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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Mesothelioma: Peritoneal

Version 2.2025 — January 14, 2025

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

PEM-D 1 of 3
- Footnote e added: Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Updates in Version 1.2025 of the NCCN Guidelines for Mesothelioma: Peritoneal from Version 3.2024 include:

PEM-1
- Initial Evaluation
  - Bullet 1 modified: CT *of chest* with contrast ~~of chest/~~ *+ CT or MRI of* abdomen/pelvis *with contrast*
  - Bullet 5 added: Tumor Ki-67 index
  - Bullet 6 modified: ~~Consider Serum CA-125,~~ Soluble mesothelin-related peptide (SMRP) *(optional)*
- Differentiation of histology (unicavitary, epithelioid, biphasic/sarcomatoid, bicavitary disease) removed

PEM-2
- This is a new page, replacing the previous PEM-2 and PEM-3 pages.

PEM-A 4 of 8
- Markers as potential prognostic and predictive markers
  - Bullet 1 added: Ki-67 labeling index by IHC staining is independently prognostic for overall survival (OS) for patients undergoing CRS + HIPEC, with Ki-67 index >9% associated with worse survival and is therefore considered a high-risk feature.

PEM-A 7 of 8
- Reference 45 added: Kusamura S, Torres Mesa PA, Cabras A, et al. The role of Ki-67 and precytoreduction parameters in selecting diffuse malignant peritoneal mesothelioma (DMPM) patients for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 2016;23:1468-1473.

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

PEM-D 2 of 3
- Reference 14 added: Favaretto AG, Aversa SML, Paccagnella A, et al. Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric phase II study. Cancer 2003;97:2791-2797.

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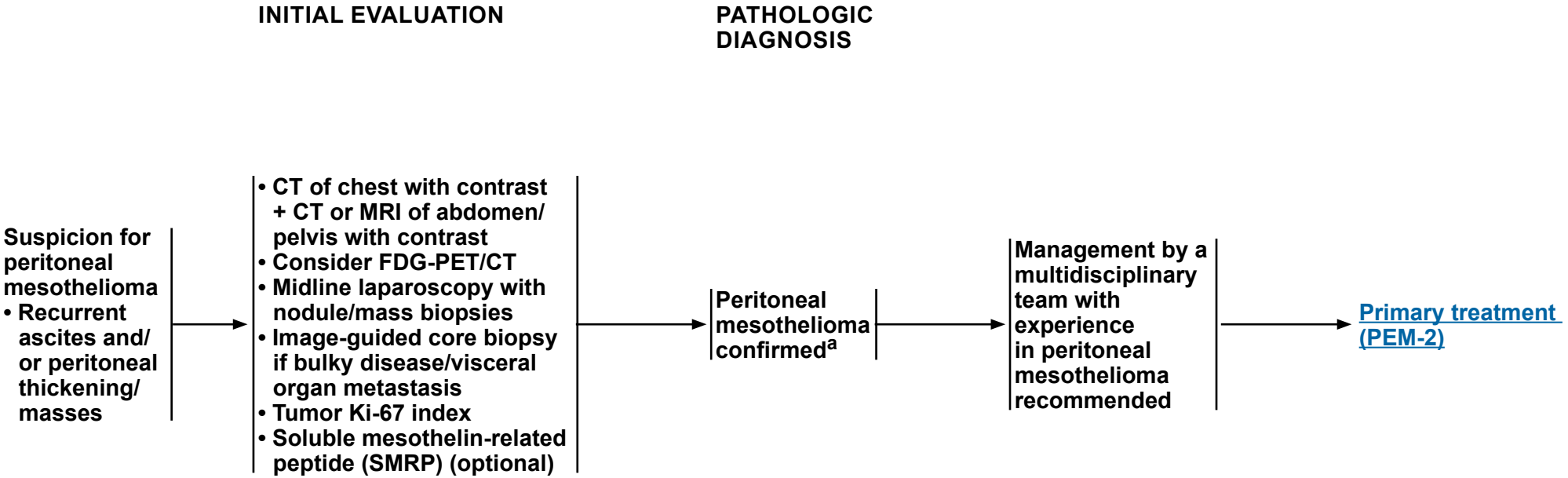
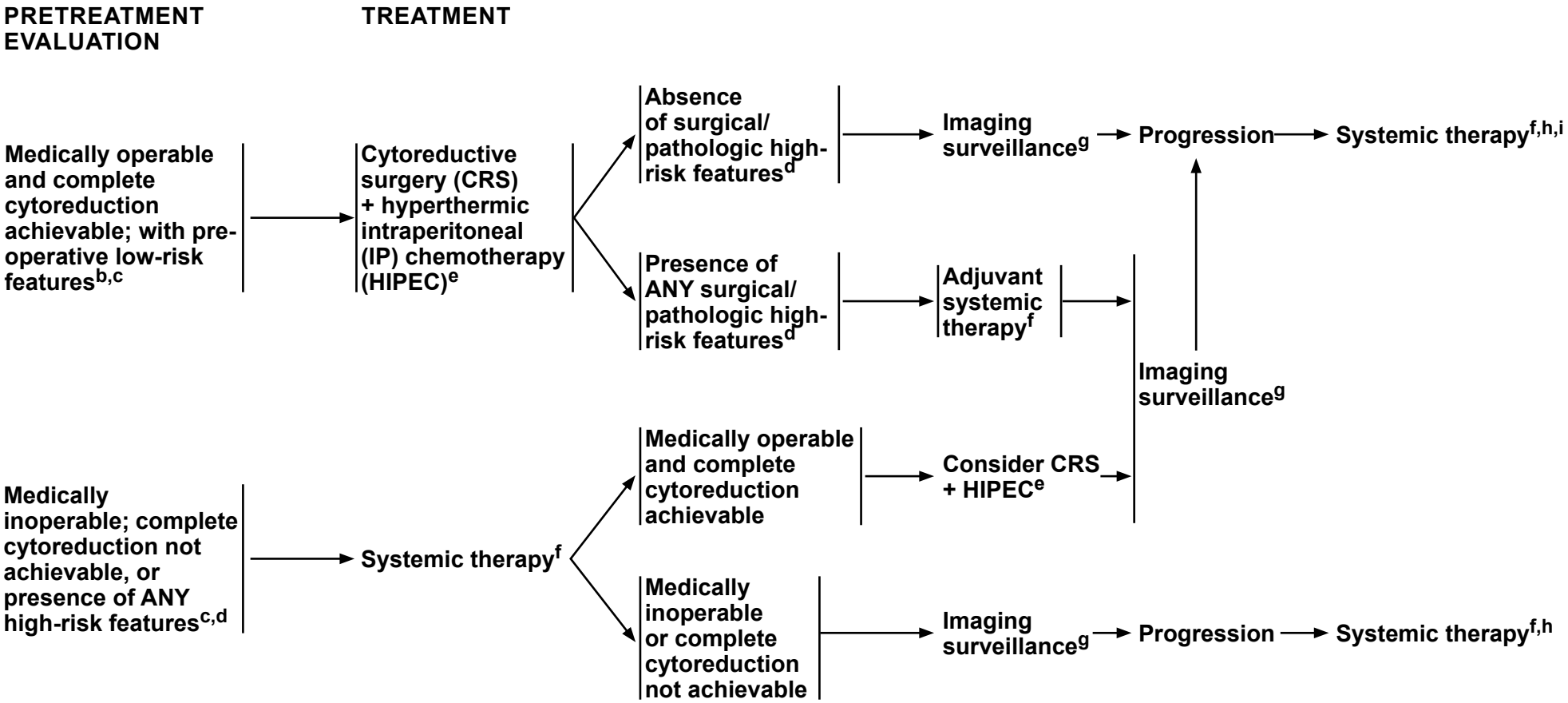


[a] Principles of Pathologic Review (PEM-A).

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



[b] Low-risk features: epithelioid histology; absence of ANY high-risk features.
[c] Best supportive care is recommended for patients presenting with PS 3–4. See Principles of Supportive Care (PEM-B).
[d] High-risk features: biphasic/sarcomatoid histology, nodal metastasis, Ki-67 >9%, thrombocytosis, performance status (PS) = 2, bicavitary disease, high disease burden/incomplete cytoreduction (Peritoneal Cancer Index [PCI] >17, completeness of cytoreduction [CC] score >1).
[e] Principles of Surgery (PEM-C).
[f] Principles of Systemic Therapy (PEM-D).
[g] Recommended surveillance: CT chest + CT or MRI of abdomen/pelvis with contrast every 3–6 months x 5 years then yearly.
[h] Principles of Supportive Care (PEM-B).
[i] Repeat CRS + HIPEC can be considered in patients who are >12 months from prior CRS and 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.

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

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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 MTAP IHC and *CDKN2A* copy number assessment by FISH may aid in the distinction in some instances (see next page).[22]

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References

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

PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry

Markers to Confirm Mesothelial Differentiation

- IHC is integral to the pathologic diagnosis of mesothelioma in clinical practice.
- Useful IHC markers include: 1) positive markers to confirm mesothelial differentiation, such as 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 carcinoma[28] 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 type[31-37] but in <20% of sarcomatoid type.[38]
  - MTAP IHC has been used as a diagnostic marker for mesothelioma.[39] *MTAP* is located near *CDKN2A* on the chromosomal region 9p21. Loss of cytoplasmic MTAP staining is considered a surrogate for chromosomal 9p loss as determined by concurrent *CDKN2A* FISH testing[39] and has been reported in ~40%–60% of mesothelioma but rarely in reactive proliferations.[35-37]
  - Although MTAP alone is not sensitive, combined use of BAP1 and MTAP IHC may improve sensitivity and specificity.[35-37] Since ~10%–20% of lung adenocarcinomas have MTAP loss,[36] MTAP IHC is not useful for distinction between mesothelioma and lung carcinoma.
  - *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]

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References

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

PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry (continued)

Markers as Potential Prognostic and Predictive Markers

- Ki-67 labeling index by IHC staining is independently prognostic for overall survival (OS) for patients undergoing CRS + HIPEC, with Ki-67 index >9% associated with worse survival and is therefore considered a high-risk feature.[45]
- Studies have 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.[46]
  - Patients with mesothelioma with germline *BAP1* mutations have a prolonged survival.[47,48]
  - *ALK* rearrangements by IHC found in rare patients with peritoneal mesothelioma[49-52] have shown dramatic response with ALK inhibitor therapies.[53,54]
- 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.[55]
- 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.[56]
- 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.[57-59]
  - 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.[60]
  - Hemizygous loss of *NF2* by FISH is present in ~50% of pleural mesotheliomas.[61]
- 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.[62]

Molecular Features

- Most mesotheliomas are characterized by recurrent mutations in tumor suppressors and epigenetic regulators, including *BAP1, NF2, TP53, SETD2*, and other genes.[62-66] 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.[64] *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.[62-64,67-69]
- 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*.[62]
- Peritoneal mesothelioma has distinct molecular features compared to pleural mesothelioma.[70]

Continued
References

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

PRINCIPLES OF PATHOLOGIC REVIEW

Molecular Features (continued)

- Oncogenic *EWSR1::ATF1* fusion has been described in pleural and peritoneal mesotheliomas from young adults.[70,71]
  - *ALK* rearrangements have been identified in rare patients with peritoneal mesothelioma.[49-51,54]
- 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*.[48,72,73] 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.[48,72,74]

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,[75] and is genetically characterized by recurrent mutations in *TRAF7* or *CDC42*.[76] Infrequently, WDPMT shows back-to-back papillae with foci of invasion,[77] 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.[78]
  - *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.

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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.

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 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 (such as 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 (see PEM-2).
- 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 whose disease recurs 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-C 2 of 3)
Completeness of Cytoreduction Score (PEM-C 2 of 3)
Peritoneal Cancer Index Scoring System (PEM-C 2 of 3)

References (PEM-C 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 minutes[15]**
- **Cisplatin 50 mg/m² + doxorubicin 15 mg/m² for 90 minutes[15]**
- **Cisplatin 100–240 mg/m² for 90–110 minutes[16,17]**
- **Carboplatin 600–800 mg/m² for 90 minutes[18]**
- **Cisplatin 25 mg/m²/L + mitomycin C 3.3 mg/m²/L for 60–90 minutes[19,20]**

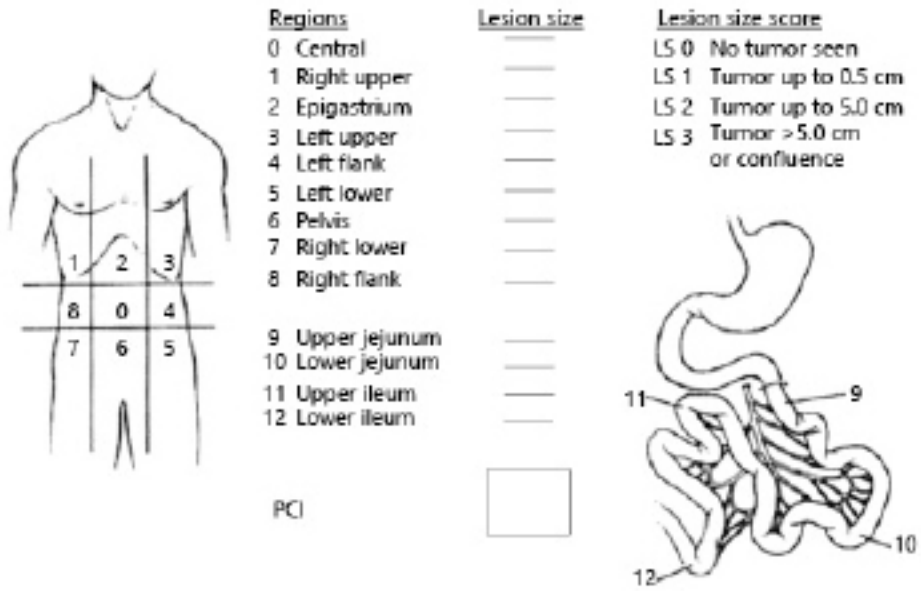
Useful in Certain Circumstances

- **Mitomycin C 30 mg/m² for 90–110 minutes[15]**
- **Mitomycin C 30 mg at time 0 followed by mitomycin C 10 mg beginning at 60 minutes and continuing for 90–110 minutes[15]**

Completeness of Cytoreduction (CC) Score[21]

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 System[21]



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

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Mesothelioma: Peritoneal

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Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

HISTOLOGY: Epithelioid

FIRST-LINE THERAPY

Preferred
- (Cisplatin or carboplatin) + pemetrexed[1-6]
- (Cisplatin or carboplatin) + pemetrexed + bevacizumab[7-9,c]
- (Cisplatin or carboplatin) + pemetrexed + pembrolizumab[10]
- Nivolumab + ipilimumab[11]

Useful in Certain Circumstances
- (Cisplatin or carboplatin) + gemcitabine[12-14]
- Pemetrexed[15]
- Vinorelbine[16]

→ Progression →

SUBSEQUENT THERAPY

Preferred (if chemotherapy first line)[d]
- Nivolumab[e] ± ipilimumab[17-19]

Preferred (if nivolumab/ipilimumab first line)
- (Cisplatin or carboplatin) + pemetrexed[1-6]
- (Cisplatin or carboplatin) + pemetrexed + bevacizumab[7-9,c]
- Pemetrexed[20,21]

Other Recommended
- Atezolizumab[f] + bevacizumab[22,c,g] or
- Gemcitabine[23,24] or
- Vinorelbine[25,26]

HISTOLOGY: Biphasic or Sarcomatoid

FIRST-LINE THERAPY

Preferred
- Nivolumab + ipilimumab[11]
- (Cisplatin or carboplatin) + pemetrexed + pembrolizumab[10]

Other Recommended
- (Cisplatin or carboplatin) + pemetrexed[1-6]
- (Cisplatin or carboplatin) + pemetrexed + bevacizumab[7-9,c]

Useful in Certain Circumstances
- (Cisplatin or carboplatin) + gemcitabine[12-14]
- Pemetrexed[15]
- Vinorelbine[16]

→ Progression →

SUBSEQUENT THERAPY

Preferred (if nivolumab/ipilimumab first-line)[d]
- (Cisplatin or carboplatin) + pemetrexed[1-6]
- (Cisplatin or carboplatin) + pemetrexed + bevacizumab[7-9,c]
- Pemetrexed[20,21]

Preferred (if chemotherapy first line)
- Nivolumab[e] ± ipilimumab[17-19]

Other Recommended
- Atezolizumab[f] + bevacizumab[22,c,g]
- Gemcitabine[23,24]
- Vinorelbine[25,26]

[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.[27,28]
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[d] Consider rechallenge if good response to front-line pemetrexed-based treatment.[29]
[e] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[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 IV atezolizumab.
[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.

References PEM-D (2 of 3)

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

ABBREVIATIONS

CC	**completeness of cytoreduction**
CEA	**carcinoembryonic antigen**
CRS	**cytoreductive surgery**
FDG	**fluorodeoxyglucose**
FISH	**fluorescence in situ hybridization**
H&E	**hematoxylin and eosin**
HIPEC	**hyperthermic intraperitoneal chemotherapy**
IHC	**immunohistochemistry**
IP	**intraperitoneal**
NGS	**next-generation sequencing**
OS	**overall survival**
PCI	**Peritoneal Cancer Index**
PD-L1	**programmed death ligand 1**
PS	**performance status**
SMRP	**soluble mesothelin-related peptide**
WDPMT	**well-differentiated papillary mesothelial tumor**

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2025
Mesothelioma: Peritoneal

Discussion

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

Table of Contents

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*,

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;

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 parietal 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

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

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

mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[7,90,92]

Although about 50% of patients with PeM have positive programed 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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