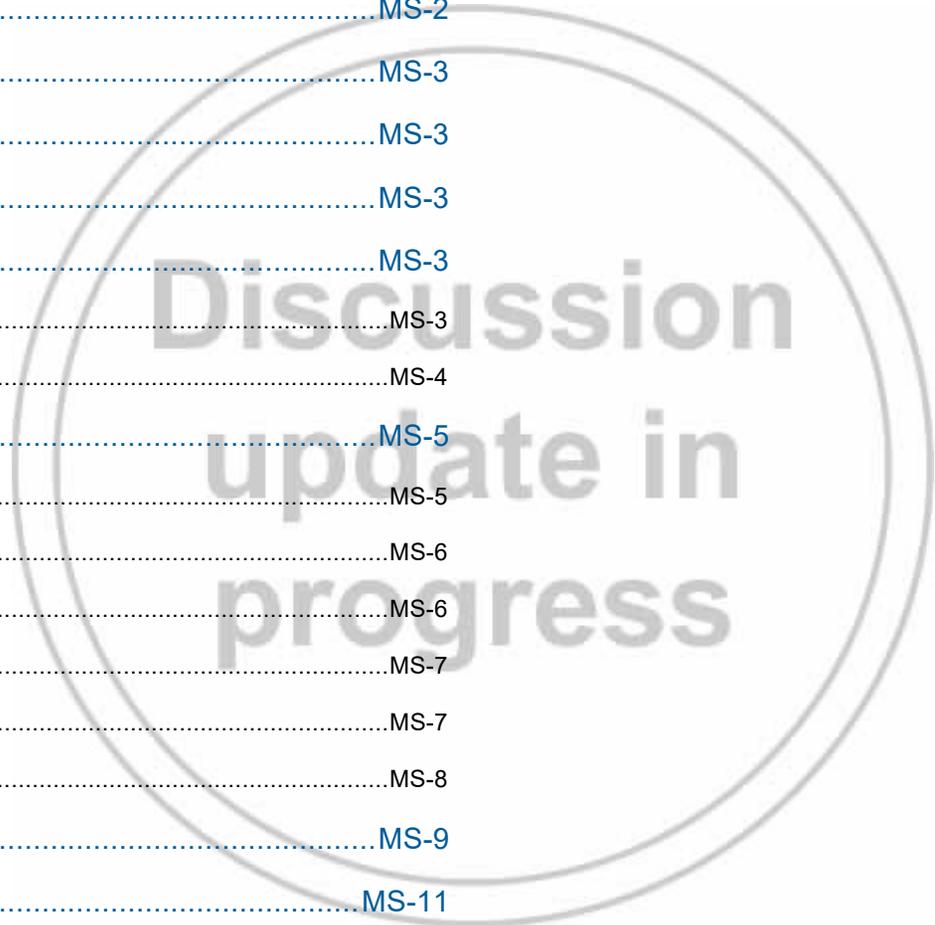
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Discussion

This discussion corresponds to the NCCN Guidelines for Mesothelioma: Peritoneal. Last updated: July 20, 2023.

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Mesothelioma: Peritoneal

Overview

Mesothelioma is a rare cancer originating in mesothelial surfaces of the peritoneum, pleura, and other sites that is estimated to occur in approximately 3500 people in the United States every year.¹⁻⁵ These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) focus on peritoneal mesothelioma (PeM), which is a less common type (approximately 15%). Most mesothelioma occurs in the pleura (approximately 85%); it can also occur very rarely in other sites, such as the pericardium and tunica vaginalis testis.⁶⁻⁹ It is estimated that PeM occurs in approximately 300 to 400 people in the United States every year.¹⁰ The true incidence may be higher because PeM may not be coded correctly; it may be misdiagnosed as other cancers that typically involve the peritoneum, such as ovarian cancer. The mean age is about 69 years at diagnosis of PeM. One-year overall survival is approximately 46% in patients with PeM, and 5-year overall survival is about 20%; cure is rare.¹¹ Survival is improved for patients who are able to undergo complete cytoreductive surgery (CRS) with intraperitoneal chemotherapy.¹²⁻¹⁶ There are multiple intravenous systemic therapy options for patients who are not candidates for CRS, or those whose disease recurs following CRS with or without hyperthermic intraperitoneal chemotherapy (HIPEC).

Similar to pleural mesothelioma, the histologic subtypes of PeM include epithelioid (most common), sarcomatoid, and biphasic (also known as mixed, containing both epithelioid and sarcomatoid components).^{4,17-19} Patients with epithelioid histology have better outcomes than those with either biphasic or sarcomatoid histologies; histology is used to direct treatment.¹⁵ Although there are similarities between PeM and pleural mesothelioma, there are unique differences.¹⁵ PeM is diagnosed in equal numbers of males and females; pleural mesothelioma is more common in males.¹¹ In addition, PeM may occur in younger patients, whereas pleural mesothelioma typically occurs in older patients. Many patients with PeM have idiopathic disease.²⁰ Pleural mesothelioma is typically caused by

asbestos exposure; however, PeM is less frequently associated with asbestos exposure.²¹⁻²⁴ The incidence of pleural mesothelioma and PeM is decreasing in the United States, because asbestos use has decreased since the 1970s.^{1,5,25-28} Although asbestos is no longer mined in the United States, it is still imported.²⁸ Genetic factors play a role in some patients with PeM, with families carrying a germline mutation in the *BRCA1*-associated protein-1 (*BAP1*) gene; a few patients have somatic mutations, such as anaplastic lymphoma kinase (*ALK*) rearrangements or rare fusions.²⁹⁻³⁷

Patients with PeM present with abdominal signs and symptoms, such as ascites, pain, distension, and an abdominal mass.^{11,38} They often have a high symptom burden compared with patients who have other types of cancer. The diagnosis of PeM may be delayed, because symptoms are nonspecific.^{11,21,24,38} Thus, many patients with PeM have advanced disease at diagnosis.¹¹ Although PeM can spread extensively in the abdomen, it less commonly metastasizes beyond the abdominal cavity.²⁴

These NCCN Clinical Practice Guidelines (NCCN Guidelines[®]) Mesothelioma: Peritoneal were first published in 2021 and will be updated at least once every year. For the 2023 update (Version 1), the NCCN Panel revised the title of the guideline to Mesothelioma: Peritoneal to align with the pleural mesothelioma guidelines; the previous title was Malignant Peritoneal Mesothelioma. The term *malignant* is no longer used to classify mesotheliomas, because all mesotheliomas are now defined as malignant.³⁹ The pathology section was also updated to include new information about markers used to identify mesothelioma, which is difficult to diagnose; PeM has distinct molecular features when compared with pleural mesothelioma (see *Principles of Pathologic Review*).⁴⁰ A new abbreviations list was also added to the guidelines. Additional supplementary material in the NCCN Guidelines[®] for Mesothelioma: Peritoneal includes the *Principles of Pathologic Review*,



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Principles of Surgery, Principles of Systemic Therapy, and Principles of Supportive Care. These NCCN Guidelines for Mesothelioma: Peritoneal were developed by panel members who also developed the NCCN Guidelines for Mesothelioma: Pleural and the NCCN Guidelines for Non-Small Cell Lung Cancer.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines for Mesothelioma: Peritoneal, an electronic search of the PubMed database was performed to obtain key literature in PeM published since the previous Guidelines update, using the search term: peritoneal 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 II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use

language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-fat-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis

Initial Evaluation

Patients with PeM present with abdominal signs and symptoms, such as ascites (77%), pain (69%), distension, and an abdominal mass (30%); they may also present with weight loss, fatigue, anorexia, asthenia, nausea, early satiety, and intestinal obstruction (see the NCCN Guidelines for Adult Cancer Pain, available at www.NCCN.org).^{11,21,38} The diagnosis of PeM may be delayed, because PeM mimics other diseases and conditions and because the disease is so rare.^{11,24,38}

To diagnose PeM, initial evaluations include CT imaging of the chest/abdomen/pelvis and laparoscopy to obtain a biopsy of the abdominal mass/nodule(s). On CT, diffuse distribution in the abdomen and the absence of lymph nodes or distant metastases suggest PeM; however, there are no specific imaging findings for PeM.^{24,41,42} Laparoscopy is also

done to assess whether complete CRS is possible.²⁴ Fine-needle aspiration (FNA) of the nodule/mass is not recommended for diagnosis, because FNA cannot differentiate between the different histologic subtypes of PeM including epithelioid, sarcomatoid, and biphasic. Using paracentesis fluid (cytology) is also not recommended for diagnosis because invasion cannot be detected using cytology.^{21,24} Measurement of soluble mesothelin-related peptide (SMRP) and CA-125 levels may be considered, and these levels may correlate with disease status. For patients suspected of having PeM, the NCCN Guidelines for Mesothelioma: Peritoneal recommend an initial evaluation including: 1) CT with contrast of the chest, abdomen, and pelvis; 2) biopsies of the nodule/mass using a midline laparoscopy; and 3) serum markers.^{21,42,43}

Pathology

Tissue biopsy of the abdominal mass/nodule(s) with histopathology is essential for an accurate diagnosis of PeM, because symptoms, imaging findings, and serum markers are not specific. Patients may have benign and preinvasive mesothelial tumors such as peritoneal inclusion cyst, well-differentiated papillary mesothelial tumor (WDPMT), or mesothelioma in situ.⁴⁴⁻⁴⁶ Peritoneal inclusion cyst is very rare; it was previously termed benign multicystic PeM but was revised based on the recent WHO classification.⁴⁷⁻⁴⁹ Diffuse PeM is malignant and further divided into specific histologic subtypes, including epithelioid, sarcomatoid, or biphasic histology (epithelioid and sarcomatoid histology, also known as mixed).^{17,50} Unless otherwise indicated, these PeM guidelines refer to diffuse PeM, because most patients have diffuse mesothelioma. Although localized pleural mesothelioma may occur, it is very rare; localized PeM is extremely rare.^{33,51-53} Accurate histology is essential, because the treatment options depend on histology. Patients with an epithelioid subtype have longer median overall survival (39 months) compared to patients who have a biphasic subtype (14 months).¹⁵ However, median survival is improved if patients are able to undergo cytoreductive surgery

(55 months for epithelial histology vs. 13 months for biphasic).⁵⁴ It is important to distinguish diffuse PeM from peritoneal inclusion cyst and WDPMT because treatment options differ; it is also important to distinguish PeM from metastatic carcinomas such as breast, gastrointestinal, liver, lung, ovarian, pancreatic, and renal cell (see *Principles of Pathologic Review* in the algorithm).⁵⁵ The differential diagnosis of PeM includes peritoneal carcinomatosis, serous peritoneal carcinoma, tuberculous peritonitis, and alcoholic cirrhosis.^{24,56}

Detailed information about the pathologic evaluation of PeM is provided in the algorithm and summarized here (see *Principles of Pathologic Review*). Because PeM and pleural mesothelioma are similar, the pathology section also contains content about pleural mesothelioma. The classification for pleural mesothelioma was revised based on new recommendations from the World Health Organization (WHO).^{39,57} The classification for PeM has also been revised. The term *malignant* is no longer used to classify mesotheliomas, because all mesotheliomas are now defined as malignant.³⁹

Histologic assessment and immunohistochemistry (IHC) are the main tools used in the diagnosis of diffuse PeM; however, cytogenetics and molecular techniques are also used. For a diagnosis of mesothelioma, the lesion needs to be diffuse, mesothelial, and malignant. There is no single IHC marker to diagnose PeM. Different IHC markers need to be used to distinguish PeMs from other carcinomas, such as gynecologic malignancies or renal cell carcinomas. A panel of markers is recommended as follows: 1) two mesothelial markers (ie, positive markers), including calretinin and podoplanin (D2-40); and 2) two carcinoma markers (ie, negative markers) including claudin 4, thyroid transcription factor 1 (TTF-1), polyclonal carcinoembryonic antigen (CEA), and paired box gene 8 (PAX8).^{17,50,58-64} Although PAX8 is a carcinoma marker, sometimes PeMs will stain for PAX8.^{17,65} Wilms tumor protein 1

(WT-1) is generally positive for PeM; however, it is also positive for papillary serous carcinoma.⁶³ For the 2023 update (Version 1), the NCCN Panel deleted WT-1 and added PAX8 for the differential diagnosis of PeM. It is important to note that IHC markers for diagnosing PeM differ slightly from those for diagnosing pleural mesothelioma. For example, TTF-1 and D2-40 are not useful for diagnosing PeM, although they are useful for diagnosing pleural mesothelioma.¹⁷

BAP1 IHC loss is a molecular marker that is useful for diagnosing mesothelioma, especially mesothelioma in situ, which is difficult to diagnose.^{11,66-71} *BAP1* is a tumor suppressor gene involved in mesothelioma and other carcinomas. Recurrent somatic and/or germline mutations in *BAP1* occur in mesothelioma.^{11,71} Aberrant *BAP1* protein expression, which is defined as absence of nuclear *BAP1* IHC staining, occurs in about 50% to 70% of patients with epithelioid mesothelioma but in less than 20% of those with sarcomatoid mesothelioma.⁷² *BAP1* IHC is useful for distinguishing mesotheliomas from benign mesothelial tumors. For the 2023 update (Version 1), the NCCN Panel clarified that complete absence of expression or cytoplasmic staining is considered a loss of *BAP1* expression. Methylthioadenosine phosphorylase (MTAP) IHC is another molecular marker that is useful for diagnosing pleural mesotheliomas. Cytoplasmic loss of MTAP IHC is used to quickly assess the presence of cyclin-dependent kinase inhibitor 2A (*CDKN2A*) deletions, which can be measured by fluorescence in situ hybridization (FISH). However, fewer patients with PeMs have *CDKN2A* deletions (8%–35%) compared with patients with pleural mesotheliomas (60%–74%).^{40,66,67,73}

Management

The NCCN Guidelines for Mesothelioma: Peritoneal recommend that patients with PeM should have their treatment managed by a multidisciplinary team with experience in PeM.^{12,21} Treatment options for patients with diffuse PeM include surgery and/or systemic therapy.^{21,74}

Select patients with medically operable diffuse PeM and good performance status (PS) are candidates for multimodality therapy, including those with epithelioid histology and unicavitary disease. Systemic therapy is recommended for patients with diffuse PeM who are not eligible for or refuse surgery. Best supportive care is recommended for patients with a PS of 3 to 4 (see *Principles of Supportive Care* in the algorithm). Radiation therapy is not recommended as a primary therapy for PeM but can be used selectively for palliation. Treatment options for patients with peritoneal inclusion cyst or WDPMT include: 1) observation with imaging surveillance for those with asymptomatic and noninvasive disease; or 2) CRS with or without HIPEC for those who have symptomatic, recurrent, or microinvasive disease.

There are no phase 3 randomized trials to determine the best treatment for patients with PeM because it is so rare, although there are a few clinical trials.^{13,14,75-77} Because PeM and pleural mesothelioma are similar, systemic therapy recommendations for PeM are based on extrapolating data from clinical trials in pleural mesothelioma; recommendations are also based on clinical trials in PeM, and on the expertise of the panel members (see *Surgery and Intraperitoneal Chemotherapy* and *Systemic Therapy* in this Discussion).²¹

Surgery and Intraperitoneal Chemotherapy

Data show good outcomes for eligible patients with PeM who have CRS and intraperitoneal chemotherapy (see *Clinical Trials* in this Discussion).^{13,14,59,75-77} Therefore, a multidisciplinary evaluation is recommended to assess whether patients are eligible for surgery. During laparoscopic biopsy, a surgical evaluation is done to assess whether patients are candidates for surgery. After a diagnosis of diffuse PeM, PET/CT is done to determine whether patients have unicavitary or bicavitary disease. Surgery is typically contraindicated in patients with bicavitary disease and those with biphasic or sarcomatoid histology;



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however, surgery may be considered in select patients with bicavitary disease or low-volume biphasic disease (see *Principles of Surgery* in the algorithm).⁷⁸ It is essential that patients receive a careful assessment before surgery is performed. Complete cytoreduction is recommended for eligible patients with epithelioid histology and unicavitary PeM who are medically operable.^{21,74,76,79}

The surgical goal for PeM is CRS to achieve macroscopic complete resection by removing all visible or palpable tumors, which frequently involves a total peritoneal peritonectomy (see *Principles of Surgery* in the algorithm). If macroscopic complete resection or near complete cytoreduction is not possible, then surgery should be aborted. Palliative surgery and/or HIPEC can be considered but only if there will be minimal morbidity. There is no accepted staging system for PeM. The peritoneal cancer index scoring system is used to indicate the severity of the symptom burden (see *Principles of Surgery* in the algorithm).⁷⁴ A completeness of cytoreduction score of zero (CC-0) indicates that there is no residual disease (see *Principles of Surgery* in the algorithm).⁸⁰ A novel staging system based on the peritoneal carcinomatosis index is available.⁸¹

Clinical Trials

A multi-institutional study assessed CRS and HIPEC in 401 patients with PeM; 46% had complete or near-complete cytoreduction and 92% received HIPEC.⁷⁶ The median overall survival was 53 months (1–235 months); 3-year and 5-year survival rates were 60% and 47%, respectively. Grade 3–4 complications occurred in 127 patients (31%); 9 patients died perioperatively. A meta-analysis assessed CRS and intraperitoneal chemotherapy in 1047 patients with PeM.¹⁶ Complete cytoreduction was done in 67% of patients (46%–93%). Survival estimates were 84% at 1 year, 59% at 3 years, and 42% at 5 years.

In a single institution study, 108 patients with PeM had CRS and HIPEC with cisplatin and either doxorubicin or mitomycin-C.⁷⁷ The median overall survival was 63.2 months (95% CI, 29.6–96.7). Nineteen patients survived more than 7 years and appeared to be cured. Major morbidity was 38.9%; two patients died perioperatively. In another single institution study, 84 patients with PeM had CRS and HIPEC with cisplatin plus doxorubicin; 66 patients had complete or near complete cytoreduction.¹⁴ Almost all patients had epithelioid histology (97.6%). The median overall survival was 38.4 months (95% CI, 23.6–54.3); 5-year survival was 42%. Grade 3–4 complications occurred in 22 patients (26.2%); acute kidney injury occurred in 30 patients (35.7%). Three patients died perioperatively.

A retrospective study (Peritoneal Surface Oncology Group International) assessed CRS and HIPEC in 34 patients with MPEM and biphasic histology; 5-year survival was 50.2% (median, 6.8 years) for those who had a complete resection (CC-0).⁷⁸ Five-year survival was 41.6% (median, 2.8 years) for those who had incomplete CC-1 resections. Median survival was only 4.3 months in those who had incomplete CC-2 resections.

NCCN Recommendations

The NCCN Panel recommends CRS and HIPEC for eligible patients with PeM based on trials for PeM and pleural mesothelioma (see *Principles of Surgery* and *Principles of Systemic Therapy* in the algorithm).^{21,74} Appropriate patients should be evaluated by surgeons, medical oncologists, and diagnostic imaging specialists to assess if they are candidates for multimodality treatment.

Complete cytoreduction and HIPEC are recommended for patients with unicavitary PeM and epithelioid histology who are medically operable if a complete cytoreduction is achievable. Perioperative systemic therapy should be considered if patients have high-risk features (such as Ki-67 >9%, nodal metastases, high tumor burden [peritoneal cancer index >17]), CC > 1, biphasic disease, or bicavitary disease). Although measuring the



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Ki-67 index is not routinely recommended at diagnosis, it may be useful for helping to define high-risk features. After perioperative therapy, patients may be eligible for CRS and HIPEC. Systemic therapy alone is recommended for patients with PS 0 to 2 who are medically inoperable or refuse surgery (see *Systemic Therapy* in this Discussion).

The NCCN Panel has preference stratified the intraperitoneal chemotherapy regimens and voted that the following regimens are preferred: 1) cisplatin plus doxorubicin; 2) cisplatin; 3) carboplatin; or 4) cisplatin plus mitomycin (see *Principles of Surgery* in the algorithm).^{74,77,82-84} The panel has voted that monotherapy mitomycin regimens are useful in certain circumstances.⁷⁴

Systemic Therapy

Only a few systemic therapy clinical trials have been done for patients with PeM who are not eligible for surgery.^{7,85-89} Therefore, recommended systemic therapy regimens for PeM are mainly based on clinical trials done in patients with pleural mesothelioma; the NCCN Panel has decided that these regimens are equally efficacious for both disease sites (see *Principles of Systemic Therapy* in the algorithm).^{21,74,85,89} Details about the systemic therapy clinical trials for pleural mesothelioma are described in the Discussion for pleural mesothelioma (see the NCCN Guidelines for Mesothelioma: Pleural, available at www.NCCN.org). For the 2023 update (Version 1), the NCCN Panel reorganized the systemic therapy recommendations based on histology and line of therapy. All of the regimens recommended for PeM and pleural mesothelioma may also be used for eligible patients with pericardial mesothelioma and tunica vaginalis testis mesothelioma, which are extremely rare cancers.^{90,91}

Clinical Trials

The International Expanded Access Program (EAP) assessed pemetrexed regimens in patients with mesothelioma who were not eligible for

surgery.⁹²⁻⁹⁴ A subset of 98 patients with PeM received pemetrexed regimens.⁸⁶ Median survival was not reached for patients receiving first-line therapy with either pemetrexed alone or pemetrexed plus cisplatin; response rates were 25%. Median survival was 13.1 months for patients with PeM receiving second-line therapy with either pemetrexed alone or pemetrexed plus cisplatin; response rates were 23.3%. Updated results from the EAP were published for 109 patients with PeM receiving pemetrexed regimens who were not eligible for surgery.⁷ Patients received pemetrexed, pemetrexed plus cisplatin, or pemetrexed plus carboplatin as either first-line or second-line therapy. For pemetrexed plus cisplatin, 1-year survival was 57.4% (95% CI, 10.3%–100%). For patients receiving pemetrexed alone, median survival was 10.3 months; 1-year survival was 41.5% (95% CI, 4.6%–78.4%). Survival rates are not available for pemetrexed plus carboplatin. The most frequent grade 3–4 adverse event was neutropenia (34.6%).

Several small studies done in Japan assessed pemetrexed regimens in patients with PeM. One study assessed first-line therapy with pemetrexed plus cisplatin in 24 patients with PeM.⁹⁵ There were two complete responses and nine partial responses. Median overall survival was 15.8 months. Another study assessed first-line therapy with pemetrexed plus cisplatin in 29 patients with PeM.⁸⁹ Median overall survival was 15.4 months (95% CI, 9.5–21.2). Grade 3–4 adverse events included leukopenia (21%), neutropenia (17%), anemia (14%), and thrombocytopenia (3%). Updated results were reported from this group in 54 patients with PeM who received first-line therapy with pemetrexed plus platinum.⁸⁷ Median overall survival was 16.6 months. This study also assessed second-line therapy in 26 patients with PeM.⁸⁷ Patients received gemcitabine (12), taxane (6), nivolumab (3), and other agents (5). Median overall survival was 16.9 months. Several small studies have reported that patients with PeM respond to first-line therapy with gemcitabine plus cisplatin.⁹⁶⁻⁹⁸ Data also show that first-line therapy with gemcitabine plus



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pemetrexed is effective, although this regimen is toxic (grade 3–4 neutropenia, 60%).⁹⁹

A phase 2 trial assessed atezolizumab plus bevacizumab as subsequent therapy for 20 patients with advanced and unresectable PeM who had progressed on or were intolerant to pemetrexed plus platinum chemotherapy.⁸⁵ Many patients were women (60%) and did not have previous exposure to asbestos (75%). The median age was 63 years. Most patients had epithelioid histology (90%); 10% had biphasic histology. One patient had previously received bevacizumab. The response rate was 40% (8/20; 95% CI, 19%–64%). Overall survival at 1 year was 85% (95% CI, 60%–95%). Grade 3 treatment-emergent adverse events occurred in 50% of patients (10/20) including hypertension (40%) and anemia (10%). Grade 3 immune-related adverse events—pancreatitis and thrombocytopenia—occurred in 2 patients (10%), which required stopping treatment.

A cohort study assessed subsequent therapy with immune checkpoint inhibitors (ICIs) in 29 patients with PeM.¹⁰⁰ Most patients had received one line of therapy (83%, 24/29). Many patients received subsequent therapy with nivolumab plus ipilimumab (69%, 20/29); some patients received single-agent ICIs (31%, 9/29), including nivolumab (n=4), pembrolizumab (n=3), or atezolizumab (n=2). The overall response rate was 19% (5/26; 95% CI, 6.6%–39%). Patients responded to ICIs regardless of whether they had responded to previous platinum-based chemotherapy. The median duration of overall survival was 19 months (95% CI, 7.4–43). The 1-year overall survival rate was 68% (95% CI, 45%–83%). Five patients (17%) had moderate or severe side effects, including edema and increased creatinine levels.

CONFIRM, a phase 3 randomized trial, assessed nivolumab (67%) versus placebo (33%) in 332 patients with pleural mesothelioma who had progressed after platinum-based chemotherapy.⁸⁸ Most patients had

pleural mesothelioma (95%) and epithelioid histology (88%); a few patients had PeM (n = 16). 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).

Somatic *ALK* rearrangements have been identified in a few young patients with PeM who did not have other genetic alterations.^{32,37,101–103} In 25 young patients (≤40 years of age) with PeM, 2 (8%) had an *ALK* rearrangement: a 14-year-old female and a 27-year-old male.¹⁰² They did not have a history of asbestos exposure or radiation therapy and did not have predisposing germline mutations. The 14-year-old female responded to therapy and survived more than 5 years from the diagnosis of PeM.¹⁰² A dramatic response with ceritinib was reported in a 13-year-old girl with PeM who had an *ALK* rearrangement.¹⁰⁴ Other case reports have reported that patients may respond to crizotinib.^{37,105}

NCCN Recommendations

The NCCN Panel recommends systemic therapy alone for patients with a PS of 0 to 2 and diffuse PeM, including those 1) who are medically inoperable, for whom a complete CRS cannot be achieved, or who refuse surgery; 2) with bicavitary disease regardless of histology and stage; 3) with sarcomatoid or biphasic histology regardless of stage; or 4) with recurrence after previous CRS and HIPEC. Surgery may be considered in select patients with bicavitary disease or low-volume biphasic disease (see *Principles of Surgery* in the algorithm).⁷⁸ The systemic therapy regimens are also recommended for eligible patients with pleural



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mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.^{7,90,92}

Although about 50% of patients with PeM have positive programmed cell death-ligand 1 (PD-L1) expression levels, the NCCN Panel does not require PD-L1 testing before using ICIs based on clinical trial data.^{61,85,88} ICIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage the adverse events, and educate their patients about possible side effects (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). Atezolizumab, nivolumab, or ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis or myocarditis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated-mediated adverse events when indicated (see prescribing information).

The NCCN Panel has preference stratified the first-line systemic therapy regimens for eligible patients with PeM and epithelioid histology who are not eligible for surgery and voted that the following regimens are preferred options: 1) pemetrexed plus cisplatin plus bevacizumab; 2) pemetrexed plus cisplatin; or 3) nivolumab plus ipilimumab.^{7,86,106,107} Carboplatin is recommended if patients are not candidates for cisplatin, regardless of histology.^{7,92} The panel voted that the following regimens are useful in certain circumstances for eligible patients with PeM and epithelioid histology: 1) gemcitabine plus cisplatin; 2) pemetrexed; or 3) vinorelbine.^{86,96,108-111}

The NCCN Panel has preference stratified the first-line systemic therapy regimens for eligible patients with PeM and biphasic or sarcomatoid histology who are not eligible for surgery and voted that nivolumab plus

ipilimumab is the preferred option.¹⁰⁷ The panel voted that the following are other recommended regimens: 1) pemetrexed plus cisplatin plus bevacizumab; or 2) pemetrexed plus cisplatin.^{7,86,106} The panel voted that the following regimens are useful in certain circumstances: 1) gemcitabine plus cisplatin; 2) pemetrexed; or 3) vinorelbine.^{86,96,108-111} Carboplatin is recommended if patients are not candidates for cisplatin, regardless of histology.

The NCCN Panel has also preference stratified the subsequent (second-line and beyond) systemic therapy regimens for eligible patients with PeM and voted that the following regimens are preferred, regardless of histology, if they were not given first line: 1) pemetrexed plus cisplatin plus bevacizumab; 2) pemetrexed plus cisplatin; 3) pemetrexed; or 4) nivolumab plus ipilimumab.^{88,112-114} However, pemetrexed regimens may be given again as subsequent systemic therapy if a good sustained response was obtained when the initial chemotherapy was interrupted.^{115,116} The panel decided that the following are other recommended subsequent therapy regimens: 1) atezolizumab plus bevacizumab; 2) vinorelbine; or 3) gemcitabine.^{85,117-120} For the 2023 update (Version 1), the NCCN Panel clarified that atezolizumab plus bevacizumab should only be considered as subsequent therapy if patients have not previously been treated with ICIs.

Summary

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) focus on PeM. This Discussion text for PeM 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. For the 2023 update (Version 1), the NCCN Panel revised the title of the guideline to Mesothelioma: Peritoneal to align with the pleural mesothelioma guidelines; the previous title was Malignant Peritoneal Mesothelioma. The term *malignant* is no

longer used to classify mesotheliomas, because all mesotheliomas are now defined as malignant.³⁹ The classification for pleural mesothelioma was revised based on new recommendations from the World Health Organization (WHO).^{39,57} The classification for PeM has also been revised. A new abbreviations list was also added to the guidelines.

Mesothelioma is a rare cancer originating in mesothelial surfaces of the peritoneum (15%), pleura (85%), and other sites that is estimated to occur in approximately 3500 people in the United States every year.¹⁻⁴ It is estimated that PeM occurs in approximately 300 to 400 people in the United States every year.¹⁰ The mean age is about 69 years at diagnosis of PeM. One-year overall survival is approximately 46% in patients with PeM, and 5-year overall survival is about 20%; cure is rare.^{2,11,121-124}

Patients with PeM present with abdominal signs and symptoms, such as pain, distension, ascites, and an abdominal mass.^{11,38} Patients with PeM often have a high symptom burden compared with patients who have other types of cancer. The diagnosis of PeM may be delayed, because symptoms are nonspecific.^{11,24,38} Thus, many patients have advanced disease at diagnosis.¹¹ Although PeM can spread extensively in the abdomen, it rarely metastasizes beyond the abdominal cavity.²⁴ For the 2023 update (Version 1), the NCCN Panel revised the pathology section to include new information about markers used to identify PeM, which is difficult to diagnose and has distinct molecular features when compared with pleural mesothelioma (see *Principles of Pathologic Review* in the algorithm).⁴⁰ There is no single IHC marker to diagnose PeM. Different IHC markers need to be used to distinguish PeMs from other carcinomas,

such as gynecologic malignancies or renal cell carcinomas. A panel of markers is recommended as follows: 1) two mesothelial markers (ie, positive markers), including calretinin and podoplanin (D2-40); and 2) two carcinoma markers (ie, negative markers) including claudin 4, TTF-1, polyclonal CEA, and PAX8.^{17,50,58-64} Although PAX8 is a carcinoma marker, sometimes PeMs will stain for PAX8.^{17,65} WT-1 is generally positive for PeM; however, it is also positive for papillary serous carcinoma.⁶³ For the 2023 update (Version 1), the NCCN Panel deleted WT-1 and added PAX8 for the differential diagnosis of PeM.

Data show good outcomes for eligible patients with PeM who have CRS and intraperitoneal chemotherapy.^{13,14,75-77} Therefore, a multidisciplinary evaluation is recommended to assess whether patients are eligible for surgery. There are multiple intravenous systemic therapy options for patients who are not candidates for CRS, or whose disease recurs following CRS with or without HIPEC. Recommended systemic therapy regimens for PeM are mainly based on clinical trials done in patients with pleural mesothelioma; the NCCN Panel has decided that these regimens are equally efficacious for both disease sites.^{21,74,89} Details about the systemic therapy clinical trials for pleural mesothelioma are described in the discussion for pleural mesothelioma (see the NCCN Guidelines for Mesothelioma: Pleural, available at www.NCCN.org). For the 2023 update (Version 1), the NCCN Panel reorganized the systemic therapy recommendations for PeM based on histology and line of therapy. The NCCN Panel also clarified that atezolizumab plus bevacizumab should only be considered as a subsequent therapy option for patients with PeM if they have not previously been treated with ICIs.



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References

- 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/.
- Special Section – Rare Cancers in Adults. American Cancer Society. Cancer Facts & Figures 2017. Available at: <https://tinyurl.com/yb4joe3c>.
- 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>.
- 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>.
- SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program National Cancer Institute. Available at: <https://seer.cancer.gov/statistics-network/explorer/>.
- 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>.
- 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>.
- 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>.
- 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>.
- Henley SJ, Peipins LA, Rim SH, et al. Geographic co-occurrence of mesothelioma and ovarian cancer incidence. J Womens Health (Larchmt) 2020;29:111-118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31314677>.
- Ullah A, Waheed A, Khan J, et al. Incidence, survival analysis and future perspective of primary peritoneal mesothelioma (PPM): A population-based study from SEER Database. Cancers (Basel) 2022;14:942. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35205689>.
- Kusamura S, Baratti D, De Simone M, et al. Diagnostic and therapeutic pathway in diffuse malignant peritoneal mesothelioma. Cancers (Basel) 2023;15: 662. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36765620>.
- Bijelic L, Darcy K, Stodghill J, et al. Predictors and Outcomes of Surgery in Peritoneal Mesothelioma: an Analysis of 2000 Patients from the National Cancer Database. Ann Surg Oncol 2020;27:2974-2982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32006127>.
- Acs M, Gerken M, Gajic I, et al. Ten-year single-center experience with treatment of primary diffuse malignant peritoneal mesothelioma (DMPM) by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Langenbecks Arch Surg 2022;407:3057-3067. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35732846>.
- Chapel DB, Schulte JJ, Absenger G, et al. Malignant peritoneal mesothelioma: prognostic significance of clinical and pathologic parameters and validation of a nuclear-grading system in a multi-institutional series of 225 cases. Mod Pathol 2021;34:380-395. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33060816>.



NCCN Guidelines Version 2.2024 Mesothelioma: Peritoneal

16. Helm JH, Miura JT, Glenn JA, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. *Ann Surg Oncol* 2015;22:1686-1693. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25124472>.
17. 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>.
18. 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>.
19. 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>.
20. Carbone M, Adusumilli PS, Alexander HR, Jr., et al. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin* 2019;69:402-429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31283845>.
21. Kusamura S, Kepenekian V, Villeneuve L, et al. Peritoneal mesothelioma: PSOGI/EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol* 2021;47:36-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32209311>.
22. Boffetta P. Epidemiology of peritoneal mesothelioma: a review. *Ann Oncol* 2007;18:985-990. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17030547>.
23. Consonni D, Calvi C, De Matteis S, et al. Peritoneal mesothelioma and asbestos exposure: a population-based case-control study in Lombardy, Italy. *Occup Environ Med* 2019;76:545-553. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31285358>.
24. Kim J, Bhagwandin S, Labow DM. Malignant peritoneal mesothelioma: a review. *Ann Transl Med* 2017;5:236. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28706904>.
25. 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>.
26. 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>.
27. 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>.
28. 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>.
29. Dagogo-Jack I, Madison RW, Lennerz JK, et al. Molecular characterization of mesothelioma: Impact of histologic type and site of origin on molecular landscape. *JCO Precis Oncol* 2022;6:e2100422. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35704798>.
30. Borczuk AC, Pei J, Taub RN, et al. Genome-wide analysis of abdominal and pleural malignant mesothelioma with DNA arrays reveals both common and distinct regions of copy number alteration. *Cancer Biol*



NCCN Guidelines Version 2.2024

Mesothelioma: Peritoneal

Ther 2016;17:328-335. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26853494>.

31. Alakus H, Yost SE, Woo B, et al. BAP1 mutation is a frequent somatic event in peritoneal malignant mesothelioma. *J Transl Med* 2015;13:122.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25889843>.

32. Hung YP, Dong F, Watkins JC, et al. Identification of ALK Rearrangements in Malignant Peritoneal Mesothelioma. *JAMA Oncol* 2018;4:235-238. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28910456>.

33. 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>.

34. Leblay N, Lepretre F, Le Stang N, et al. BAP1 is altered by copy number loss, mutation, and/or loss of protein expression in more than 70% of malignant peritoneal mesotheliomas. *J Thorac Oncol* 2017;12:724-733.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28034829>.

35. 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>.

36. Dermawan JK, Torrence D, Lee CH, et al. EWSR1::YY1 fusion positive peritoneal epithelioid mesothelioma harbors mesothelioma epigenetic signature: Report of 3 cases in support of an emerging entity. *Genes Chromosomes Cancer* 2022;61:592-602. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/35665561>.

37. Gerthofer V, Scheiter A, Luke F, et al. STRN-ALK fusion in a case of malignant peritoneal mesothelioma: Mixed response to crizotinib, mode of resistance, and brigatinib sequential therapy. *JCO Precis Oncol* 2021;5.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34568722>.

38. Garcia-Fadrique A, Mehta A, Mohamed F, et al. Clinical presentation, diagnosis, classification and management of peritoneal mesothelioma: a

review. *J Gastrointest Oncol* 2017;8:915-924. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29184697>.

39. 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>.

40. Hiltbrunner S, Fleischmann Z, Sokol ES, et al. Genomic landscape of pleural and peritoneal mesothelioma tumours. *Br J Cancer* 2022;127:1997-2005. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/36138075>.

41. Carlson B, Harmath C, Turaga K, et al. The role of imaging in diagnosis and management of malignant peritoneal mesothelioma: a systematic review. *Abdom Radiol (NY)* 2022;47:1725-1740. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/35257201>.

42. Yan TD, Haveric N, Carmignani CP, et al. Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Cancer* 2005;103:839-849.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15637690>.

43. Pickhardt PJ, Perez AA, Elmohr MM, Elsayes KM. CT imaging review of uncommon peritoneal-based neoplasms: beyond carcinomatosis. *Br J Radiol* 2021;94:20201288. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33353398>.

44. Shrestha R, Nabavi N, Volik S, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically distinct from malignant mesothelioma. *Cancers (Basel)* 2020;12:1568. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32545767>.

45. Churg A, Allen T, Borczuk AC, et al. Well-differentiated papillary mesothelioma with invasive foci. *Am J Surg Pathol* 2014;38:990-998.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24618613>.



NCCN Guidelines Version 2.2024 Mesothelioma: Peritoneal

46. Malpica A, Sant'Ambrogio S, Deavers MT, Silva EG. Well-differentiated papillary mesothelioma of the female peritoneum: a clinicopathologic study of 26 cases. *Am J Surg Pathol* 2012;36:117-127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22024662>.

47. Noiret B, Renaud F, Piessen G, Eveno C. Multicystic peritoneal mesothelioma: a systematic review of the literature. *Pleura Peritoneum* 2019;4:20190024. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31667333>.

48. Baratti D, Vaira M, Kusamura S, et al. Multicystic peritoneal mesothelioma: outcomes and patho-biological features in a multi-institutional series treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol* 2010;36:1047-1053. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20832234>.

49. Baratti D, Kusamura S, Nonaka D, et al. Multicystic and well-differentiated papillary peritoneal mesothelioma treated by surgical cytoreduction and hyperthermic intra-peritoneal chemotherapy (HIPEC). *Ann Surg Oncol* 2007;14:2790-2797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17661150>.

50. Chapel DB, Schulte JJ, Husain AN, Krausz T. Application of immunohistochemistry in diagnosis and management of malignant mesothelioma. *Transl Lung Cancer Res* 2020;9:S3-S27. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32206567>.

51. 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>.

52. Marchevsky AM, Khor 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>.

53. Jeppesen TD, Hojsgaard A, Kjaer D, Christensen TD. Localized malignant mesothelioma in the stomach and mediastinum. *Interact Cardiovasc Thorac Surg* 2022;34:485-487. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34586396>.

54. Liu S, Staats P, Lee M, et al. Diffuse mesothelioma of the peritoneum: correlation between histological and clinical parameters and survival in 73 patients. *Pathology* 2014;46:604-609. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25393250>.

55. Rizzuto I, Power T, Oehler MK. Diffuse Peritoneal Malignant Mesothelioma Presenting with Abnormal Uterine Bleeding: Case Report. *Case Rep Oncol* 2022;15:251-256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35431868>.

56. Lin LC, Kuan WY, Shiu BH, et al. Primary malignant peritoneal mesothelioma mimicking tuberculous peritonitis: A case report. *World J Clin Cases* 2022;10:3156-3163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35647134>.

57. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours Thoracic Tumours. WHO classification of tumours series, 5th ed. Lyon, France: International Agency for Research on Cancer; 2021.

58. 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.

59. Malpica A, Euscher ED, Marques-Piubelli ML, et al. Malignant mesothelioma of the peritoneum in women: A clinicopathologic study of 164 cases. *Am J Surg Pathol* 2021;45:45-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32769428>.

60. 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>.

61. 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>.

62. 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>.

63. 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>.

64. 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>.

65. Chapel DB, Husain AN, Krausz T, McGregor SM. PAX8 expression in a subset of malignant peritoneal mesotheliomas and benign mesothelium has diagnostic implications in the differential diagnosis of ovarian serous carcinoma. Am J Surg Pathol 2017;41:1675-1682. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28877056>.

66. Offin M, Yang SR, Egger J, et al. Molecular characterization of peritoneal mesotheliomas. J Thorac Oncol 2022;17:455-460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34648949>.

67. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32826526>.

68. Singhi AD, Krasinskas AM, Choudry HA, et al. The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma. Mod Pathol 2016;29:14-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26493618>.

69. Tandon RT, Jimenez-Cortez Y, Taub R, Borczuk AC. Immunohistochemistry in peritoneal mesothelioma: A single-center experience of 244 cases. Arch Pathol Lab Med 2018;142:236-242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29048219>.

70. Kawai T, Tominaga S, Hiroi S, et al. Peritoneal malignant mesothelioma (PMM), and primary peritoneal serous carcinoma (PPSC) and reactive mesothelial hyperplasia (RMH) of the peritoneum. Immunohistochemical and fluorescence in situ hybridisation (FISH) analyses. J Clin Pathol 2016;69:706-712. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26729015>.

71. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27067777>.

72. Schulte JJ, Husain AN. Update on the pathologic diagnosis of malignant mesothelioma. Transl Lung Cancer Res 2020;9:917-923. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32676357>.

73. Krasinskas AM, Bartlett DL, Cieply K, Dacic S. CDKN2A and MTAP deletions in peritoneal mesotheliomas are correlated with loss of p16 protein expression and poor survival. Mod Pathol 2010;23:531-538. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20081810>.



74. The Chicago Consensus on peritoneal surface malignancies: Management of peritoneal mesothelioma. *Cancer* 2020;126:2547-2552. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32282077>.

75. Feldman AL, Libutti SK, Pingpank JF, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. *J Clin Oncol* 2003;21:4560-4567. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14673042>.

76. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol* 2009;27:6237-6242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19917862>.

77. Baratti D, Kusamura S, Cabras AD, et al. Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Cancer* 2013;49:3140-3148. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23831335>.

78. Votanopoulos KI, Sugarbaker P, Deraco M, et al. Is cytoreductive surgery with hyperthermic intraperitoneal chemotherapy justified for biphasic variants of peritoneal mesothelioma? Outcomes from the Peritoneal Surface Oncology Group International Registry. *Ann Surg Oncol* 2018;25:667-673. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29260418>.

79. 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>.

80. 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>.

81. Yan TD, Deraco M, Elias D, et al. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database*. *Cancer* 2011;117:1855-1863. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21509762>.

82. Kusamura S, Baratti D, Younan R, et al. Impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on systemic toxicity. *Ann Surg Oncol* 2007;14:2550-2558. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17558537>.

83. Shetty SJ, Bathla L, Govindarajan V, et al. Comparison of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin or carboplatin for diffuse malignant peritoneal mesothelioma. *Am Surg* 2014;80:348-352. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24887664>.

84. Kepenekian V, Elias D, Passot G, et al. Diffuse malignant peritoneal mesothelioma: Evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE Database: Multi-Institutional Retrospective Study. *Eur J Cancer* 2016;65:69-79. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27472649>.

85. Raghav K, Liu S, Overman MJ, et al. Efficacy, safety, and biomarker analysis of combined PD-L1 (atezolizumab) and VEGF (bevacizumab) blockade in advanced malignant peritoneal mesothelioma. *Cancer Discov* 2021;11:2738-2747. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34261675>.

86. Janne PA, Wozniak AJ, Belani CP, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer* 2005;7:40-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16098243>.

87. Kitadai R, Shimoi T, Sudo K, et al. Efficacy of second-line treatment and prognostic factors in patients with advanced malignant peritoneal mesothelioma: a retrospective study. *BMC Cancer* 2021;21:294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33743636>.



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88. 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>.
89. Nagata Y, Sawada R, Takashima A, et al. Efficacy and safety of pemetrexed plus cisplatin as first-line chemotherapy in advanced malignant peritoneal mesothelioma. *Jpn J Clin Oncol* 2019;49:1004-1008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31287877>.
90. 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>.
91. 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>.
92. 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>.
93. 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>.
94. Obasaju CK, Ye Z, Wozniak AJ, et al. Single-arm, open label study of pemetrexed plus cisplatin in chemotherapy naive patients with malignant pleural mesothelioma: outcomes of an expanded access program. *Lung Cancer* 2007;55:187-194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17092602>.
95. Fujimoto E, Kijima T, Kuribayashi K, et al. First-line chemotherapy with pemetrexed plus cisplatin for malignant peritoneal mesothelioma. *Expert Rev Anticancer Ther* 2017;17:865-872. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28594258>.
96. 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>.
97. Tanida S, Kataoka H, Kubota E, et al. Combination chemotherapy with cisplatin and gemcitabine in malignant peritoneal mesothelioma. *Int J Clin Oncol* 2009;14:266-269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19593622>.
98. Kobayashi S, Waragai T, Sano H, et al. Malignant peritoneal mesothelioma in a child: chemotherapy with gemcitabine and platinum was effective for the disease unresponsive to other treatments. *Anticancer Drugs* 2014;25:1102-1105. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25010395>.
99. Simon GR, Verschraegen CF, Janne PA, et al. Pemetrexed plus gemcitabine as first-line chemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. *J Clin Oncol* 2008;26:3567-3572. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18640937>.
100. Raghav K, Liu S, Overman M, et al. Clinical efficacy of immune checkpoint inhibitors in patients with advanced malignant peritoneal mesothelioma. *JAMA Netw Open* 2021;4:e2119934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34357397>.
101. Miyagawa C, Takaya H, Sakai K, et al. A novel malignant peritoneal mesothelioma with STRN exon 2 and ALK exon 20: a case report and literature review. *Oncologist* 2021;26:356-361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33555117>.
102. Mian I, Abdullaev Z, Morrow B, et al. Anaplastic lymphoma kinase gene rearrangement in children and young adults with mesothelioma. *J*



NCCN Guidelines Version 2.2024

Mesothelioma: Peritoneal

Thorac Oncol 2020;15:457-461. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/31783178>.

103. 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. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/33399341>.

104. Ruschoff JH, Gradhand E, Kahraman A, et al. STRN -ALK rearranged malignant peritoneal mesothelioma with dramatic response following ceritinib treatment. JCO Precis Oncol 2019;3. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32914035>.

105. Murumagi A, Ungureanu D, Arjama M, et al. STRN-ALK rearranged pediatric malignant peritoneal mesothelioma - Functional testing of 527 cancer drugs in patient-derived cancer cells. Transl Oncol 2021;14:101027. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/33530027>.

106. 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>.

107. 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>.

108. 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>.

109. 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>.

110. Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol 2008;3:764-771. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18594323>.

111. 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>.

112. 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>.

113. 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>.

114. 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>.

115. 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. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/22943698>.

116. Gilani SN, Gridley R, Searle G, Jegannathan A. Malignant peritoneal mesothelioma (MPM) who responded to rechallenge with cisplatin and



NCCN Guidelines Version 2.2024 Mesothelioma: Peritoneal

pemetrexed with current literature review. *BMJ Case Rep* 2013;2013. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23291819>.

117. 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>.

118. 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>.

119. 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>.

120. 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>.

121. 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>.

122. 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>.

123. 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>.

124. 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>.