

# MALIGNANT PLEURAL MESOTHELIOMA

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The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Malignancies Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

## BACKGROUND

Mesothelioma is a rare asbestos-related tumour that arises from mesenchymal cells that are found in the lining of the pleural cavity (Malignant Pleural Mesothelioma; MPM) in 70 to 90 percent of cases, and the peritoneal cavity in 10 to 30 percent of cases.<sup>1, 2</sup> Due to the long latency period between exposure and disease, which has been reported to be between 30 and 50 years, most cases of mesothelioma being diagnosed today are the result of asbestos exposure in the 1960s and 1970s.<sup>3</sup> Although safety measures for the use of asbestos were adopted in most countries several decades ago, the incidence rates, which are highly age-specific, are still rising, and are expected to peak over the next two decades.<sup>4-6</sup> In Canada, the number of men diagnosed with mesothelioma has been steadily increasing over the past 20 years: there were 153 cases reported in 1984 versus 344 cases reported in 2003.<sup>3</sup> Mesothelioma is less common in women: there were 78 Canadian women diagnosed with mesothelioma in 2003.<sup>3</sup> In the United States, the peak mesothelioma incidence occurred in the early to mid-1990s and has possibly started to decline since then. Information from the Surveillance, Epidemiology, and End Results (SEER) database, which includes 13 registries and is a representative sample of approximately 12 percent of the population, indicates that cases in adult Caucasian males ranged from 256 per year to 301 per year between 1992 and 2007.<sup>7</sup> There was no obvious recent trend over time, with the exception of an observed but small decrease in the rate in recent years (2.7 per 100,000 in 2004-5 to 2.3 per 100,000 in 2006-7).<sup>7</sup>

In addition to workplace exposure, the risk of mesothelioma from non-occupational or environmental exposure to asbestos is substantial: one meta-analysis reported the relative risk from household asbestos exposure to be 8.1 (95% CI, 5.3-12) and from neighbourhood asbestos exposure to be 7.0 (95% CI, 4.7-11).<sup>8</sup> Sources of household exposure include the installation, degradation, removal, or repair of asbestos-containing products. In addition, family members of asbestos workers may be exposed to asbestos dust brought home from the workplace on clothing.<sup>9</sup> Neighbourhood exposure occurs mainly due to asbestos mining and manufacturing facilities close to the place of residence.<sup>8, 9</sup>

Mesothelioma is a difficult disease to treat and, at the present time there are few established standard treatment regimens. Median overall survival (OS) rates reported in the literature range from four months to 30 months, but are variable due to the rarity of the disease, few randomized controlled trials, variable staging of patients in trials, and histologic heterogeneity of patients included in trials.<sup>10</sup>

## GUIDELINE QUESTIONS

- What is the recommended management strategy for patients with malignant pleural mesothelioma?

## DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Thoracic Malignancies Tumour Team. Members of the Alberta Provincial Thoracic Malignancies Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, thoracic surgeons, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic Malignancies Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

## SEARCH STRATEGY

Medical journal articles were searched using the PubMed (January 1 2010 to December 6 2012), Medline (2010 to 2012), and CINAHL (2010 to 2012) electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The MeSH heading Mesothelioma was combined with the search terms “Surgery”, “Radiotherapy”, “Drug Therapy”, and “Therapy”. The results were limited to adults, humans, clinical trials, comparative studies, controlled clinical trials, government publications, journal articles, meta-analyses, multicentre studies, practice guidelines, randomized controlled trials, reviews and systematic reviews. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, involved less than 10 patients, or were published before the year 2010. A review of the relevant existing practice guidelines for mesothelioma was also conducted by accessing the guidelines of the British Columbia Cancer Agency, Cancer Care Ontario, European Society for Medical Oncology, National Comprehensive Cancer Network, National Cancer Institute, and the National Institute for Health and Clinical Excellence. The appropriateness of these guidelines for inclusion in the final evidence review were assessed using portions of the AGREE tool.<sup>11</sup>

## TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years diagnosed with mesothelioma. Although mesothelioma can also rarely occur in the peritoneum, this guideline focuses on MPM, which is the most common and therefore has the greatest levels of evidence supporting the recommendations.

## RECOMMENDATIONS

1. Treatment options for patients with malignant pleural mesothelioma can include chemotherapy, radiotherapy, and/or surgery in a select number of patients. All patients diagnosed with malignant pleural mesothelioma should therefore be managed by a multidisciplinary treatment team. Whenever possible, patients should be considered for participation in ongoing clinical trials.
2. Chest wall invasion, nodal disease, distant metastases, and sarcomatoid histology preclude surgical intervention outside of a clinical trial setting. If surgery is indicated, it should only be performed in an experienced surgical centre in the context of a multidisciplinary treatment team.
3. Symptomatic treatment of patients with advanced malignant pleural mesothelioma may also include drainage of effusions, chest tube pleurodesis, or thorascopic pleurodesis.
4. Chemotherapy is recommended either alone for medically inoperable patients, or as part of a multimodality regimen for medically operable patients with malignant pleural mesothelioma. The combination of cisplatin and pemetrexed is the recommended first-line chemotherapy regimen.
5. Second line chemotherapy may include single-agent pemetrexed (if not used with cisplatin for first-line therapy), gemcitabine, or vinorelbine.
6. Adjuvant radiotherapy can be used in selected patients to improve local control.
7. Radiotherapy should also be considered for palliation. The timing, dose, and fractionation of radiation should be based on the intent of treatment.
8. Radiotherapy may also be considered to prevent instrumentation (i.e., chest tube) tract recurrence after surgical interventions.
9. Select patients may be candidates for aggressive multimodality therapy; patient cases being considered for this approach should be presented and discussed within a multidisciplinary tumour board setting.

## DISCUSSION

### Staging

Accurate initial staging is essential to treatment planning, and disease stage at diagnosis is an important prognostic factor for patients with MPM. Tables 1 and 2 describe the staging system of the International Mesothelioma Interest Group (IMIG), which was recently adopted and approved by the American Joint Committee on Cancer (AJCC).<sup>12</sup>

**Table 1.** AJCC/IMIG staging system for malignant pleural mesothelioma.<sup>12</sup>

<b>Primary Tumour (T) Definitions</b>	
T0	No evidence of primary tumour
T1	Tumour limited to ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement
T1a	No involvement of the visceral pleura
T1b	Tumour also involving the visceral pleura
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: <ul style="list-style-type: none"> <li>• Involvement of the diaphragmatic muscle</li> <li>• Extension of tumour from visceral pleura into the underlying pulmonary parenchyma</li> </ul>
T3	Locally advanced but potentially resectable tumour Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: <ul style="list-style-type: none"> <li>• Involvement of the endothoracic fascia</li> <li>• Extension into the mediastinal fat</li> <li>• Solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall</li> <li>• Nontransmural involvement of the pericardium</li> </ul>
T4	Locally advanced, technically unresectable tumour Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: <ul style="list-style-type: none"> <li>• Diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction</li> <li>• Direct transdiaphragmatic extension of tumour to the peritoneum</li> <li>• Direct extension of tumour to the contralateral pleura</li> <li>• Direct extension of tumour to the mediastinal organs</li> <li>• Direct extension of tumour into the spine</li> </ul>
<b>Regional Lymph Node (N) Definitions</b>	
N0	No regional lymph node metastasis
N1	Metastasis in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastasis in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes
N3	Metastasis in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes
<b>Distant Metastasis (M) Definitions</b>	
M0	No distant metastasis
M1	Distant metastasis present

**Table 2.** TNM stage groupings for malignant pleural mesothelioma.<sup>12</sup>

Stage	T	N	M
Stage I	T1	N0	M0

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

## Histology

MPM is often classified into four broad histopathologic subtypes for diagnostic and prognostic utility: epithelioid, biphasic (mixed), sarcomatoid, and desmoplastic.<sup>2, 12</sup> Epithelial mesothelioma is the most common, accounting for 50 to 60 percent of all cases.<sup>2</sup> In general, the pure epithelioid tumours are associated with a better prognosis than the sarcomatoid and biphasic tumours; desmoplastic tumours appear to be associated with the worst prognosis.<sup>2, 12</sup>

## Prognostic Indicators

Several poor prognostic factors have been identified in patients with MPM.<sup>13-19</sup>

- non-epithelioid histology
- advanced stage disease
- poor performance status
- pleural involvement
- lactose dehydrogenase (LDH) greater than 500 IU/L
- platelets greater than 400,000  $\mu$ L
- white blood cell count greater than  $8.3 \times 10^9$ /L
- age greater than 75 years
- male gender
- low CRP

## Diagnosis

Patients with MPM typically present with chest pain and dyspnea; less frequently, patients will also present with cough, fatigue, and/or weight loss.<sup>20</sup> An accurate and detailed history of asbestos exposure, a physical examination, and imaging studies are important in the diagnosis of MPM. A chest x-ray can show pleural thickening, pleural effusion, nodularity, pleural masses, contraction, and mediastinal shift toward the volume loss.<sup>20, 21</sup> In patients with pleural effusion, sampling of the fluid for cytologic testing can help to confirm the diagnosis; however, negative cytologic results do not exclude the possibility of mesothelioma.<sup>2,</sup>

<sup>20</sup> Histologic assessment is therefore preferred, with samples obtained through a closed pleural biopsy (Abrams needle), a computed tomography (CT) guided biopsy or a thoracoscopic video-assisted thoracic surgery (VATS).<sup>21, 22</sup> A contrast-enhanced CT scan is also essential for determining the extent of the disease and for accurate clinical staging.<sup>23</sup> While magnetic resonance imaging (MRI) is not routine, it may be used to obtain additional staging information, particularly for patients with potentially resectable disease. In addition, MRI can be used for patients for whom the CT contrast medium is contraindicated.<sup>20, 23, 24</sup>

## Treatment

Treatment options for patients with malignant pleural mesothelioma can include chemotherapy, radiotherapy, and/or surgery in a select number of patients. All patients diagnosed with MPM should therefore be managed by a multidisciplinary treatment team. Members of the Alberta Provincial Thoracic Malignancies Tumour Team agree that, whenever possible, patients diagnosed with mesothelioma should be considered for participation in ongoing clinical trials (**recommendation #1**).

## Surgery

In addition to supportive measures, surgical techniques for patients with MPM can include pleurectomy/decortication or extrapleural pneumonectomy. Selection criteria for either surgical intervention include good performance status (KPS > 70), early stage disease with not more than localized involvement of the thoracic wall, and adequate cardiopulmonary function.<sup>25, 26</sup> Chest wall invasion, nodal disease, distant metastases, and sarcomatoid histology preclude surgical intervention outside of a clinical trial setting. If surgery is indicated, members of the Alberta Provincial Thoracic Malignancies Tumour Team recommend that it should only be performed in an experienced surgical centre in the context of a multidisciplinary treatment team (**recommendation #2**).

**Pleurectomy/decortication.** Pleurectomy/decortication (P/D) involves the removal of the parietal pleura and the pleura over the mediastinum, pericardium, and diaphragm, as well as stripping of the visceral pleura for decortication.<sup>10</sup> While this procedure allows for the debulking of the tumour, it does not remove the tumour completely; in addition, the preservation of the underlying lung makes postoperative radiotherapy challenging, due to the risk of pulmonary side effects.<sup>20</sup> When P/D is performed in an experienced surgical centre, the mortality rate is between one and two percent.<sup>27</sup> The median survival for patients who undergo P/D is between nine and 20 months.<sup>27, 28</sup>

**Extrapleural pneumonectomy.** Extrapleural pneumonectomy (EPP) involves en bloc removal of tissues in the hemithorax, including the parietal and visceral pleura, involved lung, mediastinal lymph nodes, diaphragm, and pericardium.<sup>10</sup> The operative mortality rate associated with EPP is between 2.2 and 10 percent, which is comparable to the rates reported for other oncologic surgeries; however, significant peri-operative complications have been documented.<sup>29</sup> In an analysis of 328 consecutive patients who underwent EPP between 1980 and 2000, *Sugarbaker et al.* reported that 198 (60.4%) patients experienced minor and major complications, and 11 of 328 patients died, for an overall mortality rate of 3.4%.<sup>30</sup>

In a large retrospective analysis of 663 patients with MPM, *Flores et al.* reported that patients who underwent P/D (n=278) had a longer median survival compared to patients who underwent EPP (n=385) (16 months versus 12 months,  $p < 0.001$ ).<sup>31</sup> However, there was no statistically significant difference in survival by surgical procedure at any individual tumour stage. The authors therefore concluded that the intra-operative findings should be used to decide on the appropriate surgical procedure, with the goal of achieving the most complete resection possible.<sup>31</sup>

Several recent prospective studies have compared EPP with other surgical procedures and found EPP to confer no additional survival benefit while significantly impairing quality of life.<sup>32-34</sup> *Nakas et al.* assessed long-term survival in 165 patients after EPP versus Lung Sparing Total Pleurectomy (LSTP). They found significantly more complications and greater distal progression of disease after EPP with similar OS and

DFI.<sup>32</sup> *Rena et al* compared long-term quality of life after EPP and multimodal treatment versus P/D and multimodal treatment and found that patients who underwent EPP had higher post-operative complications, worse long term quality of life assessments with similar long-term survival as those receiving P/D and multimodal treatment.<sup>33</sup> Similar results were observed in a retrospective study comparing RP and intra-operative PDT versus a modified EPP procedure and intra-operative PDT, although this group also observed longer median OS values for the RP cohort.<sup>34</sup>

*Treasure et al* conducted a multi-centre, randomized, controlled trial on 50 patients undergoing EPP and trimodality therapy versus patients who underwent trimodality therapy without EPP. Three patients within the EPP group died within 30 days and 10 serious adverse events were recorded in the EPP group compared to 2 in the non-EPP group. Furthermore, researchers observed OS values of 14.4 months and 19.5 months for the EPP group and non-EPP group, respectively.<sup>35</sup>

Finally, *Sharif et al* conducted a systematic review of 14 studies regarding EPP for the management of EPP. In 10 studies they observed median OS values of 13 months, perioperative mortality of 5.7%, 30 day mortality of 9.1%, morbidity of 37%, recurrence of 73% at a median follow-up time of 10 months and an improvement in symptoms of 68% at 3 months post-surgery. The authors questioned the value of EPP given its relatively poor survival and symptoms outcomes for MPM coupled with its high operative mortality, morbidity and recurrence rate.<sup>36</sup>

**Management of pleural effusion.** Symptomatic treatment of patients with advanced mesothelioma may also include drainage of effusions, chest tube pleurodesis, or thoroscopic pleurodesis (**recommendation #3**).

Early pleurodesis is essential for the palliation of symptoms and also decrease the probability that the patient will develop a trapped lung.<sup>20,24</sup> Talc pleurodesis, which can be performed either through a chest tube or via thoracoscopy, is the preferred method of pleurodesis for patients with MPM, and is associated with a success rate between 80 and 90 percent.<sup>24,37</sup> Placement of a tunneled pleural catheter should also be considered for the management of pleural effusions, particularly in patients who have a shorter expected survival and who prefer a less invasive intervention. This procedure is associated with rapid and long-lasting symptomatic improvement and low complication rates; in addition, tunneled pleural catheters can be inserted and managed on an outpatient basis, where the facilities and expertise exist.<sup>38-41</sup>

## **Chemotherapy**

Chemotherapy is recommended either alone for medically inoperable patients, or as part of a multimodality regimen for medically operable patients with MPM. The members of the Alberta Provincial Thoracic Malignancies Tumour Team recommend the combination of cisplatin and pemetrexed as the standard first-line chemotherapy regimen for patients with MPM (**recommendation # 4**).

In a multicentre randomized clinical trial, *Vogelzang* and colleagues treated medically inoperable, chemotherapy-naïve patients with either cisplatin alone (75 mg/m<sup>2</sup>; n=222) or the combination of cisplatin and pemetrexed (500 mg/m<sup>2</sup>; n=226) every 21 days.<sup>42</sup> Patients treated with the combination regimen had a better median OS (12.1 versus 9.3 months,  $p<0.02$ ), longer median time to disease progression (5.7 versus 3.9 months,  $p<0.001$ ), and a higher objective response rate (41.3% versus 16.7%,  $p<0.0001$ ). Supplementation with folic acid and vitamin B<sub>12</sub> also led to significant reductions in grade 3/4 toxicities in the patients treated with the combination regimen. In addition, combination therapy was associated with improvements in quality of life, cough, dyspnea, pain, fatigue, and anorexia.<sup>42</sup>

The results of a large non-randomized trial and several smaller phase II trials suggest that the combination of carboplatin (AUC 5) and pemetrexed (500 mg/m<sup>2</sup>) is a reasonable alternative to the cisplatin/pemetrexed regimen for patients with poor performance status, significant comorbidities, or if cisplatin toxicity is a concern.<sup>43-47</sup> Other regimens that have demonstrated efficacy and acceptable toxicity in first-line treatment of MPM are cisplatin and LD<sup>48</sup> as well as low-dose gemcitabine in combination with cisplatin.<sup>49</sup>

Several recent studies of new chemotherapy drugs and drug combinations have been conducted which have shown limited efficacy in the treatment of MPM. Chemotherapy drugs that have recently been tested and shown to have failed as first line treatments include: sorafenib<sup>50</sup>, and vatalanib.<sup>51</sup> *Kindler et al* conducted a phase II randomized controlled trial on 108 patients with MPM and found that adding bevacizumab to a gemcitabine/cisplatin combination did not improve PFS or OS rates. Median control group rates were 6.0 months (PFS) and 4.7 months (OS) whereas median experimental group rates were 6.9 months (PFS) and 5.6 months (OS).<sup>52</sup>

At the present time, a standard second-line chemotherapy regimen for patients with medically inoperable MPM has not been established. However, reasonable second-line options may include single-agent pemetrexed (if not used in combination with cisplatin for first-line therapy), platinum-based compounds (such as cisplatin or carboplatin), gemcitabine, vinorelbine, or combinations of these (**recommendation #5**).

In a phase III non-randomized expanded-access study, *Jänne et al.* described outcomes in patients with MPM who had previously been treated with chemotherapy and had disease progression.<sup>53</sup> The patients received second-line pemetrexed alone (n = 91) or in combination with cisplatin (n = 96) for a maximum of six cycles; the disease control rate and median survival was 46.6 percent and 4.1 months for the patients treated with pemetrexed alone, and 68.7 percent and 7.6 months for the patients treated with pemetrexed and cisplatin.<sup>53</sup> An acceptable level of toxicity was also reported for both treatment groups. Similar results were observed in a smaller study comparing the same treatments with reported disease control rates of 48% and median OS of 10.5 months.<sup>54</sup> Although the data are limited, second-line treatment with single-agent vinorelbine or a combination of gemcitabine/vinorelbine has also been associated with moderate response rates and acceptable toxicity profiles in two small phase II studies.<sup>55, 56</sup> A combination of gemcitabine and a platinum-containing compound (such as cisplatin or carboplatin) for the second-line treatment of advanced MPM was able to yield stable disease rates of 67% with moderate toxicity in a recent, small (n=17), retrospective analysis.<sup>57</sup>

In 2011, *Garland et al* studied the efficacy of cediranib in the second-line treatment of MPM.<sup>58</sup> All 47 subjects had previously been treated with platinum-containing chemotherapies. They observed an objective response of 9%, a stable disease rate of 34%, median OS of 9.5 months, 1-year OS of 36% and median PFS of 2.6 months. Dose reduction due to toxicity was required in 91% of patients.<sup>58</sup> Two studies examining the efficacy of dasatinib<sup>59</sup> and sunitinib<sup>60</sup> as second-line therapies for advanced MPM have shown negative results and the authors conclude that neither therapy is effective as a single-agent. Preliminary experimental investigations with NGR-hTNF, on the other hand, have shown tolerability and disease control for patients who have previously failed pemetrexed-based therapy.<sup>61</sup> In 2011 *Scherpereel et al*<sup>62</sup> assessed the use of valproic acid in combination with doxorubicin and *Tourkantonis et al*<sup>63</sup> examined the efficacy of gemcitabine with docetaxel; both for the second-line treatment of MPM. *Tourkantonis et al* observed the best results, with 62.2% of patients achieving stable disease, 18.9% partially responding and a mean OS of 16.2 months. *Scherpereel et al* observed partial responses in



16.9% of patients with KPS scores of 80-100. The authors concluded that valproic acid and doxorubicin were only effective second-line agents for individuals with KPS scores in that range.

In a phase III trial comparing pemetrexed plus best supportive care versus best supportive care alone, *Jassem et al.* reported improved response rates (18.7% versus 1.7%,  $p < 0.0001$ ) and progression-free survival rates (3.6 versus 1.5 months,  $p = 0.01$ ) for the patients treated with pemetrexed; OS rates, however, did not differ between the two groups (8.4 versus 9.7 months,  $p = 0.74$ ).<sup>64</sup> *Trafalis et al.* in a smaller prospective study of 9 patients found the combination of topotecan and PLD to produce significant palliative effects for patients with advanced MPM. Quality of life measures improved in all patients by the second cycle of treatment with no grade 3 or 4 toxicities reported.<sup>65</sup>

### **Radiotherapy**

Malignant pleural mesothelioma often involves extensive areas throughout the pleural cavity, and radiotherapy is therefore limited by the large treatment volumes required. For patients with unresected disease, delivery of high-dose radiotherapy to the entire hemithorax in the setting of an intact lung has been associated with significant mortality, as well as toxicity to the lungs, esophagus, liver, spinal cord, and heart; in addition, no survival benefit has been demonstrated.<sup>66, 67</sup> Radiotherapy plays an integral role, however, as an adjunct to surgery, for the palliation of pain, and in the prevention of tract recurrence after surgical interventions. The most appropriate timing of radiotherapy delivery should be discussed by members of the multidisciplinary team.<sup>22</sup>

**Adjuvant radiotherapy.** For patients with resectable malignant pleural mesothelioma, radiotherapy is an integral part of disease management, and the members of the Alberta Provincial Thoracic Malignancies Tumour Team agree that adjuvant radiotherapy can be used in selected patients to improve local control (**recommendation #6**).

In a phase II study involving patients with early-stage malignant pleural mesothelioma, *Rusch et al.* reported on the use of high-dose hemithoracic radiation after complete surgical resection of all gross tumours in 57 patients at the Memorial-Sloan Kettering Cancer Center (MSKCC).<sup>68</sup> For patients who underwent EPP ( $n = 54$ ), adjuvant external-beam radiotherapy was started three to five weeks postoperatively, delivered at a total dose of 54 Gy in 30 daily fractions. The dose to the liver, heart, and stomach was limited through the use of blocks, and electrons were used in the blocked regions to prevent under-dosing to the pleura and diaphragm. For patients who underwent P/D ( $n = 3$ ), a dose of 15 Gy was delivered to the mediastinum and diaphragm intraoperatively, with a reduction to 10 Gy over the heart and esophagus. External-beam radiotherapy was also started 3 to 5 weeks postoperatively, at a dose of 45 to 54 Gy. The median survival was 33.8 months for patients with stage I and II tumours, and 10 months for patients with stage III and IV tumours ( $p = 0.04$ ). For the patients who underwent EPP, there were two locoregional recurrences, five locoregional and distant recurrences, and 30 distant recurrences, with the most common distant sites being the peritoneum, contralateral pleura, and contralateral lung. The authors concluded that, for patients with early stage disease, surgical resection and adjuvant hemithoracic radiotherapy reduces local recurrence and may prolong survival.<sup>68</sup> Another prospective study of 56 patients with MPM evaluated the efficiency of adjuvant RT ( $n = 4$  3DCRT,  $n = 50$  IMRT,  $n = 2$  helical tomotherapy) after EPP.<sup>69</sup> With an RT dose of 45-50Gy in 25 fractions to the hemithorax and ipsilateral mediastinum and simultaneous integrated boosts to microscopic sites up to 60Gy in  $n = 20$  patients they observed 3 year locoregional control, distant metastasis free rates, disease free survival, disease specific survival and overall survival in 90%, 66%, 57%, 62% and 60% of patients, respectively. The authors suggested post-operative RT (via various methods) was an effective way to treat MPM after EPP.<sup>69</sup>

Several published series have addressed the toxicity of external beam radiotherapy, as well as patterns of recurrence. In a follow-up to the *Rusch et al.* study, *Yajnik* and colleagues reported the results of 35 patients with malignant pleural mesothelioma who were treated with EPP followed by hemithoracic radiation therapy (median dose: 54 Gy, range: 45-54 Gy) at MSKCC between 1990 and 2001.<sup>70</sup> At a median follow-up of 55 months, two patients were alive with recurrent disease, while five patients were alive and disease-free. The most common toxicities were grades one and two nausea and vomiting, as well as lung, esophageal, and skin toxicities. Similarly, *Gupta et al.* reported on 86 patients with malignant pleural mesothelioma who underwent EPP followed by hemithoracic radiotherapy (median dose 54 Gy, range 45-54 Gy), also at MSKCC, between 1993 and 2008.<sup>71</sup> There were no deaths associated with radiotherapy, and eight patients developed late grade three pulmonary toxicity. Of the 78 patients who completed EPP and radiotherapy, the local and nodal failure rate after EPP and adjuvant radiotherapy was approximately 40 percent.<sup>71</sup> A dosimetric analysis conducted by *Hill-Kayser* and colleagues involved a comparison between patients treated with the electron-photon external beam radiotherapy techniques described by the MSKCC group (median dose 54 Gy) and those treated with intensity-modulated radiotherapy (IMRT) (median dose 45 Gy).<sup>72</sup> The authors reported a significant reduction in contralateral lung, median heart, and contralateral kidney doses with the modified external beam radiotherapy technique versus IMRT. Dose coverage of planning target volume and doses to the spinal cord, liver, and ipsilateral kidney were similar with use of the two techniques. *Sylvestre et al* compared IMRT after EPP with helical tomotherapy after EPP and found the latter to be associated with higher radiation dose and better coverage with similar toxicity profiles.<sup>73</sup>

The use of adjuvant IMRT following EPP has been associated with good local control in limited recent reports; however, high rates of toxicity and morbidity have also been reported.<sup>74-79</sup> At the present time, adjuvant IMRT following surgery is not considered standard of care for patients with malignant pleural mesothelioma.<sup>10, 26</sup>

**Palliative radiotherapy.** Radiotherapy is an effective means of symptom palliation for patients with advanced cancers, and should also be considered for palliation of symptoms in patients with malignant pleural mesothelioma. The timing, dose, and fractionation of radiation should be based on the intent of treatment (**recommendation #7**).

Results from retrospective and uncontrolled series suggest that approximately 50 to 70 percent of patients with advanced MPM treated with palliative radiotherapy experience relief from symptoms such as pain, dyspnea, superior vena cava obstruction, and dysphagia.<sup>67, 80-83</sup> Daily doses of 4 Gy appear to provide greater symptom relief than fractions of less than 4 Gy, although the optimal daily and total doses in this setting are yet to be established.<sup>22, 84</sup> Conventional radiotherapy can also be used for palliation of distant sites, such as bone and brain metastases.<sup>67</sup> Further details and recommendations regarding palliative radiotherapy can be found in the [Palliative Radiotherapy Clinical Practice Guideline](#).

**Prophylactic radiotherapy.** Tumour cell seeding in the tracts made by biopsies, chest tubes, and surgical incisions occurs in as many as 15 to 20 percent of all cases of malignant pleural mesothelioma.<sup>2, 84</sup> To date, three small randomized trials have published conflicting results regarding the use of prophylactic radiotherapy in patients with malignant pleural mesothelioma. In the first study, *Boutin et al.* compared 20 patients with malignant pleural mesothelioma who received 21 Gy of radiation in three daily doses over three days, 10 to 15 days after thoracoscopy with 20 patients who did not receive radiotherapy.<sup>85</sup> None of the 20 patients treated developed entry tract metastasis, while eight of the 20 (40%) patients who were not treated developed metastases ( $p < 0.001$ ). Of note, the patients with a mixed or sarcomatoid tumour

histology had a higher rate of tumour recurrence than patients with epithelioid histology (29% versus 14%), suggesting that histology might be a risk factor for tract metastases.<sup>85</sup> In the second randomized trial, *Bydder et al.* compared 28 patients who received a single dose of electron beam radiotherapy to the chest wall (10 Gy/ single fraction) with 30 patients who received no prophylactic therapy.<sup>86</sup> Radiotherapy was delivered within 15 days of thoracic procedures using 9 MeV electrons. The authors reported that there was no statistically significant difference in tract metastasis between the two arms of the trial, with three metastases in the control arm and two in the radiotherapy arm (10% versus 7%,  $p=0.53$ ).<sup>86</sup> Similarly, *O'Rourke et al.* randomly assigned patients who had undergone an invasive pleural procedure in the past 21 days to receive either 21 Gy of radiotherapy in three consecutive fractions ( $n=31$ ), or best supportive care ( $n=30$ ).<sup>87</sup> The authors reported tract metastases in four patients who had undergone radiotherapy, and in three patients who had received best supportive care ( $p=0.748$ ).<sup>87</sup> A recent retrospective study also assessed the efficiency of RT for preventing malignant seeding and found prophylactic RT to be effective and well tolerated.<sup>88</sup>

The varied results in these three small randomized trials may be due to differences in reported radiotherapy techniques, doses, and fractionation schedules, as well as the lack of reporting of tumour histology and disease stage. It is therefore difficult to make definitive conclusions regarding the use of prophylactic radiotherapy.<sup>84</sup> At the present time, however, the members of the Alberta Provincial Thoracic Malignancies Tumour Team agree that the use of prophylactic radiotherapy to prevent instrumentation (i.e., chest tube) tract recurrence after surgical interventions should be considered in patients with malignant pleural mesothelioma (**recommendation #8**).

### **Multimodality Therapy**

Select patients with malignant pleural mesothelioma may be candidates for aggressive multimodality therapy (**recommendation #9**).

Several combinations of adjuvant chemotherapy and radiotherapy in conjunction with EPP have been reported in the literature. *Sugarbaker* and colleagues, from the Brigham and Women's Hospital in Boston,<sup>89</sup> retrospectively reported the results of 183 patients treated over 20 years with EPP followed by platinum-based chemotherapy and up to 54 Gy of postoperative radiotherapy to the hemithorax. For the 176 patients who survived the EPP surgery, the two- and five-year survival rates were 38 and 15 percent, respectively. The best prognosis was seen in patients who had epithelioid histology (median OS=26 months,  $p=0.0001$ ), negative resection margins (median OS=23 months,  $p=0.02$ ), and no extrapleural metastases (median OS=21 months,  $p=0.004$ ). The 31 patients with all three positive variables had a 68 percent two-year survival, and a 46 percent five-year survival, with a median OS of 51 months ( $p=0.013$ ). In addition, the authors reported a low rate of perioperative mortality (3.8%).<sup>89</sup> This series has recently been updated to include 496 patients, of which 418 underwent EPP.<sup>90</sup> The median survival was 18.9 months, and the five-year OS rate was 13.9 percent. Similar results have since been confirmed in several smaller prospective studies, with median OS values ranging from 10 to 35 months.<sup>91-95</sup>

In 2011 *Lang-Lazdunski et al* reported results from a study of 79 patients with MPM that assessed the efficacy of neoadjuvant chemotherapy, adjuvant radiotherapy and EPP versus prophylactic radiotherapy, adjuvant chemotherapy, hyperthermic pleural lavage with povidone-iodine and P/D.<sup>96</sup> The 30 day mortality was 4.5% in the EPP group and 0% in the P/D group and complications were observed in 68% of the EPP cohort and 27.7% of the P/D cohort. Median OS values were higher in the P/D group relative to the EPP group (23 months versus 12.8 months) as were 2-year OS values (49% and 18.2%, respectively) and 5-year OS values (30.1% and 9%, respectively). The authors concluded that a multimodality approach

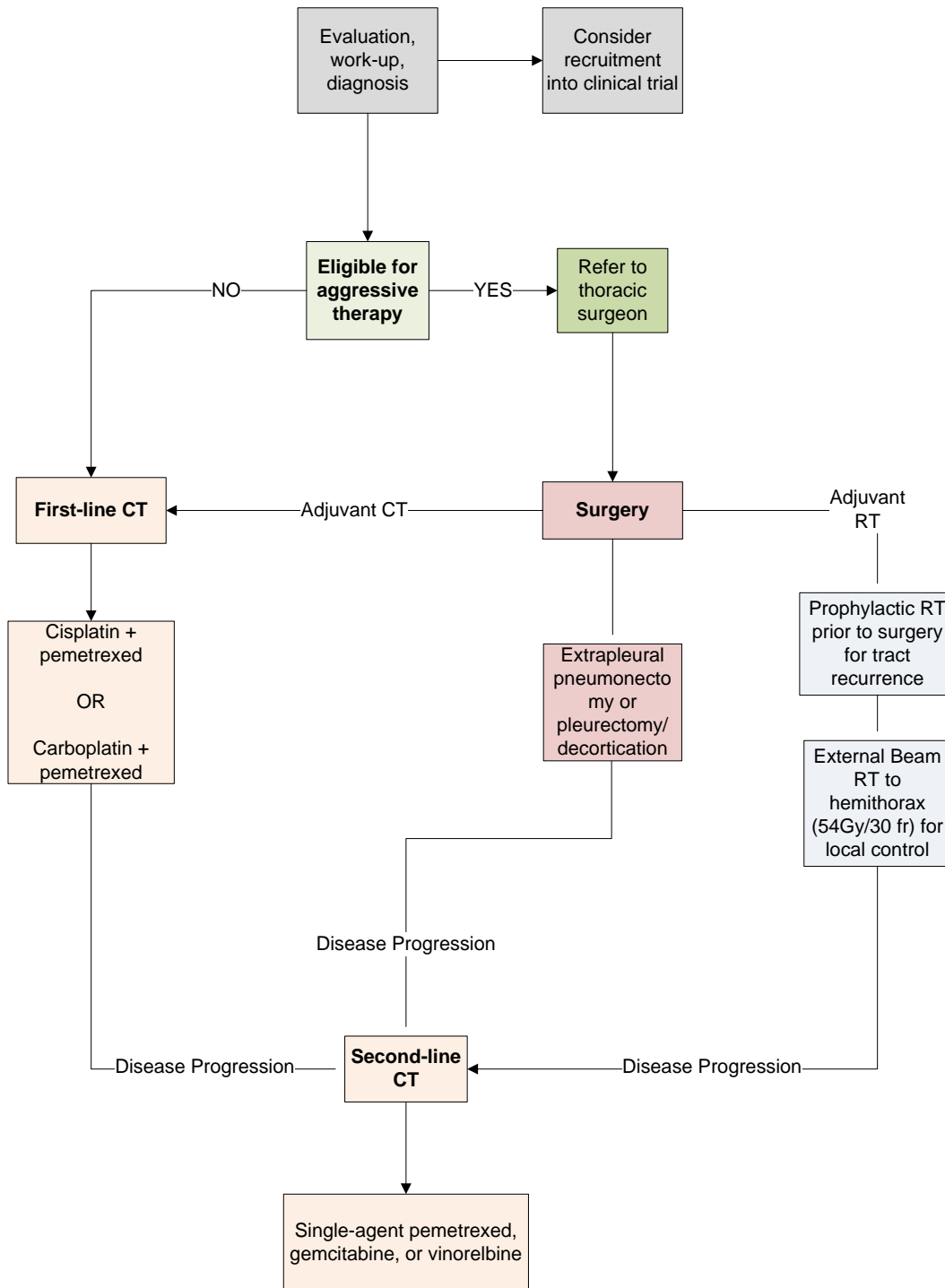
consisting of P/D, hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy and adjuvant chemotherapy may be superior to multimodality therapies including EPP.<sup>96</sup>

Studies of multimodality therapy in which neoadjuvant chemotherapy is followed by EPP and radiation have also shown promising results in several recent small prospective series. *Weder* and colleagues recently published the results of a phase II study involving 61 patients with stages I to III malignant pleural mesothelioma who received induction chemotherapy with three cycles of cisplatin/gemcitabine followed by EPP and postoperative radiotherapy (50-60 Gy/25-30 fractions).<sup>97</sup> The median OS was 19.8 months (95% CI 14.6 - 24.5) in the intent-to treat population, and 23 months (95% CI 16.6 - 32.9) for patients who completed the multimodality regimen. Tumour recurrence was documented in 38 patients, with a median time to recurrence of 13.5 months (95% CI 10.2 - 18.8). Patients with epithelial tumours tended to have a better median OS than patients with sarcomatoid and mixed tumours (21.9 months versus 11.1 months), although this difference was not statistically significant.<sup>97</sup> In a similar phase II trial, *Krug et al.* treated 77 patients with stages I to III malignant pleural mesothelioma with four cycles of neoadjuvant cisplatin/pemetrexed, followed by EPP and postoperative radiotherapy (54 Gy/30 fractions).<sup>98</sup> The median OS rates in the intent-to-treat population and those who completed the multimodality therapy were 16.8 months (95% CI 13.6 - 23.2) and 29.1 months (95% CI 19.3 - not reached), respectively. Twenty-three patients (40.4%) had documented recurrent disease, with a median time to recurrence of 18.3 months. A large-scale, phase II multi-centre clinical trial by *Van Schil et al* in 2010, which involved 58 patients, was also conducted to assess the efficacy of trimodality therapy on MPM prognosis. An induction chemotherapy regimen of cisplatin and pemetrexed was followed by EPP and post-operative radiotherapy. The group observed median OS values of 18.4 months and median PFS values of 13.9 months.<sup>99</sup> Similar results have been reported in several smaller phase II trials and case reports.<sup>100-102</sup>

In Canada, a retrospective review of 60 patients with stages I to III malignant pleural mesothelioma treated at a single centre was recently published by *de Perrot et al.*<sup>103</sup> Neoadjuvant chemotherapy regimens included cisplatin in combination with vinorelbine, pemetrexed, raltitrexed, or gemcitabine. Forty-five patients underwent EPP, and 30 patients underwent postoperative hemithoracic radiotherapy to at least 50 Gy. In the absence of mediastinal node involvement, completion of the multimodality regimen was associated with the best median OS (59 months versus less than 14 months in the remaining patients,  $p=0.0003$ ). The type of induction chemotherapy had no significant impact on survival, and nodal status remained a significant predictor of poor survival despite completion of the multimodality regimen.<sup>103</sup>

At the present time, there is no definitive combination of multimodality therapy that may be most beneficial to patients who are eligible for this treatment approach. The members of the Alberta Provincial Thoracic Malignancies Tumour Team agree that all patient cases being considered for multimodality treatment should be presented and discussed within a multidisciplinary tumour board setting (**recommendation #9**).

**TREATMENT ALGORITHM**



*Palliative treatment can be administered at any time for symptom control*

## GLOSSARY OF ABBREVIATIONS

Acronym	Description
AJCC	American Joint Committee on Cancer
AUC	area under the curve
CI	confidence interval
CRP	C-Reactive Protein
CT	computed tomography scan
EPP	extrapleural pneumonectomy
Gy	gray
IMIG	International Mesothelioma Interest Group
IMRT	intensity-modulated radiotherapy
KPS	Karnofsky performance status
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
MSKCC	Memorial-Sloan Kettering Cancer Center
OS	overall survival
P/D	pleurectomy/decortication
SEER	Surveillance, Epidemiology, and End Results database
TNM	tumour-node-metastasis
VATS	video-assisted thoracic surgery

## DISSEMINATION

- Present and review the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in May 2013. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Thoracic Malignancies Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Thoracic Malignancies Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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