Mesothelioma is a rare cancer originating in mesothelial surfaces of the peritoneum, pleura, and other sites. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) focus on peritoneal mesothelioma (PeM). The NCCN Guidelines for PeM provide recommendations for workup, diagnosis, and treatment of primary as well as previously treated PeM. The diagnosis of PeM may be delayed because PeM mimics other diseases and conditions and because the disease is so rare. The pathology section was recently updated to include new information about markers used to identify mesothelioma, which is difficult to diagnose. The term “malignant” is no longer used to classify mesotheliomas, because all mesotheliomas are now defined as malignant.


ABSTRACT

Mesothelioma is a rare cancer originating in mesothelial surfaces of the peritoneum, pleura, and other sites. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) focus on peritoneal mesothelioma (PeM). The NCCN Guidelines for PeM provide recommendations for workup, diagnosis, and treatment of primary as well as previously treated PeM. The diagnosis of PeM may be delayed because PeM mimics other diseases and conditions and because the disease is so rare. The pathology section was recently updated to include new information about markers used to identify mesothelioma, which is difficult to diagnose. The term “malignant” is no longer used to classify mesotheliomas, because all mesotheliomas are now defined as malignant.


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

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

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

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

PLEASE NOTE

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The complete NCCN Guidelines for Mesothelioma: Peritoneal are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Mesothelioma: Peritoneal Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Mesothelioma: Peritoneal Panel members can be found on page 979. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Mesothelioma is a rare cancer originating in mesothelial surfaces of the peritoneum, pleura, and other sites that is estimated to occur in approximately 3,500 people in the United States every year. 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. It is estimated that PeM occurs in approximately 300 to 400 people in the United States every year. The true incidence may be higher because PeM may not be coded correctly; it can 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. Survival is improved for patients who are able to undergo complete cytoreductive surgery (CRS) with intraperitoneal chemotherapy. 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). Patients with epithelioid histology have better outcomes than those with either biphasic or sarcomatoid histologies; histology is used to direct treatment. PeM is diagnosed in equal numbers of males and females; pleural mesothelioma is more common in males. PeM may occur in younger patients, whereas pleural mesothelioma typically occurs in older patients. Many patients with PeM have idiopathic disease. Pleural mesothelioma is typically caused by asbestos exposure; however, PeM is less frequently associated with asbestos exposure. The incidence of pleural mesothelioma and PeM is decreasing in the United States because asbestos use has decreased since the 1970s. Although asbestos is no longer mined in the United States, it is still imported. 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.
Patients with PeM present with abdominal signs and symptoms, such as ascites, pain, distension, and an abdominal mass.\textsuperscript{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.\textsuperscript{11,21,24,38} Thus, many patients with PeM have advanced disease at diagnosis.\textsuperscript{11} Although PeM can spread extensively in the abdomen, it less commonly metastasizes beyond the abdominal cavity.\textsuperscript{24}

These NCCN Guidelines for 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 Meso-thelioma.” The term “malignant” is no longer used to classify mesotheliomas, because all mesotheliomas are now defined as malignant.\textsuperscript{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” in the algorithm, page 967).\textsuperscript{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” (page 967), “Principles of Surgery” (page 972), “Principles of Systemic Therapy” (page 974), and “Principles of Supportive Care” (page 975). 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 (available at NCCN.org).

**Guidelines Update Methodology**
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 and 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; antiracist, anticlassist, antismisogynist, antiageist, antiableist, and anti-fat–biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate nongendered 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 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.11,21,24,38 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.\textsuperscript{24-42} Laparoscopy is also performed to assess whether complete CRS is possible.\textsuperscript{24} Fine-needle aspiration of the nodule/mass is not recommended for diagnosis, because fine-needle aspiration 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.\textsuperscript{21,24} Measurement of soluble mesothelin-related peptide and CA-125 levels may be considered, and these levels may correlate with disease status. For patients with suspected 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.\textsuperscript{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, or mesothelioma in situ.\textsuperscript{44-46} Peritoneal inclusion cyst is very rare; it was previously termed “benign multicystic PeM,” but this term was revised based on the recent WHO classification.\textsuperscript{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”).\textsuperscript{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.\textsuperscript{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 with patients who have a biphasic subtype (14 months).\textsuperscript{15} However, median survival is improved if patients are able to undergo cytoreductive surgery (55 months for epithelial histology vs 13 months for biphasic).\textsuperscript{54} Distinguishing diffuse PeM from peritoneal inclusion cyst and well-differentiated papillary mesothelial tumor is important 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, page 967).\textsuperscript{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 (see “Principles of Pathologic Review,” page 967) and summarized in this discussion. 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 WHO.39,57 The classification for PeM has also been revised to align with the pleural mesothelioma guidelines. 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 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 fewer than 20% of those with sarcomatoid mesothelioma.72

BAP1 IHC is useful for distinguishing mesotheliomas from benign mesothelial tumors. For the 2023 update
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 tools, 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 (WDPTM, 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.

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 3–4 (see “Principles of Supportive Care” in the algorithm, page 975). 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 well-differentiated papillary mesothelial tumor 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.

No phase III randomized trials to determine the best treatment for patients with PeM exist 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,” next section, and “Systemic Therapy,” page 969).21

Surgery and Intrapерitoneal Chemotherapy

Data show good outcomes for eligible patients with PeM who have CRS and intraperitoneal chemotherapy (see “Clinical Trials,” page 968).13,14,28,79–77 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, page 972). 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.

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, page 972). 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,” page 972).

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. 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 1,047 patients with PeM. 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. 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%; 2 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 PeM 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 and pleural mesothelioma (see “Principles of Surgery” and “Principles of Systemic Therapy” in the algorithm, pages 972 and 974, respectively).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 bicaudal 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 of 0–2 who are medically inoperable or refuse surgery (see “Systemic Therapy,” next section).

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, page 972).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 performed for patients with PeM who are not eligible for CRS and HIPEC. The NCCN panel has recommended that cisplatin plus doxorubicin is the preferred regimen for patients with PeM who are medically operable. However, the efficacy of this regimen has not been confirmed in randomized trials. Other regimens, such as carboplatin plus gemcitabine, have been shown to be effective in phase II trials. The NCCN panel recommends that patients with high-risk features (such as Ki-67 >9%, nodal metastases, high tumor burden [peritoneal cancer index >17]), CC >1, biphasic disease, or bicaudal disease) should be considered for perioperative therapy. After perioperative therapy, patients may be eligible for CRS and HIPEC. Systemic therapy alone is recommended for patients with PS of 0–2 who are medically inoperable or refuse surgery (see “Systemic Therapy,” next section).
for surgery. 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,” page 974). Details about the systemic therapy clinical trials for pleural mesothelioma are described in the NCCN Guidelines for Mesothelioma: Pleural (available at 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.

**Clinical Trials**

The International Expanded Access Program assessed pemetrexed regimens in patients with mesothelioma who were not eligible for surgery. A subset of 98 patients with PeM received pemetrexed regimens. Median survival was not reached for patients receiving first-line therapy with either pemetrexed alone or pemetrexed plus cisplatin; response rate was 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 Expanded Access Program were published for 109 patients with PeM receiving pemetrexed regimens who were not eligible for surgery. 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 events were 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. There were 2 complete responses and 9 partial responses. Median overall survival was 15.8 months. Another study assessed first-line therapy with pemetrexed plus cisplatin in 31 patients with PeM. 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. Median overall survival was 16.6 months. This study also assessed second-line therapy in 26 patients with PeM. 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 PeM responds to first-line therapy with gemcitabine plus cisplatin. Data also show that first-line therapy with gemcitabine plus pemetrexed is effective, although this regimen is toxic (grade 3–4 neutropenia, 60%).

A phase II trial assessed atezolizumab plus bevacizumab as subsequent therapy for 20 patients with advanced and unresectable PeM who had progression on or were intolerant to pemetrexed plus platinum chemotherapy. 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. 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 III randomized trial, assessed nivolumab (67%) versus placebo (33%) in 332 patients with pleural mesothelioma who had progressed after platinum-based chemotherapy. 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 (hazard ratio, 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 0–2 and diffuse PeM, including those (1) who are medically inoperable, for whom a complete CRS cannot be achieved, or who refuse surgery; (2) with bivacary 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 bivacary disease or low-volume biphasic disease (see “Principles of Surgery” in the algorithm, page 975). 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 PD-L1 expression levels, the NCCN panel does not require PD-L1 testing before using ICIs based on clinical trial data. ICIIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy. Therefore, healthcare 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 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.\textsuperscript{7,86,106-107} Carboplatin is recommended if patients are not candidates for cisplatin, regardless of histology.\textsuperscript{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.\textsuperscript{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.\textsuperscript{86,112-114} However, pemetrexed regimens may be given again as subsequent systemic therapy if a good sustained response was obtained when the initial chemotherapy was interrupted.\textsuperscript{115,116} The panel decided that the following are other recommended subsequent therapy regimens: (1) atezolizumab plus bevacizumab; (2) vinorelbine; or (3) gemcitabine.\textsuperscript{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 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 WHO.39,57 The classification for PeM has been revised to align with the pleural mesothelioma guidelines. 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. It is estimated to occur in approximately 3,500 people in the United States every year.1–4 PeM is estimated to occur in approximately 300 to 400 people in the United States every year.20 The mean age is approximately 69 years at diagnosis of PeM. One-year overall survival is approximately 46% in patients with PeM, and 5-year overall survival is approximately 20%; cure is rare.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, page 967).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 PeM 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. Therefore, a multidisciplinary evaluation is recommended to assess whether patients are eligible for surgery. Multiple intravenous systemic therapy options exist for patients who are not candidates for CRS or whose disease recurs after CRS with or without HIPEC. Recommended systemic therapy regimens for PeM are mainly based on clinical trials with patients with pleural mesothelioma; the NCCN panel has decided that these regimens are equally efficacious for both disease sites. 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 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.

References

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### Individual Disclosures for the Mesothelioma: Peritoneal Panel

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