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# Mesothelioma: An Evidence-Based Review

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Additional information is available at the end of the chapter

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## 1. Introduction

The initial discovery of mesothelioma can be traced back to 1767 when Dr. Joseph Lieutaud, an anatomy pathologist in France, first identified a tumour in the chest wall of a young boy [1]. Mesothelioma is a rare, aggressive form of cancer that develops from transformed cells originating in the mesothelium, which is the protective lining covering many of the body's internal organs. Mesothelioma arises in the pleura but also occurs in the peritoneum, the tunica vaginalis, and the pericardium [2]. Mesothelioma tends to have a local progression. While disseminated disease has sometimes been reported in a very late stage of the disease [3– 7], patients usually die from local progression.

## 2. Incidence

In Canada, there are 459 new reported cases of mesothelioma per year [8], compared to 3,000 in the United States of America. According to Connelly RR et al, the incidence of mesothelioma in the United States is 10 cases per million people per year [9]. Men are more commonly affected than women, with a male predominance of 90%. While there is a correlation between increasing age and reported cases, there is no peak and the mean age at diagnosis is 60 years.

The number of cases recorded in the Quebec Tumour Database from 1982 to 2002 (for the province of Quebec, Canada; see table 1) reveals that the incidence of pleural and peritoneal mesothelioma was higher for men than women. The overall annual rate of increase from 1982 to 2002 in Quebec was estimated to be 3.6%, which was lower than that measured from 1982 to 1996. In comparison to the international level, only Australia and Scotland showed significant increases in mesothelioma among women [10].

Type of Mesothelioma:	Pleural		Peritoneal	
	Men	Women	Men	Women
Gender:	Men	Women	Men	Women
Reported Cases:	1,210	320	98	72
Rate per 100,000 people per year:	1.98	0.41	0.15	0.09

**Table 1.** Incidence of Pleural and Peritoneal Mesothelioma

### 3. Epidemiology

#### 3.1. Asbestos

The primary risk factor for mesothelioma is asbestos exposure. Asbestos is a generic term for a group of six naturally occurring silicate minerals classified as either serpentine or amphibole. The amphibole (rod-like) group contains five types: amosite, crocidolite, anthophyllite, tremolite, and actinolite. Serpentine (chrysotile) asbestos has a sheet or layered structure and differs from the amphibole varieties both structurally and chemically. Chrysotile, the only asbestos mineral in the serpentine group, is the main form of asbestos still mined. It is generally accepted that chrysotile asbestos is less dangerous and does less damage to the lungs than the amphiboles. Although 70% to 80% of pleural mesothelioma cases are associated with asbestos exposure, the lifetime risk of developing pleural mesothelioma among asbestos workers is thought to be 10% [11]. Furthermore, despite the lack of evidence between the relationship of asbestos exposure and peritoneal mesothelioma, one study indicates that this correlation is less significant than that between asbestos exposure and pleural mesothelioma [12].

Asbestos is still used industrially for its fire-resistance and sound-absorption properties. The association between asbestos and mesothelioma was first documented in South African miners [13]. Moreover, the Occupational Safety and Health Administration (OSHA) established that 0.2 fibres per cubic millilitre of air is the standard acceptable exposure rate for fibres longer than 5  $\mu\text{m}$  [14].

Construction, boiler, and shipyard workers are at increased risk. Other sources of exposure may include a spouse or close relatives of asbestos workers. Patients from certain regions of the world (i.e. Greece, Central Turkey, California, and Bulgaria) also have endogenous environmental asbestos exposure as their soil contains high level of tremolite asbestos fibres [15–19]. Furthermore, greater environmental exposure increases incidence of mesothelioma and is also proportionate to the latency period [20–21].

In the majority of patients, the disease develops after a latency period of up to 40 years after initial exposure [22]. Fortunately, today's strict industry standards have significantly reduced asbestos exposure by 100 to 1,000 times compared to the past [23]. For example, Great Britain recorded fewer annual deaths related to mesothelioma in 1968 [153] than in 2001 [1,84,8], largely due to the latency period. The peak in mesothelioma deaths is expected to occur in 2015

(2,450 deaths) [24]. Nevertheless, the rate of deaths in Great Britain associated with mesothelioma is expected to drop significantly after 2015, most likely because of reduced asbestos exposure and stricter industry standards.

Although it was once thought that smoking could lead to mesothelioma, we now know that is not the case. It does, however, increase the risk associated with asbestos exposure [25].

### **3.2. Carbon nanotubes**

Carbon nanotubes are stronger than steel yet lighter than aluminum. As a result, they can be found in a wide range of items such as high-performance bicycle frames, textiles (i.e. waterproofing fabrics), body armour, and concrete. Nevertheless, animal studies have demonstrated that carbon nanotubes can produce mesothelioma-like changes and may therefore cause mesothelioma [26,27]. Furthermore, it has been suggested that the mechanism involved may be either attributed to "changes in gene expression, epigenetic changes, and receptor-mediated or other intracellular signalling cascades" [28].

### **3.3. Radiation therapy**

Ionizing radiation to supradiaphragmatic fields appears to be a risk factor for developing mesothelioma. Data from patients treated with radiation therapy for Hodgkin's lymphoma [29], non-Hodgkin's lymphoma [30], and testicular cancer [31] revealed an excess rate of mesothelioma. Although the reported number of mesotheliomas was small, the risks were statistically significant. This might be the result of broader radiation therapy for Hodgkin's and non-Hodgkin's lymphoma, since mantle-field radiation had once been the standard method of treatment. Afterwards, extended-field radiation therapy became the standard of care. Since today's preferred method of radiation therapy for lymphomas is involved-field radiation, the incidence of mesotheliomas in patients with Hodgkin's or non-Hodgkin's lymphomas should drop because the smaller radiation-therapy fields should result in fewer secondary neoplasms. Moreover, since mediastinal radiation therapy is no longer given for testicular seminomatous germ-cell tumours, such patients should evidence a decrease in radiation-induced mesothelioma.

### **3.4. Genetic factors**

Another cause for mesothelioma may be the nuclear deubiquitinase enzyme BAP1, which plays an important role in transcriptional deregulation in the pathogenesis of mesothelioma. BAP1 deubiquitinase is known to target histones (proteins that package DNA in the cell nucleus) and HCF1 (a transcriptional co-factor involved in the cell cycle), which also affects the E2F and Polycomb (a group of genes that codifies a family of transcription factors) target genes. Inactivating mutations of BAP1 were found in about one quarter of mesothelioma tumour tissues tested [32, 33]. Common genetic changes, involving the loss of the tumour suppressor genes p14, p16 [34], NF-2 [35], and P53, have been associated with mesothelioma [2].

### 3.5. Viral oncogenes

Simian virus 40 (SV40) continues to raise controversy, as it has been suggested that SV40 may have been a contaminant in the poliomyelitis vaccine in the 1950s and 1960s. A review of mesothelioma case studies have revealed an important presence of SV40 nucleic acid in affected patients. SV40 is a DNA polyomavirus, which is thought to suppress tumour genes of the retinoblastoma family by a peptide known as SV40 large T antigen [36–40].

## 4. Pathology

The histopathologic subtypes of mesothelioma are epithelioid (40%), mixed or biphasic (35%), and sarcomatous or mesenchymal (25%). Needle biopsy mesothelioma can often be mistaken for adenocarcinoma. Mesothelioma under electron microscopy reveals cells with long microvilli with a needle-like shape and form. Mesothelioma is positive for calretinin, vimentin, WT1, and cytokeratin, but negative for periodic acid-shift stain, mucicarmine stain, carcinoembryonic antigen, and Leu-M1. Adenocarcinoma under electron microscopy reveals short microvilli [41].

## 5. Pathogenesis

Inhaled asbestos fibres create lung irritation that may lead to scarring, fibrosis, and plaques. On a cellular level, injuries caused by asbestos fibres can be followed by cell repair. Repeated cell injuries, however, may lead to DNA-strand impairment and transform into malignancy [42]. It has also been suggested that long, thin asbestos fibres are generally more carcinogenic than shorter, thicker ones and interfere more with mitosis, causing chromosome abnormalities leading to cell transformation and neoplastic progression [43]. Mesothelial cells may have increased interleukin-6 secretion, which would result in increased production of vascular endothelial growth factor (VEGF), a signal protein produced by tumour cells that stimulates angiogenesis [44].

## 6. Clinical presentation

Dyspnea and non-pleuritic chest pain are the most common presenting symptoms of mesothelioma. X-rays often reveal recurrent pleural effusion or pleural thickening, which should prompt the clinician to suspect mesothelioma [45].

Early malignant pleural mesothelioma presents as small pleural nodules. As the tumour progresses, the nodules increase in number and coalesce to form a thickened tumour. As the tumour replaces the pleural fluid that lies between the two pleura, the parietal and visceral pleura fuse. This results in dyspnea and hypoxemia, which are often refractory to supplemental oxygen when deoxygenated blood is shunted through the encased lung.

Mesothelioma spreads by direct extension [46] and seeding throughout the pleural space, including fissures, diaphragmatic, and pericardial surfaces; through the chest wall; and into the mediastinum and lymph nodes. The malignancy may also extend into the abdominal cavity. Metastasis, although uncommon, may occur in the opposite lung, brain, and other extrathoracic sites.

## 7. Physical exam

The performance status should be evaluated. Visual inspection may reveal thorax nodules or ulcers and scoliosis may be observed towards the side of the malignancy [47]. The clinician should look at all sites of previous instrumentation for evidence of tumour seeding. Unilateral dullness to percussion at the lung base may be observed. Decreased air entry on the involved side may also be perceived.

## 8. Lab work

Tests should include a CBC, electrolytes, creatinine, and a complete metabolic panel. Serum soluble mesothelin-related peptide and osteopontin levels could be performed, although most Canadian centres do not currently do so.

Mesothelin is a glycoprotein usually expressed on normal mesothelial cells but is overexpressed in epithelioid and mixed mesotheliomas [48, 49]. A meta-analysis showed that sensitivity ranged from 19% to 68%, depending on the criteria chosen to establish positivity [50]. The glycoprotein osteopontin is also overexpressed in mesothelioma, but a study pointed to lower diagnostic accuracy than mesothelin in patients with suspected malignant mesothelioma [51].

## 9. Imaging

### 9.1. CT scan

Thoracic, abdominal, and pelvic CT scans with contrast are useful in staging the disease. Pleural thickening is the most common finding on CT scans (92% of mesothelioma patients). Pleural thickening is defined as either extension of more than 8 cm in the craniocaudal direction or more than 5 cm of the chest wall when visualized in cross section, or when the pleural thickness exceeds 3 mm [52–54].

The second most common finding is involvement of the fissure (about 85% of cases), followed by pleural effusion (75% of patients). Other findings include contraction of a hemithorax, contralateral shift of the mediastinum, chest-wall involvement, and rib destruction [55–58]. As

the disease progresses, irregular pleura-based masses are common and the interlobular fissures are often involved. CT scanning may underestimate the extent of disease.

Although CT scanning is used for tumour detection, its accuracy for detecting intrathoracic lymph-node involvement is limited [59, 60]. Mesothelioma spreads into paraesophageal nodes, pulmonary-ligament nodes, and diaphragmatic nodes more commonly than other lung cancers.

## 9.2. MRI

Combining magnetic resonance imaging (MRI) with CT scanning may improve evaluation of the local extent of disease. MRI helps to determine chest-wall, diaphragmatic, or apical invasion as well as transdiaphragmatic tumour growth [57].

## 9.3. PET-CT scan

PET-CT scanning may be useful in detecting mediastinal lymph-node involvement or extrathoracic diseases and to reclassify patients as inoperable [61–65].

## 10. Surgical staging

Although radiographic staging evaluation is warranted, accurate staging is only possible at the time of surgery in a substantial number of patients. Pulmonary-function tests are often performed prior to surgery. For surgical staging, mediastinoscopy or endobronchial ultrasound is used in the case of suspicious nodes. An open biopsy or CT-guided core biopsy is acceptable, but thoracentesis or video-assisted thorascopic surgery (VATS) is preferred. If necessary, based on the CT scan, laparoscopy can be used to rule out transdiaphragmatic extension, and VATS to rule out contralateral disease.

## 11. TNM staging of mesothelioma

The TNM (Tumour, Node, Metastasis) Classification is used by both the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The 2010 version is the most recent.

### Primary Tumour (T)

- Tx: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- T1: Tumour limited to the 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 involves each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:
- (1) Involvement of diaphragmatic muscle
  - (2) Extension of tumour from visceral pleura into underlying pulmonary parenchyma
- 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:
- (1) Involvement of the endothoracic fascia
  - (2) Extension into the mediastinal fat
  - (3) Solitary completely resectable focus of tumour extending into the soft tissue of the chest wall
  - 4) Nontransmural involvement of the pericardium
- 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:
- (1) Diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction
  - (2) Direct diaphragmatic extension of the tumour to the peritoneum
  - (3) Direct extension of the tumour to a mediastinal organ
  - (4) Direct extension of the tumour to the contralateral pleura
  - (5) Direct extension of the tumour into the spine
  - (6) Tumour extending through to the internal surface of the pericardium with or without a pericardial effusion or tumour involving the myocardium

#### **Regional Lymph Nodes (N)**

- Nx: Regional lymph nodes cannot be assessed
- N0: No regional lymph-node metastases
- N1: Metastases in the ipsilateral bronchopulmonary and/or hilar lymph nodes
- N2: Metastases in the subcarinal or ipsilateral mediastinal lymph node (including ipsilateral internal mammary and peridiaphragmatic nodes)
- N3: Metastases in the contralateral mediastinal, internal, mammary, or hilar nodes and/or the ipsilateral or contralateral supraclavicular or scalene lymph nodes

#### **Distant Metastasis (M)**

- Mx: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

#### **Stage Groups**

- I T1N0M0
- IA T1aN0M0

IB	T1bN0M0
II	T2N0M0
III	T1-2N1M0
	T1-2N2M0
	T3N0-2M0
IV	T4 and any NMO
	Any T and N3M0
	Any T and any N and M1

## 12. Differential diagnosis

Even though most pleural tumours are malignant, the differential diagnosis also includes benign tumours and inflammatory reactions.

Primary tumours, such as fibrosarcoma and malignant fibrous histiocytoma, can present in a similar fashion and infiltrate like sarcomatous mesotheliomas. Metastatic diseases that can involve the pleura and mimic epithelioid mesothelioma include breast, lung, lymphoma, thymoma, stomach, kidney, ovarian, and prostate cancer. Finally, benign chronic organized empyema can also mimic pleural thickening.

## 13. Treatments

The median survival of patients with mesothelioma is poor, ranging from 7 to 17 months [66]. The overall survival (OS) rate at 5 years is 9%. Even with new therapy interventions, the overall patient survival rate has not been significantly improved. In some specific cases, in which patients were specifically chosen due to their localized disease, treatment with aggressive multimodality therapy improved their survival rates.

The first thing to consider when treating mesothelioma is whether the tumour is resectable or not. Since the tumour spreads by direct extension, only 5% of mesotheliomas are resectable at diagnosis. Usually T1 to T3 and N0-1 tumours are considered resectable. T4 and N2-3 tumours are considered unresectable. Mediastinoscopy has to be performed to rule out N2-N3 lymph nodes. In addition, patients with sarcomatoid histology have a poorer prognosis and should not be considered for extrapleural pneumonectomy [67]. Patients must be able to tolerate trimodal therapy, since it is important to ensure that they do not have postoperative morbidities without deriving the full benefits of surgery.

The treatment paradigms for resectable mesothelioma are:

Extrapleural pneumonectomy (EPP), then chemotherapy followed by hemithorax radiation therapy [7, 68–71]



Neoadjuvant chemotherapy, then EPP followed by hemithorax radiation therapy [72–73]

If the tumour is unresectable:

A combination of chemotherapy is the standard treatment. Prophylactic drain-site irradiation should be considered.

Talc pleurodesis with a pleural catheter or pleurectomy may also be considered to palliate symptoms of pleural effusion.

## 14. Surgery

Prior to surgery, it is important to have proper patient selection. Patients must have:

Performance status of 0–1

PaO<sub>2</sub> of more than 65 mm Hg

PaCO<sub>2</sub> of less than 45 mm Hg

A predicted post op FEV<sub>1</sub> of more than 1 L

An ejection fraction of more than 40%

A mean pulmonary arterial pressure of less than 30 mm Hg

An epithelioid histology

### 14.1. Extrapleural Pneumonectomy (EPP)

EPP involves the removal of parietal pleura, lung, pericardium, and ipsilateral diaphragm. Mediastinal node dissection is usually performed. Finally, a graft is inserted to prevent herniation of abdominal contents through the diaphragmatic defect. Although no survival benefit was observed from randomized trials, observational studies indicated that EPP is the only intervention that has been demonstrated to result in long-term, disease-free survival in highly selected patients with favourable prognostic indication [7]. In a review of 83 patients who underwent EPP, the observed 5-year survival rate was 15% [74].

The benefits of EPP is that it allows complete resection or at least a cytoreduction, permitting higher radiation doses to be delivered safely to the ipsilateral hemithorax. This procedure has the disadvantage of being technically complex and associated with significant perioperative morbidity and mortality. Complications include atrial fibrillation (44.2%), prolonged intubation (7.9%), vocal-cord paralysis (6.7%), deep-vein thrombosis (6.4%), technical complications (patch dehiscence, haemorrhage, or both; 6.1%), tamponade (3.6%), acute respiratory-distress syndrome (3.6%), cardiac arrest (3%), constrictive physiology (2.7%), aspiration (2.7%), renal failure (2.7%), empyema (2.4%), tracheostomy 1.8%, myocardial infarction (1.5%), pulmonary embolus (1.5%), and bronchopleural fistula (0.6%) [75]. In extensive experience, the early postoperative mortality rate approaches 7% [76] but can be as high as 30%. The mean survival (MS) rate after surgery is 4 to 20 months.

## 14.2. Pleurectomy/Decortication (P/D)

In case of more advanced disease, mixed histology, and medically high-risk operable patients, pleurectomy/decortication is preferred over EPP. Pleurectomy/decortication is performed in two phases. Phase 1 is pleurectomy and involves removing the pleural lining. Phase 2 is decortication, which is the removal of any tumour growing inside the lining. The procedure's perioperative mortality is 4% [76].

Retrospective studies have indicated that parietal pleurectomy and decortication may be as efficient as extrapleural pneumonectomy [76]. When comparing EPP to PD, it was observed that PD patients had a greater local recurrence of disease, while EPP patients experienced higher mortality and surgical morbidity.

## 15. Radiotherapy (RT)

### 15.1. Adjuvant radiation therapy after EPP

Radiation therapy is a local treatment that uses ionizing radiation to destroy tumour cells. As mentioned above, aggressive surgery alone does not improve survival. Observational data do not provide evidence that adjuvant RT following pleurectomy offers a survival benefit [77]. That notwithstanding, the MSKCC phase-II trial with hemithorax radiotherapy to 54 Gy following EPP showed improved mean survival rates at 34 months for stage I-II disease and at 10 months with later-stage disease compared to historical controls [78]. In addition to a small survival benefit demonstrated in the MSKCC study, the rationale for using radiation therapy is local control. The disease is of a diffuse nature and manipulating the exposed tumour during EPP puts the entire ipsilateral chest wall, diaphragm insertion, pericardium, mediastinum, and bronchial stump at a very high risk of local recurrence, as high as 80% of patients, as reported in [78]. The evaluation of high-dose radiation therapy showed that the use of adjuvant radiation decreased the risk of local recurrence to 13% [78].

Mesothelioma is considered a tumour sensitive to external-beam radiation therapy. The recommended postoperative doses are 50 Gy for negative surgical margins, 54 to 60 Gy for close or positive margins, and 60 Gy for gross tumours [79–83]. The radiation dose has to be limited, however, due to the treatment required to the entire hemithorax and the sensitivity of critical organs such as the heart, lungs, oesophagus, liver, kidneys, and spinal cord to radiation [68].

Treatment volumes include ipsilateral mediastinum even for node-negative tumours. The superior border should include the thoracic inlet. The medial border should include the trachea, subcarinal lymph nodes, and the vertebral body. The inferior border is the insertion of the diaphragm, ranging from L1 to L4. Radiation oncologists should be careful to include the anteromedial pleural reflection of the sternopericardial recess, the medial and inferior extent of the crus of the diaphragm, and the inferior insertion of the diaphragm in the treatment volume. Nowadays, radiation therapy is delivered using three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) [70, 71, 84, 85].

IMRT can be delivered according to the method published by the MDACC experiment using 13 to 27 fields with 8 to 11 gantry angles with 100 segments/fields. The target volume was the entire hemithorax, all surgical clips, all sites of instrumentation, and the ipsilateral mediastinum with an initial dose to 45-50 Gy, with a boost to 60 Gy for a close/positive margin. The two-year survival rate was 62% and the three-year disease-free survival (DFS) rate was 45% for negative lymph nodes and epithelioid histology. Five patients with stage-I disease had a three-year DFS of 100%. IMRT has the potential to decrease pulmonary toxicity if correct treatment algorithms are applied.

In order to decrease the side effects of radiation therapy, several dose-volume restrictions are applied. The V20 (the volume receiving 20 Gy or more) of the lung must not exceed 7%, since Rice DC et al. [86] showed a relative risk of 42% for fatal pneumonitis. The oesophagus V55 should be less than 30%; the liver V30 should be less than 30%. The kidneys V15 should be less than 20%; the heart V40 less than 50%; the spinal cord V45 less than 10%; no volume should be more than 50 Gy.

### **15.2. Radiation therapy to the biopsy site**

A debate in radiation oncology for mesothelioma remains whether to offer radiation therapy to inoperable patients following an invasive procedure or following a biopsy in order to avoid needle-tract seeding from the tumour. The incidence of tumour seeding along the biopsy tract may range from 0% to 43% and may lead to the formation of painful subcutaneous lesions [87]. Three randomized trials [88-90] evaluated RT following thoracoscopy or thoracotomy to prevent tumour seeding. The radiation-therapy regimen was generally 3 fractions of 7 Gy (total of 21 Gy). O'Rourke et al. showed, in their randomized trial with 61 patients, that prophylactic radiation therapy to drain sites did not statistically reduce the rate of seeding. Boutin's study (40 patients) revealed a clear benefit of radiation at the biopsy site with reduction of biopsy-tract metastasis from 40% to 0% ( $p < 0.001$ ). At the Hôtel-Dieu de Québec Hospital, however, Marie-Anne Froment et al. [91] reported a benefit of radiation therapy to avoid needle-tract seeding from the tumour. At 6 months, local progression-free survival for the intervention sites was 91% with prophylactic radiation therapy and 74% without irradiation ( $p = 0.002$ ). During follow-up, 6 patients (13%) in the treated group had tumour invasion of the subcutaneous tissue compared to 40 patients (33%) in the group without radiation ( $p = 0.008$ ). Because recurrence is morbid and this treatment is easily feasible, Hôtel-Dieu de Québec Hospital generally offers radiation therapy to such patients.

### **15.3. Side effects of radiation therapy after EPP**

The side effects of radiation therapy can be classified according to time of occurrence: acute, intermediate, or late. Acute effects, if they appear, are expected to start during treatment and be resolved within 3 months following treatment. Potential acute side effects are fatigue, skin reactions, nausea, vomiting, dysphagia, odynophagia, and cough. Potential intermediate side effects include pneumonitis and Hermitte's syndrome. If intermediate side effects occur, they usually do so 3 months after treatment and resolve within 6 months.

Finally, potential late effects would occur 6 months following treatment and could include pulmonary fibrosis, pericarditis, restrictive cardiomyopathy, myocardial infarction, congestive heart failure, and radiation myelopathy.

## 16. Chemotherapy

### Adjuvant or Neoadjuvant Chemotherapy

Anthracyclines have historically been the most commonly used pharmacologic agents, with reported response rates of 19% [92]. Recent trials using platinum in combination with folate analogues have improved cytotoxic activity against mesothelioma. The preferred treatment during these recent trials was a combination of chemotherapy incorporated with a trimodal regimen, as adjuvant or neoadjuvant chemotherapy options are either pemetrexed/cisplatin or gemcitabine/cisplatin.

#### 16.1. Adjuvant chemotherapy

Patients treated with EPP, followed by radiation therapy and adjuvant chemotherapy, had a median survival rates of 36 % and 14% at two to five years, respectively. Historically, the chemotherapy used was doxorubicin, cyclophosphamide, and cisplatin for four to six cycles [93]. A Harvard retrospective [93] review of 183 patients treated with a trimodality approach using adjuvant chemotherapy of Cytosan/Adriamycin/cisplatin (CAP) or carboplatin/Taxol with concurrent radiation therapy followed by adjuvant chemotherapy had an overall mean survival rate of 19 months and a 5-year overall survival (OS) rate of 15%.

#### 16.2. Neoadjuvant chemotherapy

The rationale for using neoadjuvant chemotherapy prior to surgery is that it may increase tolerance and improve response to surgery. A multicenter phase-II trial [72] evaluated the role of neoadjuvant chemotherapy prior to EPP and RT. The chemotherapy consisted of four cycles of pemetrexed plus cisplatin. The median survival rate of the patients who completed the therapy was 29 months; the two-year survival rate was 61%. De Perrot et al. [73] reported a median survival rate of 59 months in a subgroup of patients who had completed trimodal therapy with neoadjuvant chemotherapy, EPP, and then RT. The median survival rate was less than 14 months for the patients who did not complete the treatment regimen.

#### Chemotherapy as a definitive treatment

#### 16.3. Combination chemotherapy

Combination-chemotherapy regimens using pemetrexed and platinum-based agents have yielded superior outcomes than single agents. Volgezang NJ et al. [94] showed that, for unresectable tumours, cisplatin/pemetrexed improved the response rate of 17% vs. 40% and the MS rate from 9 to 12 months compared to cisplatin alone. In 2004, pemetrexed became the

first agent to receive Food and Drug Administration (FDA) approval for use in combination with cisplatin. The combination of pemetrexed and carboplatin were studied in two phase-II studies, the response rates and mean survival rates were 18.6% and 12.7 months in the Ceresoli study [95] and 25% and 14 months in the Castagneto study [96].

Several trials [97, 98] have evaluated the addition of gemcitabine, a cytidine analogue. Only 38% of patients received the four cycles as prescribed and the response rate was 26% among those who completed the treatment [98]. It should be noted that the study only included early-stage mesothelioma. Vinca alkaloid-containing regimen was compared to MVP (mitomycin, vinblastine, and cisplatin) in terms of symptom control. The median survival benefit was an additional 2 months [99].

#### **16.4. Single-agent chemotherapy**

Pemetrexed as a single agent has been studied. In one phase-II trial [100], the study design was revised to incorporate folic acid and cynocobalamin in addition to dexamethasone. The median progression-free survival was 16.3 months in the pemetrexed/vitamin-supplemented group versus 9.5 months for the pemetrexed group. Other single agents such as gemcitabine, anthracyclines, and taxanes have been tested but resulted in low response rates, such as 10%

#### **16.5. Chemotherapy side effects**

Cisplatin and carboplatin are platinum analogues. The potential side effects of platinum agents include dose-limiting myelosuppression, nausea, vomiting, renal impairment, hearing impairment, and peripheral neuropathy. Pemetrexed is an antifolate compound. Potential side effects include myelosuppression, nausea, skin rash, alopecia, diarrhoea, and fatigue.

### **17. Molecular target therapy**

Recent anticancer agents focus on molecular targets such as surface receptors and cell-signalling proteins. Although it has been shown that mesothelial cells express the vascular endothelial growth factor (VEGF) receptor, a recent study [101] failed to demonstrate survival improvement with bevacizumab. Erlotinib, a tyrosine-kinase inhibitor of the epidermal growth-factor receptor (EGFR), was tested in a phase-II trial. EGFR is expressed primarily in the epithelial subtype of mesothelioma. Of the 63 patients who were enrolled, only 29 were assessed for outcomes; no objective responses were reported [102].

### **18. Prognosis and overall survival**

The European Organisation for Research and Treatment of Cancer (EORTC) reviewed data for 204 adults who were enrolled in five consecutive phase-II trials over nine years. The EORTC poor prognostic factors [103] for mesothelioma are:

- White-blood-cell count greater than  $8.3 \times 10^9$ / dL
- Performance status (PS) 1-2
- Sarcomatous histology
- Male gender

For low risk: 1-year OS rate is 40%; 2-year OS rate is 14%. For high risk: 1-year OS rate is 12% and 2-years OS rate is 0%. The MS rates are 4 and 12 months, respectively.

## 19. Palliative treatment

Surgical procedures, radiation therapy, and chemotherapy can be used to palliate symptoms.

### 19.1. Surgery

Large pleural effusions can cause persistent dyspnea and pain. Complete drainage of the pleural effusion by tube thoracostomy or video thoracoscopy followed by the introduction of an irritative agent to obliterate the pleural space can provide palliation. There is an ongoing randomized trial in the United Kingdom comparing the palliative benefits of VATS pleurectomy to talc pleurodesis.

### 19.2. Radiation therapy

In the case of palliative treatments, radiation therapy can be used for pain relief. Either 30 Gy in 10 fractions or 20 Gy in 5 fractions can be delivered. Furthermore, palliative radiation therapy with daily dose of 4 Gy appears to be more effective than fractionations of less than 4 Gy for a total dose of 20 to 40 Gy to relieve pain associated with skin nodules in the CW. Radiation therapy can alleviate symptoms in 50% of patients [104].

### 19.3. Chemotherapy

For unresectable tumours, palliative chemotherapy with cisplatin/pemetrexed or cisplatin/gemcitabine can be used. There are no standard second line of chemotherapy. Therefore, a combination or single agent such as gemcitabine, vinorelbine, paclitaxel, or docetaxel may be considered.

## 20. Conclusion

The highest risk factor for mesothelioma is exposure to asbestos. Treatment for mesothelioma involves a trimodal approach for early-stage disease, which includes surgery, radiation, and systemic chemotherapy. In the case of locally advanced disease, nonsurgical candidates, or metastatic disease, surgery, chemotherapy, or radiation therapy can be used. Mesothelioma

has a poor prognosis, but recent studies of pemetrexed and platinum-analogue combination therapies have demonstrated improved response rates over other treatments. Although conducting research on mesothelioma is extremely difficult, since it is an uncommon disease, further study is required to improve patient outcomes.

## **Nomenclature**

AP Anterior-posterior field

BAP1 A gene that encodes a nuclear localizing protein with a ubiquitin carboxy-terminal hydrolase domain that gives BAP1 its deubiquitinase activity.

CAP Cytosine/Adriamycin/cisplatin

CBC Complete blood count

CW Chest wall

DFS Disease-free survival

E2F Group of genes that codifies a family of transcription factors

EGFR Epidermal growth-factor receptor

EORTC European Organisation for Research and Treatment of Cancer

EPP Extrapleural pneumonectomy

FDA Food and Drug Administration

Gy Gray

HCF1 A transcriptional cofactor involved in the cell cycle

MS Mean survival

MVP Mitomycin, vinblastine, and cisplatin

NF-2 Neurofibromatosis type-2 gene

OS Overall survival

P14 Tumour suppressor gene

P16 Tumour suppressor gene

P53 Tumour suppressor gene

PA Posterior-anterior field

P/D: Pleurectomy/decortication

PS Performance status

RT Radiation therapy

VATS Video-assisted thoracoscopic surgery

VEGF Vascular endothelial growth factor

WT1 Wilm's tumour gene

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