

# ASCO® Guidelines

## TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA: AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE

| Clinical Question  | Recommendation   | Evidence Rating   |
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| <b>Diagnosis</b>   |  |   |
| <p>What is the optimal way to make a diagnosis of pleural mesothelioma?</p> <p>Options include:</p> <ul style="list-style-type: none"> <li>a. Thoracentesis</li> <li>b. Core needle biopsy</li> <li>c. Thorascopic biopsy</li> <li>d. Open pleural biopsy</li> </ul> | <p>Clinicians should perform an initial thoracentesis when patients present with symptomatic pleural effusions and send pleural fluid for cytologic examination for initial assessment for possible mesothelioma.</p>  | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |
|  | <p>In patients for whom antineoplastic treatment is planned, it is strongly recommended that a thorascopic biopsy should be performed. This will:</p> <ul style="list-style-type: none"> <li>a) enhance the information available for clinical staging</li> <li>b) allow for histologic confirmation of diagnosis</li> <li>c) enable more accurate determination of the pathologic subtype of mesothelioma (epithelial, sarcomatoid, biphasic)</li> <li>d) make material available for additional studies (e.g. molecular profiling).</li> </ul> | <p>Type: evidence-based<br/>Evidence quality: high<br/>Strength of recommendation: strong</p>           |
|  | <p>When performing a thorascopic biopsy, the minimal number of incisions (2 or fewer) is recommended and should ideally be placed in areas that would be used for subsequent definitive resection in order to avoid tumor implantation into the chest wall.</p>  | <p>Type: evidence-based<br/>Evidence quality: high<br/>Strength of recommendation: strong</p>           |
|  | <p>In patients with suspected mesothelioma in whom treatment is planned, an open pleural biopsy should be performed if the extent of tumor prevents a thorascopic approach. The smallest incision possible is encouraged (generally 6 cm or less is recommended).</p>  | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: moderate</p> |

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|  | In patients who are not candidates for thoracoscopic biopsy or open pleural biopsy, who also have a non-diagnostic thoracentesis or do not have a pleural effusion, clinicians should perform a core needle biopsy of an accessible lesion.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
| Is cytology of pleural fluid as sensitive and specific as histology in making a diagnosis of pleural mesothelioma?                                   | Cytologic evaluation of pleural fluid can be an initial screening test for mesothelioma, but it is not a sufficiently sensitive diagnostic test. Whenever definitive histologic diagnosis is needed, biopsies via thoracoscopy or CT guidance offer a better opportunity to reach a definitive diagnosis.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
| What panel of IHC stains is required to make a diagnosis of mesothelioma?  | Histologic examination should be supplemented by immunohistochemistry using selected markers expected to be positive in mesothelioma (e.g., calretinin, keratins 5/6, and nuclear WT1) as well as markers expected to be negative in mesothelioma (e.g., CEA, EPCAM, Claudin 4, TTF-1). These markers should be supplemented with other markers that address the differential diagnosis in that particular situation. | Type: evidence-based<br>Evidence quality: Intermediate<br>Strength of recommendation: strong   |
| Do the pathological subtypes of mesothelioma have prognostic significance? What is the optimal way to report histological composition?               | Mesothelioma should be reported as epithelial, sarcomatoid or biphasic, because these subtypes have a clear prognostic significance.  | Type: evidence-based<br>Evidence quality: high<br>Strength of recommendation: strong           |
|  | In surgical, thoracoscopic, or open pleural biopsies with sufficient tissue, further subtyping and quantification of epithelial vs. sarcomatoid components of mesothelioma may be undertaken.   | Type: Informal consensus<br>Strength of recommendation: moderate                               |
| Are there any non-tissue based biomarkers that can be used to diagnose patients with mesothelioma, to predict outcome, or to monitor tumor response? | The non-tissue based biomarkers that are under evaluation at this time do not have the sensitivity or specificity to predict outcome or monitor tumor response and are therefore not recommended.   | Type: evidence-based<br>Evidence quality: Intermediate<br>Strength of recommendation: moderate |

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| Is there a role for tumor genomic sequencing in mesothelioma?  | While tumor genomic sequencing is currently done on a research basis in mesothelioma and may become clinically applicable in the near future, it is not recommended at this time.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: moderate |
| <b>Staging</b>   |   |  |
| What are the optimal tests required to stage patients with mesothelioma?<br>a. CT<br>b. PET/CT<br>c. MRI<br>d. Mediastinoscopy<br>e. Thoracoscopy<br>f. Laparoscopy<br>g. EBUS | A CT scan of the chest and upper abdomen with IV contrast is recommended as the initial staging in patients with mesothelioma.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
|  | An FDG PET/CT should usually be obtained for initial staging of patients with mesothelioma. This may be omitted in patients who are not being considered for definitive surgical resection.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
|  | If abnormalities that suggest metastatic disease in the abdomen are observed on a chest and upper abdomen CT or on a PET/CT then consideration should be given to perform a dedicated abdominal (+/- pelvic) CT scan, preferably with IV and oral contrast. | Type: evidence-based<br>Evidence quality: intermediate; Strength of recommendations: strong    |
|  | An MRI (preferably with IV contrast) may be obtained to further assess invasion of the tumor into the diaphragm, chest wall, mediastinum and other areas.   | Type: evidence-based<br>Evidence quality: intermediate<br>strength of recommendation: moderate |
|  | For patients being considered for maximal surgical cytoreduction, a mediastinoscopy and/or endobronchial US should be considered if enlarged and/or PET avid mediastinal nodes are present.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
|  | In the presence of contralateral pleural abnormalities detected on initial PET/CT or chest CT scan, a contralateral thoracoscopy may be performed to exclude contralateral disease.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: moderate |

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|   | In patients with suspicious findings for intra-abdominal disease on imaging and no other contraindications to surgery, it is strongly recommended that a laparoscopy be performed.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
| <p>What are the limitations of the current staging system for surgical and clinical staging of pleural mesothelioma?</p> <p>a. What are the key discrepancies between clinical and pathological staging?</p> <p>b. What are the limitations of staging in predicting prognosis?</p> | The current AJCC/UICC staging classification remains difficult to apply to clinical staging with respect to both T and N components and thus may be imprecise in predicting prognosis. Physicians should recognize that in patients with clinical stage I/II disease upstaging may occur at surgery.  | Type: evidence-based<br>Evidence quality: high<br>Strength of recommendation: strong         |
| <p>What is the optimal approach to radiologic based tumor measurement and response classification (RECIST 1.1, modified RECIST for mesothelioma, volumetrics)?</p>  | The optimal approach to mesothelioma measurement requires the expertise of a radiologist to identify measurement sites on CT as per modified RECIST for mesothelioma. This approach requires calculating the sum of up to 6 measurement sites with at least 1 cm thickness, measured perpendicular to the chest wall or mediastinum, with no more than 2 sites on each of 3 CT sections, separated by at least 1cm axially. | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
|   | Assessment of tumor volume by CT scan may enhance clinical staging and provide prognostic information but remains investigational and thus is not recommended.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
|   | It is recommended that tumor response classification be determined based on RECIST criteria from the comparisons of these sums across serial CT scans.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |

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| <b>Chemotherapy</b>   |   |  |
| <p>In patients with newly diagnosed pleural mesothelioma, is there a role for chemotherapy and does it improve survival and QOL?</p> <p>a. Who should receive supportive care instead of chemotherapy?</p> <p>b. Is there a role for additional modalities in these patients?</p> | <p>Chemotherapy should be offered to patients with mesothelioma because it improves survival and quality of life.</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendations: strong</p>     |
|   | <p>In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be offered prior to the initiation of chemotherapy.</p>   | <p>Type: informal consensus<br/>Strength of recommendation: moderate</p>                                   |
|   | <p>Selected patients with a poor performance status (PS 2) may be offered single agent chemotherapy or palliative care alone. Patients with a PS of 3 or greater should receive palliative care.</p>  | <p>Type: evidence-based<br/>Evidence quality: low<br/>Strength of recommendation: moderate</p>             |
| <p>What is the best chemotherapy regimen for patients with newly diagnosed pleural mesothelioma who are not candidates for surgery?</p>   | <p>The recommended first-line chemotherapy for patients with mesothelioma is pemetrexed plus platinum. However patients should also be offered the option of entering in a clinical trial.</p>  | <p>Type: evidence-based<br/>Evidence quality: high<br/>Strength of recommendation: strong</p>              |
| <p>What is the role of adding bevacizumab to the chemotherapy regimen of pemetrexed and cisplatin? Are there patients with mesothelioma who should not get bevacizumab?</p>   | <p>The addition of bevacizumab to pemetrexed-based chemotherapy improves survival in select patients and therefore may be offered to patients with no contraindications to bevacizumab. The randomized clinical trial demonstrating benefit with bevacizumab utilized cisplatin/pemetrexed; data with carboplatin/pemetrexed plus bevacizumab is insufficient for a clear recommendation.</p> | <p>Type: evidence-based<br/>Evidence quality: high<br/>Strength of recommendation: moderate</p>            |
|   | <p>Bevacizumab is not recommended for patients with PS <math>\geq</math> 2, substantial cardiovascular comorbidity, uncontrolled hypertension, age <math>&gt;</math>75, bleeding or clotting risk, or other contraindications to bevacizumab.</p>   | <p>Type: evidence-based;<br/>Evidence quality: intermediate;<br/>Strength of recommendations: moderate</p> |

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| When should carboplatin be used instead of cisplatin in patients with pleural mesothelioma?   | In patients who may not be able to tolerate cisplatin, it is recommended that carboplatin may be offered as a substitute for cisplatin.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
| What is the most effective second-line therapy for patients with pleural mesothelioma? Can patients who have previously received pemetrexed be treated again with pemetrexed? | Re-treatment with pemetrexed-based chemotherapy may be offered in pleural mesothelioma patients who achieved durable (>6 months) disease control with first-line pemetrexed-based chemotherapy.                                       | Type: evidence-based<br>Evidence quality: low<br>Strength of recommendation: moderate        |
|   | Given the very limited activity of 2 <sup>nd</sup> line chemotherapy in patients with mesothelioma, participation in clinical trials is recommended.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
|   | In patients for whom clinical trials are not an option, vinorelbine may be offered as second line therapy.  | Type: evidence-based<br>Evidence quality: low<br>Strength of recommendation: Moderate        |
| What is the optimal duration of frontline chemotherapy for mesothelioma? Is there a role for pemetrexed maintenance therapy in pleural mesothelioma?                          | In select asymptomatic patients with epithelial mesothelioma and a low disease burden who are not surgical candidates, a trial of expectant observation, with close monitoring, may be offered before initiation of systemic therapy. | Type: evidence-based<br>Evidence quality: low<br>Strength of recommendation: moderate        |
|   | Frontline pemetrexed based chemotherapy should be given for 4-6 cycles. For patients with stable disease or responding disease, a break from chemotherapy is recommended at that point.   | Type: evidence-based<br>Evidence quality: low<br>Strength of recommendation: moderate        |
|   | There is insufficient evidence to support the use of maintenance chemotherapy and thus it is not recommended.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |

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|   | There is insufficient evidence to support the use of pemetrexed maintenance in mesothelioma patients and thus it is not recommended.   | Type: evidence-based<br>Evidence quality: low<br>Strength of recommendation: strong          |
| <b>Surgical Cyto-reduction</b>  |  |  |
| <p>What is the role of surgical cyto-reduction in mesothelioma: does it improve survival or QOL?</p> <p>a. Is surgery for pleural mesothelioma ever curative, and does it prolong survival compared to chemotherapy alone?</p> <p>b. Is there a role for additional modalities in these patients?</p> <p>c. Which patient should not be considered for surgical cyto-reduction?</p> | In selected patients with early stage disease, it is strongly recommended that a maximal surgical cyto-reduction should be performed.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
|   | Maximal surgical cyto-reduction as a single modality treatment is generally insufficient; additional anti-neoplastic treatment (chemotherapy and/or radiation therapy) should be administered. It is recommended that this treatment decision should be made with multidisciplinary input involving thoracic surgeons, pulmonologists, medical and radiation oncologists.                          | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
|   | Patients with transdiaphragmatic disease, multifocal chest wall invasion or histologically confirmed contralateral mediastinal or supraclavicular lymph node involvement should undergo neoadjuvant treatment before consideration of maximal surgical cyto-reduction. Contralateral (N3) or supraclavicular disease (N3) disease should be a contraindication to maximal surgical cyto-reduction. | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
| Does histology and mediastinal lymph node status affect selection of patients for surgery?  | Patients with histologically confirmed sarcomatoid mesothelioma should not be offered maximal surgical cyto-reduction.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |
|   | Patients with ipsilateral, histologically-confirmed mediastinal lymph node involvement should only undergo maximal surgical cyto-reduction in the context of multimodality therapy (neoadjuvant or adjuvant chemotherapy). Optimally, these patients should be enrolled in clinical trials.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong |

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| Clinical Question  | Recommendation   | Evidence Rating   |
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| <p>What should surgeons consider when deciding the extent of maximal cytoreductive surgery (lung sparing vs. non-lung sparing)? What are the differences in outcomes (morbidity, QOL, survival) between lung sparing and non-lung sparing maximal cytoreductive surgery?</p> | <p>Maximal surgical cytoreduction involves either extrapleural pneumonectomy (EPP) or lung-sparing options (pleurectomy/decortication (P/D), extended P/D). When offering maximal surgical cytoreduction, lung-sparing options should be the first choice, due to decreased operative and long-term risk. EPP may be offered in highly selected patients when performed in centers of excellence.</p>  | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p> |
| <p>What are the differences in outcome between surgeries with palliative vs. curative intent?<br/>a. Which patients are most appropriate for surgery with curative intent?<br/>b. Which patients are most appropriate for procedures with palliative intent?</p>             | <p>A maximal cytoreduction (either lung sparing or non-lung sparing) should only be considered in patients who meet specific preoperative cardiopulmonary functional criteria, have no evidence of extrathoracic disease, and are able to receive multimodality treatment (adjuvant or neoadjuvant).</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p> |
|  | <p>In patients who have a symptomatic pleural effusion, who are PS 2 or greater, or those in whom a maximal cytoreduction cannot be performed (due to disease extent or co-morbid conditions), palliative approaches such as a tunneled permanent catheter placement or thoracoscopic exploration with partial resection and/or pleurodesis should be offered. In the latter case, additional biopsy to confirm pathological diagnosis should be performed during the procedure. If the patient is being evaluated for investigational therapy, material for additional studies (e.g. molecular and/ or immunological profiling) should be obtained.</p> | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p> |
|  | <p>In patients who have a symptomatic pericardial effusion, percutaneous catheter drainage or pericardial window may be performed.</p>   | <p>Type: evidence-based<br/>Evidence quality: high<br/>Strength of recommendation: strong</p>         |



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| <p>Should maximal surgical cytoreduction be combined with chemotherapy and/or radiation?</p> <p>a. In patients who are candidates for maximal surgical cytoreduction, should chemotherapy be given before or after surgery?</p> <p>b. What is the optimal duration of neoadjuvant or adjuvant chemotherapy in the multimodality setting?</p> | <p>Since surgical cytoreduction is not expected to yield an R0 resection, it is strongly recommended that multimodality therapy with chemotherapy and/or radiation therapy should be administered.</p>  | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |
|  | <p>Chemotherapy may be given pre or postoperatively in the context of multimodality treatment.</p>  | <p>Type: evidence-based<br/>Evidence quality: low<br/>Strength of recommendation: moderate</p>          |
|  | <p>Adjuvant radiation therapy may be associated with a decreased risk of local recurrence and may be offered to patients who have undergone maximal cytoreduction. Treatment is complex and it is recommended that it should be delivered at experienced centers of excellence.</p> | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: moderate</p> |
|  | <p>In the context of multimodality treatment, four to six cycles of pemetrexed/platin based chemotherapy may be administered pre or post operatively.</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: moderate</p> |
| <p>What is the role of peri or intraoperative intracavitary therapies (chemotherapy, photodynamic therapy)?</p>  | <p>Intracavitary therapies (chemotherapy or photodynamic therapy) may be administered safely in experienced centers of excellence, preferably in the context of a clinical trial. Their role in improving outcome is indeterminate.</p>   | <p>Type: evidence-based<br/>Evidence quality: low<br/>Strength of recommendation: weak</p>              |
| <p>What is the optimal management of pleural effusion in patients with mesothelioma? What is the role of pleurodesis vs. tunneled pleural</p>  | <p>Tunneled pleural catheters are not recommended in patients who are candidates for maximal surgical cytoreduction, because of the risk of tumor implantation into the chest wall.</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |

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| catheters in mesothelioma?   | In patients who are not candidates for maximal surgical cytoreduction, tunneled pleural catheters or pleurodesis (performed via chest tube or thoracoscopy) may be offered. Multidisciplinary input including surgical consultation with a center of excellence should be sought to optimize management of a pleural effusion and consideration of investigational intracavitary therapies. | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
| <b>Radiation Therapy</b>   |   |  |
| Should patients receive prophylactic irradiation of intervention tracts (thoracentesis, tunneled pleural catheters, thoracoscopy, and needle biopsy) to prevent tract recurrences? | Prophylactic irradiation of intervention tracts should generally not be offered patients to prevent tract recurrences.  | Type: evidence-based<br>Evidence quality: high<br>Strength of recommendation: moderate         |
|  | It is recommended that adjuvant radiation should be offered to patients who have resection of intervention tracts found to be histologically positive.  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: moderate |
| What is the role of palliative radiation therapy? What is the optimal radiation dose and fractionation?  | Radiation therapy should be offered as an effective treatment modality to palliate patients with symptomatic disease.   | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
|  | It is recommended that standard dosing regimens used in other diseases be offered to patients with mesothelioma (800 cGy x 1 fraction, 400 cGy x 5 fractions or 300 cGy x 10 fractions).  | Type: evidence-based<br>Evidence quality: intermediate<br>Strength of recommendation: strong   |
| What is the role of radiation therapy for asymptomatic recurrence? What is the optimal radiation dose and fractionation?   | Radiation therapy may be offered to patients with localized asymptomatic recurrence. The dosing fractionation is dependent on the site and extent of disease and should be determined by the radiation oncologist in consultation with the patient.   | Type: informal consensus<br>Strength of recommendation: moderate                               |

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| <p>What is the role of radiation therapy in patients who get non-lung sparing cytoreductive surgery? What is the optimal adjuvant radiation approach in this setting?</p> | <p>Hemi-thoracic adjuvant radiation therapy may be offered to patients who undergo non-lung sparing cytoreductive surgery (EPP), preferably in centers of excellence with experience in this modality for mesothelioma.</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |
|   | <p>Hemi-thoracic neo-adjuvant radiation therapy may be offered to patients who undergo non-lung sparing cytoreductive surgery. This potentially toxic regimen remains experimental and should only be performed in highly experienced centers within the context of a clinical trial.</p>         | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: moderate</p> |
| <p>What is the role of radiation therapy in patients who get lung sparing cytoreductive surgery? What is the optimal radiation approach in this setting?</p>              | <p>Hemi-thoracic adjuvant Intensity modulated radiation therapy may be offered to patients who undergo lung sparing cytoreductive surgery (P/D or EPD). This potentially toxic regimen should only be performed in highly experienced centers, preferably in the context of a clinical trial.</p> | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: moderate</p> |
|   | <p>Due to the potential for severe pulmonary toxicity, neoadjuvant radiation therapy is not recommended for patients who undergo lung sparing surgical cytoreductive surgery.</p>   | <p>Type: informal consensus<br/>Strength of recommendation: strong</p>                                  |
| <p>What are the appropriate radiation techniques (electrons, 2D, 3D, IMRT and protons)?</p>   | <p>For palliative radiation therapy, electrons, 2D, 3D, and IMRT may be considered appropriate techniques depending on location of the treatment target and organs at risk.</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |
|   | <p>For adjuvant or neoadjuvant hemithoracic radiation therapy, 3D or IMRT may be offered respecting guidelines of organs at risk. Proton therapy may be considered in centers with significant experience, preferably in the context of a clinical trial.</p>                                     | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |
| <p>What are predictors of radiation toxicity (after lung sparing or non-lung sparing cytoreductive surgery or after palliative pleurectomy)?</p>                          | <p>It is recommended that standard dosimetric guidelines for organs at risk be used as established predictors of radiation toxicity</p>   | <p>Type: evidence-based<br/>Evidence quality: intermediate<br/>Strength of recommendation: strong</p>   |