Malignant Pleural Mesothelioma Backgrounder

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1. OVERVIEW

Mesothelioma is a rare cancer that affects the cells that make up the mesothelium. The mesothelium is the lining or membrane that covers and protects various internal organs in the body including the lungs, abdomen, heart and testes. Mesothelioma most commonly originates in the pleura (the membrane that lines the lungs and chest cavity) and less commonly in the peritoneum (the membrane that lines the inside of the abdomen). Mesothelioma can also very rarely originate in the pericardium (the membrane that lines the heart) or the tunica vaginalis (the membrane that lines the testes).\(^1\) While several causes of mesothelioma have been identified, approximately 70% - 90% of cases can be attributed to asbestos exposure.\(^1\) Only 5% - 10% of mesothelioma patients live beyond five years\(^2\) and it is predicted that around 90,000 deaths worldwide will occur from the cancer by 2050.\(^3\)

2. WHAT IS PLEURAL MESOTHELIOMA?

Pleural mesothelioma is an aggressive cancer arising from the mesothelial cells lining the pleura and can be broadly categorised by their cell type, or histology:\(^4\)

- **Epithelioid**: Mesothelioma tumours made up of epithelioid cells are the most common, accounting for 50-70% of all diagnoses. It is the most treatable and patients with this cell type have the best prognosis.
- **Sarcomatoid**: The least common cell type, sarcomatoid mesothelioma accounts for approximately 15% of all mesothelioma diagnoses and has fewer treatment options than other cell types. Sarcomatoid mesothelioma is the most aggressive form of the disease and patients diagnosed with this cell type have the least favourable prognosis.
• **Biphasic (mixed):** Mesothelioma tumours made up of both epithelioid and sarcomatoid cells are called biphasic. This subtype accounts for ~30% of all pleural mesothelioma cases and is associated with poor prognosis.

Like other cancers, pleural mesothelioma starts in a small area (the lungs/chest) and can spread to other parts of the body via the bloodstream or lymphatic system. Pleural mesothelioma often goes undetected until it reaches an advanced stage, as the malignancies (tumours) commonly cause non-specific symptoms that mimic other conditions such as metastatic adenocarcinoma (a form of lung cancer) which can lead to misdiagnosis or delayed detection. The median survival of patients with pleural mesothelioma is less than 12 months.

3. **HOW COMMON IS PLEURAL MESOTHELIOMA?**

Pleural mesothelioma is a rare cancer that represents less than 1% of all cancers. It is estimated that up to 43,000 people worldwide die from the disease each year, although this is likely to be significantly higher due to unreported cases occurring in developing countries. The highest annual rates of pleural mesothelioma, approximately 30 cases per million of population, are reported in Australia and Great Britain, but current research suggests peak incidence has not yet been reached, and in developed countries, this is expected to occur in the next 10 to 20 years. In Europe, it is anticipated that cases of pleural mesothelioma will peak in 2015 – 2020, with a predicted incidence of 250,000 cases over the next 40 years. Due to occupational exposure of asbestos, men are five times more likely to be diagnosed with pleural mesothelioma than women and it is more frequent in advanced ages as a result of the long latency period (from 20 - 60 years).

4. **WHAT ARE THE RISK FACTORS FOR PLEURAL MESOTHELIOMA?**

The most significant risk factor for pleural mesothelioma is long-term exposure to asbestos – a history of exposure has been reported in over 90% of cases. Asbestos is a fibrous material that is resistant to fire, resulting in its use as insulation and in fire safety products. Different types of asbestos fibre include serpentine (long and curvy) and amphibole (straight and needle-like). Due to their shape, serpentine fibres are more easily cleared from the lungs. Crocidolite fibres (a subtype of amphibole fibres) are most commonly associated with pleural mesothelioma.

Although asbestos exposure is the major risk for developing mesothelioma, other associated causes can include germline mutation in the BRCA1 associated protein 1 (BAP1) gene exposure to a volcanic mineral called erionite. Erionite is a fibrous material that belongs to a group of minerals called zeolites, which are chemically related to asbestos.

In rare cases, individuals can also develop pleural mesothelioma without asbestos or erionite exposure. These cases are usually classified into:

- **Idiopathic mesothelioma**, a sporadic malignancy occurring in childhood or adolescence
- **Spontaneous mesothelioma**, a spontaneous transformation of one type of cell to another
It is also possible that other, unidentified, causative agents exist that result in the development of pleural mesothelioma such as certain chemicals, radiation, or viruses.

5. WHAT ARE THE SIGNS AND SYMPTOMS OF PLEURAL MESOTHELIOMA?

Symptoms of pleural mesothelioma are unspecific and can mimic or be mimicked by other diseases. The most common signs and symptoms include:

- Shortness of breath
- Chest pain
- Fatigue
- Cough
- Unexplained weight loss

6. HOW IS PLEURAL MESOTHELIOMA DIAGNOSED?

When diagnosing pleural mesothelioma, accurate history and the identification of at-risk occupations to ascertain previous asbestos exposure is the first essential step followed by a combination of tests:

**Imaging tests**

Imaging tests are used to help establish whether a suspicious area might be cancerous and to learn how far the cancer may have spread. Imaging tests that may be used to diagnose pleural mesothelioma include:

- **X-ray**, the most simple and practical diagnostic method for pleural mesothelioma which can identify pleural thickening, pleural nodules or pleural effusion - although this alone cannot confirm a diagnosis due to the lack of specificity
- **CT scan**, most commonly used to help diagnose pleural mesothelioma as it can display the surface of the whole pleura, the diaphragm and the status of lymph nodes
- **PET scan**, used to show how the lungs and associated tissues are working in the body
- **MRI scan**, not frequently used to diagnose pleural mesothelioma but can provide additional information to ascertain if a patient is a candidate for surgery

**Biopsy**

If pleural mesothelioma is suspected, a pleural biopsy will be taken and analysed under a microscope to determine if the tissue is cancerous (malignant) or benign (not malignant). Pleural biopsies are also undertaken to help differentiate mesothelioma from metastatic adenocarcinoma or other diseases that exhibit similar symptoms. A pleural biopsy can be obtained in several ways including:

- **A needle** to withdraw tissue or fluid. This may be performed by a radiologist using either an ultrasound or CT scan to guide placement of the needle
- **An endoscope**, which looks at the chest through a thin, lighted tube, inserted though the mouth. Doctors then use a tool to remove tissue samples through the tube to analyse whether they are cancerous
- **Surgery**, a thoracoscopy-guided biopsy is most commonly used to diagnose pleural mesothelioma, which uses real-time imaging to identify the exact sampling point with adequate tissue for biopsy
**Pleural fluid can be used to examine the cytology**

**Blood tests**  
Blood samples are taken and analysed to determine high or low levels of cells in a patient’s body that could be a sign of pleural mesothelioma (such as a high weight blood cell count).\(^1\),\(^5\)

**Clinical evaluation**  
A clinical evaluation is the last step to diagnosing pleural mesothelioma and takes a holistic look at a patient’s physical condition, medical history and laboratory examinations (such as biopsy and blood test results) to confirm a diagnosis and prognosis.\(^1\)

7. **WHAT ARE THE AVAILABLE TREATMENT OPTIONS FOR PLEURAL MESOTHELIOMA?**

The current treatment options for pleural mesothelioma include surgery, radiotherapy and chemotherapy.\(^2\) To determine the most appropriate treatment, cancers are ‘staged’ to establish how far the cancer has advanced in the body.\(^5\) The most practical and commonly used system is the ‘tumour-node-metastasis system’ (TNM) developed by the International Mesothelioma Interest Group.\(^4\) This system is used to give each case of pleural mesothelioma a score according to:\(^11\)

- The extent to which the surrounding tissue has been attacked (T)
- The extent of lymph nodes involved (N)
- The extent to which the cancer has spread to other organs in the body (M)

Depending on the above scores, the cancer is graded 0, I, II, III or IV to determine the most appropriate treatment option.\(^11\)

**Surgery**  
Surgery may be used to remove the tumour or pleural fluid in the lung to relieve pain and other symptoms.\(^10\) The type of surgery chosen will depend on the stage of cancer, the cardiopulmonary reserve\(^4\) (the interdependence of the heart, lungs and O\(_2\) - carrying capacity of a patient) and the planned adjuvant therapy.\(^10\) Surgery is mostly used in combination with radiotherapy, chemotherapy and/or immunotherapy.\(^4\)

**Radiotherapy**  
Radiotherapy uses high-energy rays (such as X-rays) or particles to destroy cancer cells and shrink tumours. It can be used before surgery (to shrink the size of the tumour), during surgery (to directly target the tumour without passing through the skin) and after surgery (to kill any cancer cells that remain).\(^7\) For patients with pleural mesothelioma, radiotherapy is mainly used as an adjuvant treatment to relieve symptoms.\(^4\)

**Chemotherapy**  
Most pleural mesothelioma patients are candidates for chemotherapy, which is used to kill the tumour cells,\(^10\) and can be used in a combination of ways:\(^11\)

- **Palliative chemotherapy** to shrink tumours, alleviate symptoms and prolong life when surgery is not an option (often when pleural mesothelioma is diagnosed in an advanced stage)
- **Neoadjuvant chemotherapy** to shrink a tumour before surgery or radiotherapy so it can be removed with fewer complications
- **Adjuvant chemotherapy** to kill cancer cells that may remain following surgery
Research is also being undertaken to determine the long-term safety and effectiveness of targeted therapy and immunotherapy for the treatment of pleural mesothelioma; there are currently no targeted therapies or immunotherapies approved to treat this cancer.

8. WHAT ARE THE OTHER TYPES OF MESOTHELIOMA?

There are three other types of mesothelioma including:

**Peritoneal mesothelioma**, an aggressive cancer of the peritoneum (the membrane that lines the inside of the abdomen). \(^1\) 20% - 33% of all mesotheliomas arise from the peritoneum and 50% of these can be linked to asbestos exposure. \(^12\) The symptoms can include abdominal pain, abdominal swelling, marked weight loss and, less frequently, night sweats and hypercoagulability. \(^12\) Like pleural mesothelioma, peritoneum mesothelioma is difficult to diagnose and consequently, is often detected once the cancer is in an advanced stage. \(^12\)

**Pericardial mesothelioma**, an extremely rare cancer of the pericardium (the membrane that lines the heart). \(^1\) The reported prevalence of this type of mesothelioma is 0.0022% and to date, only a few hundred cases have been reported. Unlike peritoneal and pleural mesothelioma, there has been no definite correlation between asbestos and pericardium mesothelioma. \(^13\)

**Testicular mesothelioma**, another, extremely rare cancer of the tunica vaginalis (the membrane that covers the testes) \(^1\) This type of mesothelioma represents 0.3% to 5% of all mesotheliomas \(^14\) and to date, there have only been 250 cases reported. \(^15\) Like other types of mesothelioma, asbestos exposure is considered to be the main risk factor – 30% - 40% of cases can be attributed to asbestos. \(^15\)

REFERENCES

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6 Allen T. Diffuse malignant mesothelioma. Springer. 2015:3.