PLEURAL MESOTHELIOMA

B A C K G R O U N D E R

1. Overview

Mesothelioma is a rare cancer that typically originates in the pleura, and less commonly in the peritoneum, pericardium or the tunica vaginalis.[1,2] Although some patients are believed to have a genetic predisposition to the disease,[3] the large majority of mesothelioma cases are caused by exposure to asbestos.[2] Few patients with mesothelioma survive beyond 2 years,[4,5] with women surviving longer than men.[6]

Accurate diagnosis of malignant pleural mesothelioma (MPM) can be challenging, as it is uncommon and often difficult to distinguish from benign conditions.[3] Diagnosis requires appropriate clinical and radiographic investigations, ideally with analysis of adequate tissue samples.[3]

To further establish whether MPM is epithelioid or biphasic requires identification of two positive and two negative immunohistochemistry (IHC) markers.[7]

In terms of treatment, pemetrexed–cisplatin is the only recommended regimen for unresectable MPM that is categorised as being based on high-level evidence by the European Society for Medical Oncology (ESMO) guidelines.[8] In addition to the lack of treatment options for advanced disease, there is a lack of tumour biomarkers to guide treatment selection and prognosis.

2. What is pleural mesothelioma?

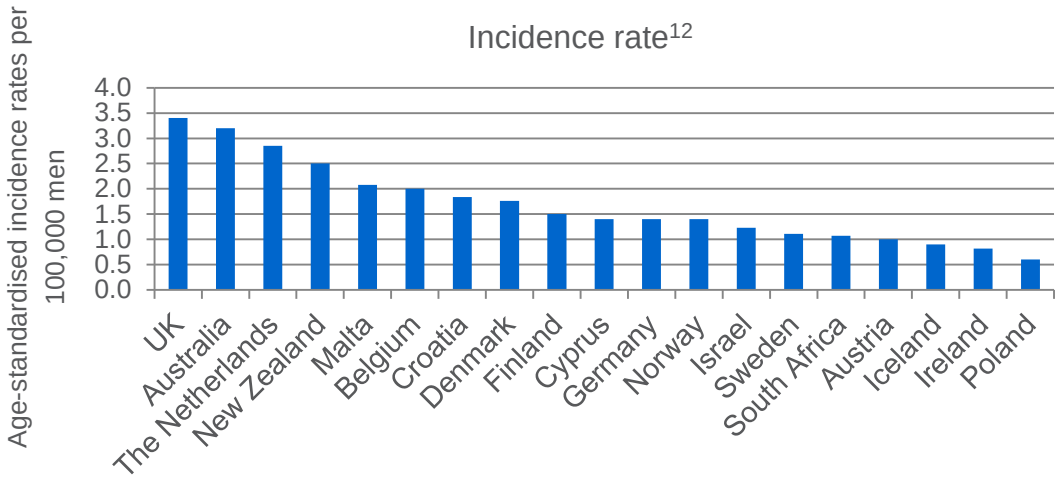
Mesothelioma is a rare and aggressive cancer in which tumours develop in the mesothelial or sub-mesothelial cells of different tissues.[2] The large majority of pleural mesothelioma cases are caused by exposure to asbestos[2] or to similar mineral particles that occur naturally[9] although recent studies have also identified a possible genetic predisposition in a minority of patients.[3]

This disease is characterised by a long latency period (30−50 years) between asbestos exposure and the development of symptoms.[8] Latency appears to be dependent on the degree of exposure to asbestos, with heavily exposed patients presenting earlier.[10] Owing to the fact that many symptoms are difficult to distinguish from those of other benign conditions, mesothelioma is typically diagnosed when the disease has already reached an advanced stage, meaning that most patients have a poor prognosis.[5]

Few patients with mesothelioma survive beyond 2 years.[5] One retrospective analysis of 1,353 patients with MPM found that survival in the overall population was 47% after 1 year, 20% after 2 years, and 15% after 3 years.[5] Overall survival has been found to be longer in women than in men.[6] Analysis of data from the Surveillance, Epidemiology, and End Results Program (SEER) database in US which included 14,228 patients diagnosed between 1973–2009 found that the 5-year survival rate was 13.4% in women but only 4.5% in men ($p<0.0001$).[6] Mesothelioma subtype and patient age at diagnosis also affects survival rate, with rates lower in the sarcomatoid subtype, and lower with increasing age.[5]

Incidence of mesothelioma

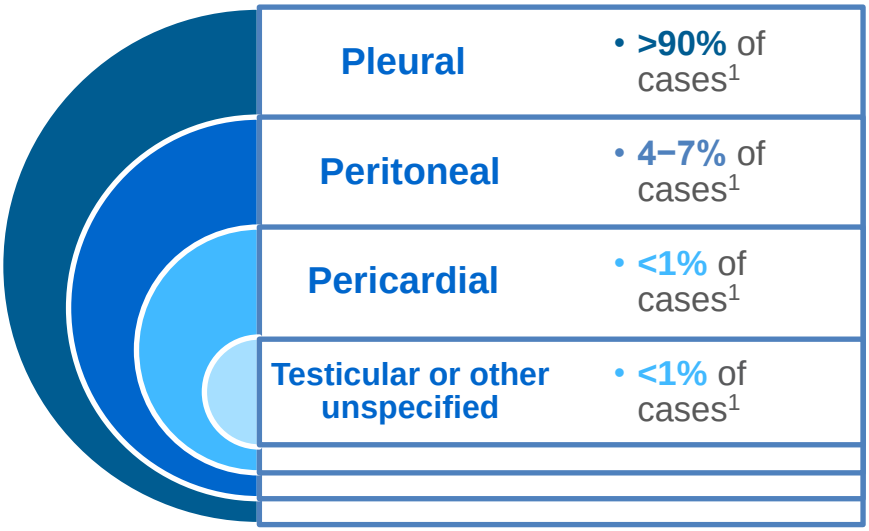
The incidence of mesothelioma is difficult to access accurately due to variable reporting rates worldwide and the fact that mesothelioma is often not specified in global databases.[11,12]



In most European countries and in Japan, the incidence of mesothelioma is still increasing, but it has peaked in the US and in Sweden.[13] Once a country introduces asbestos control measures, the number of mesothelioma cases is expected to plateau and then fall.[14] However, as many developing countries continue to use asbestos, it is predicted that mesothelioma prevalence in those countries will increase for many years.[8,13,14]

Types of mesothelioma

The most common form of mesothelioma – accounting for >90% of cases – is pleural mesothelioma.[1] Mesothelioma can also occur in the peritoneum, the pericardium, and in other tissues, including in the membrane that covers the testis.[1]



Histological subtypes of MPM

The three main histological subtypes of MPM are:

- Epithelioid (~60%)[15]
- Sarcomatoid (10–20%)[1,15]
- Biphasic (~30%)[1,15]

Epithelioid is the most common subtype and is associated with better outcomes than other histologies, with a median survival of up to 2 years.[15] The sarcomatoid subtype is far less common, and has been found to be resistant to therapy. Patients with this subtype of MPM have a poor prognosis, with predicted survival often <1 year from diagnosis.[5] The biphasic subtype is also associated with worse outcomes to therapy; it is characterised by the presence of a combination of mixed epithelioid and sarcomatoid histologies (≥10% epithelioid and ≥10% sarcomatoid areas).[1]

3. What are the risk factors for pleural mesothelioma?

The main risk factor for MPM is occupational or indirect exposure to asbestos, which accounts for ~80% of cases.[8] The term 'asbestos' includes six types of minerals used commercially that form fibres: cummingtonite-grunerite, chrysotile, actinolite, anthophyllite, riebeckite and tremolite.[9] All types of asbestos are classified as Class I carcinogens.[16] While the exact pathogenesis by which asbestos causes MPM has not yet been fully established, it is known that inhaled asbestos fibres enter the visceral pleura and the pleural space resulting in chronic inflammation, DNA damage, and cytotoxicity.[16] Development of asbestosis, pleural plaques and, in some cases, mesothelioma may follow.[16]

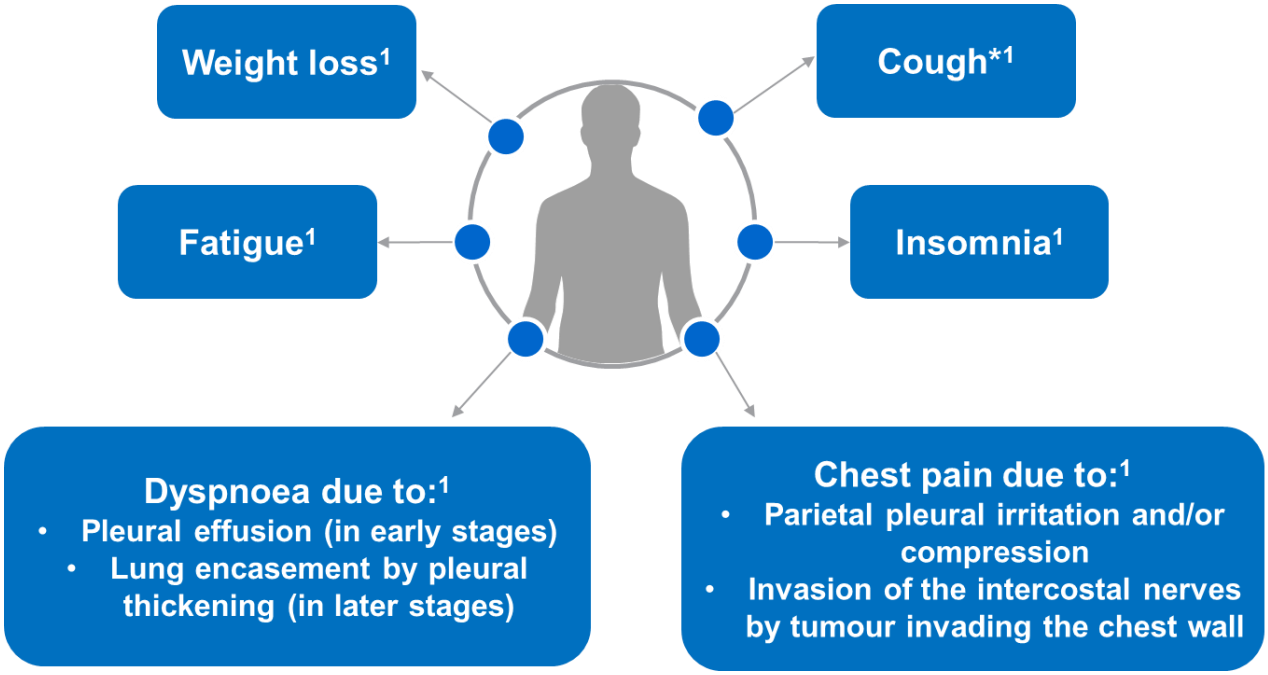
Exposure to other elongated mineral particles that occur naturally and are not categorised as 'asbestos' has also been associated with MPM.[9]

Other less common risk factors include genetic factors, in particular a germline mutation in the BAP1 gene.[8] Some studies have raised the possibility that infection with simian virus 40 (SV40) might increase the risk of developing mesothelioma.[17]

4. What are the clinical features of pleural mesothelioma?

Symptoms of MPM

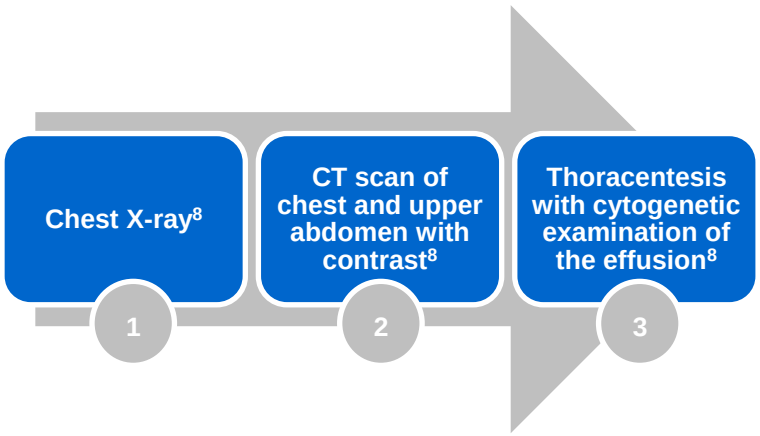
In patients with MPM, symptoms may have developed over the course of many months;[8] they often seek medical advice with a higher symptom burden than is typical of patients who present with other types of cancer.



*A less prominent symptom.

Diagnosis of pleural mesothelioma

A definitive primary diagnosis usually requires IHC assessment of tissue biopsies, using at least two 'mesothelial' markers and at least two '(adeno) carcinoma' markers.[8] The sarcomatoid subtype may not exhibit typical 'mesothelial' markers.[8]



Note: cytological samples are often inconclusive or negative, even when patients have malignant mesothelioma.

- Occupational history to establish asbestos exposure
- Computed Tomography (CT) scan of the thorax

- In patients who have a unilateral pleural thickening, with or without fluid and/or calcified asbestos plaques, a pathological specimen should be obtained if possible, as there are no specific clinical features of MPM

Disease staging is assessed according to depth of tumour invasion (T), extent of lymph nodal metastasis (N) and extent of distant metastases (M).[18]

Disease staging of malignant pleural mesothelioma[18]

Stage	TNM stage			Comments
	T	N	M	
I	T1	N0	M0	Primary tumour limited to ipsilateral parietal pleura
IA	T1a	N0	M0	No involvement of the visceral pleura
IB	T1b	N0	M0	Involvement of the visceral pleura
II	T2	N0	M0	As Stage I plus involvement of diaphragmatic muscle or extension of tumour from visceral pleura into underlying pulmonary parenchyma
III	T3	N0, N1, N2	M0	Locally advanced tumour, but potentially resectable
	T1, T2	N1	M0	Metastases in the ipsilateral, bronchopulmonary or hilar lymph node
	T1, T2	N2	M0	Metastases in the subcarinal or ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes
IV	T4	Any N	M0	Locally advanced, technically unresectable tumour
	Any T	N3	M0	Metastases in the contralateral mediastinal, internal mammary, and ipsilateral or contralateral supraclavicular lymph nodes
	Any T	Any N	M1	Distant metastases present

Biomarkers

A number of biomarkers can be assessed in MPM to help ascertain subtype and prognosis. Epithelioid and biphasic MPM diagnosis requires a combination of two positive and two negative IHC markers:[7]

- Calretinin, cytokeratins 5/6, D2-40, and Wilms' tumour-1 protein (WT-1) are mesothelioma markers[7, 19] with sensitivities ranging from 70−100% in epithelioid MPM[21]
- Mesothelin may be assessed in serum and pleural fluid, has a sensitivity of 68–90%,[7] and is elevated in 50% of MPM patients[7]
- BAP1 mutations are potential predictive markers of mesothelioma[7,20] and may be potential markers of the epithelioid subtype[21]
- p16/CDKN2A homozygous deletion may be found in 90–100% of sarcomatoid,[19] and 70% of epithelioid/biphasic mesotheliomas and is linked with poor prognosis[21]

There is a need for biomarkers of malignancy that can be used to guide treatment selection and prognosis. In a study investigating the genetic landscape of MPM for biomarkers to inform future treatment, frequency and type of genetic alteration was analysed using next-generation sequencing in 23 patients with MPM.[21] The most common gene alterations or losses were BAP1 (60.9%), CDKN2A/B (52.2%), and NF2 (34.8%).[21] Research is also ongoing to assess whether analysing both BAP1 and p16INK4A (encoded by p16/CKDN2A) in samples increases their specificity and sensitivity.[22,23]

Currently, there are a lack of accurate biomarkers to aid diagnosis, prognosis and treatment of MPM, but a number of other potential diagnostic biomarkers for MPM are also under investigation.

Potential diagnostic biomarkers for MPM:[7,24–31]

Category	Marker	
Immune checkpoints	PD-1/PD-L1+/– TIL TIM-3 LAG-3	
DNA	Hyperacetylated HMGB1	
RNA	miRNA (various assays) miRNA + SMRP lncRNA	
Genomics	Gene panels Gene expression ratios	
Proteomics	SOMAmers	
Other	Col3A1 BDNF + fibulin 3 Circulating plasma C4d	Leucocyte count + fibrinogen EPHA2 ENOX2

5. What are the treatment options for pleural mesothelioma?

Surgery may be an option where resection is possible. For unresectable MPM, cisplatin-based doublet chemotherapy is recommended. Pemetrexed–cisplatin is approved as a first-line regimen for unresectable MPM in both the EU[32] and US.[33] A summary of the ESMO recommendations for first-line treatment of unresectable MPM is as follows:

Treatment	ESMO recommendation[8]
Pemetrexed + cisplatin (Day 1 every 3 weeks)	**Category 1A**

Raltitrexed + cisplatin (Day 1 every 3 weeks)	Category 1A
Pemetrexed + cisplatin (Day 1 every 3 weeks for 6 cycles) + bevacizumab (Day 1 every 3 weeks until disease progression)	NR
Pemetrexed + carboplatin (Day 1 every 3 weeks)	Alternative to cisplatin in elderly patients
Gemcitabine (Days 1, 8 and 15) + cisplatin (Day 1) administered in 3- to 4-week cycles	NR
Pemetrexed (Day 1 every 3 weeks)	NR
Vinorelbine (weekly)	NR

NR, not recommended.

As yet, there is no standard of care for the second-line treatment of these patients, although studies of single-agent chemotherapy and novel agents are ongoing. Radiation therapy can be used for palliation, although it is not part of standard treatment in the adjuvant setting.[8]

Emerging treatment options for MPM

The role of targeted therapies in the treatment of MPM is likely to increase as therapeutic advances continue.[34]

Targets and therapies that are currently under investigation in a number of Phase III trials include:

- Angiogenesis, e.g. bevacizumab (Phase III results published),[35] nintedanib (Phase III trial ongoing)[36]
- Immune targets, e.g. nivolumab combined with ipilimumab (Phase III trial ongoing)[37]

Targets and therapies that are currently under investigation in a number of Phase II trials include:

- Immune targets, e.g. pembrolizumab,[38] atezolizumab,[39] durvalumab[40]
- Proliferative signalling, e.g. cetuximab, cixutumumab[34]
- Mesothelin, e.g. anetumab ravtansine,[41] amatuximab[42]

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