



Draft PMB definition guideline for mesothelioma

DISCLAIMER

The mesothelioma benefit definition has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore Regulation 15(h) and 15(l) may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs and nursing care. However, these interventions form part of care and are Prescribed Minimum Benefits.

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ABBREVIATIONS

CMS	-	Council for Medical Schemes
PMB	-	Prescribed Minimum Benefit
ARD	-	Asbestos Related Disease
MPM	-	Malignant Pleural Mesothelioma
IHC	-	Immunohistochemistry
RT	-	Radiotherapy
VATS	-	Video-Assisted thoracoscopic surgery

1. INTRODUCTION

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, 131 of 1998 (the Act). With regards to some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the Council for Medical Schemes (CMS) with the aims of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. SCOPE AND PURPOSE

2.1. The guidelines are intended as a recommendation for the diagnosis, treatment and care of individuals with mesothelioma in any clinically appropriate setting as outlined in the Act.

2.2. The purpose of this guideline is to provide a detailed clarification in respect of benefits and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for identifying mesothelioma

C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified

3. EPIDEMIOLOGY AND BURDEN OF DISEASE

- 3.1. Mesothelioma is a rare tumour of the mesothelial cells, accounting for less than 1% of all cancers. Mesothelial cells make up the mesothelium, a membrane which forms the lining of body cavities including the thoracic cavity (pleura), abdominal cavity (peritoneum), and heart sac (pericardium) or forms a membranous cover for the internal male reproductive organs (tunica vaginalis of testis) (Shavelle, Vavra-Musser, Lee & Brooks, 2017).
- 3.2. Pleural mesothelioma is the most common form (80–85% of cases) and peritoneal mesothelioma accounts for about 10–15% of cases. Mesothelioma of the pericardium and tunica vaginalis of testis make up less than 5% of cases. Most cases are closely related to asbestosis exposure (Offermans, Vermeulen, Burdorf, Goldbohm, Kauppinen, Kromhout & van den Brandt, 2014), with a stronger correlation found in pleural than peritoneal cases (Shavelle et al 2017). Asbestos comprises of silicate minerals with thin fibres: chrysotile, crocidolite as serpentines, amosite, anthophyllite, tremolite, and actinolite from the amphibole group (Barlow, Lievense, Gross, Ronk, & Paustenbach, 2013).
- 3.3. Chrysotile is biologically active and detectable in the lungs for a shorter time. Chrysotile, amosite, and crocidolite were mined and used in ship and railway construction as well as in fire protection engineering. The first evidence of their high carcinogenic potential was found in the United Kingdom and South Africa as early as the 1960s (Wagner, Sleggs, & Marchand, 1960). Amosite and crocidolite seem to have a higher carcinogenicity than the other types of asbestos (Barlow et al 2013). When ranked by the number of incident cases, mesothelioma is ranked 31st globally and number 29 in South Africa (Global Burden of Disease Cancer Collaboration, 2016).
- 3.4. Asbestos exposure is typically labour-dependent and is recognised as an occupational disease. More recently, a shift has been observed from asbestos-removal workers to professionals involved in post-construction work, e.g., electricians, plumbers, or heat protection technicians (Geltner, Errhalt, Baumgartner, Ambrosch, Machan, Eckmayr, Klikovits, Hoda, Popper, & Klepetko, 2016).
- 3.5. There is a correlation between the amount of asbestos exposure and the incidence of malignant pleural mesothelioma (MPM). The mean latency period between exposure to asbestos and the onset of symptoms is up to 40 years, and 99% of cases show a latency of more than 15 years (Lanphear & Buncher, 1992).
- 3.6. This is paralleled by a profession-dependent gender distribution, as more than 80% of affected individuals are men (Delfino, Anton-Culver, & Saltzstein, 1995).

3.7. Occupational exposure to asbestos accounts for more than 80% of the cases and makes MPM a preventable disease. Although the Western world is moving towards a levelling-off of asbestos related diseases (ARD) incidence, the continued use of asbestos in the developing world could lead to a global epidemic of MPM. The use of asbestos is banned in Europe, however, other developed countries have only controlled the import, but not abolished handling of asbestos products. Other potential cofactors for developing mesothelioma besides exposure to asbestos are exposure to synthetic materials (ceramics, nanoparticles), ionizing radiation, and SV-40 virus infections (Kanbay, Ozer Simsek, Tutar, Yilmaz, Buyukoglan, Canoz, & Demir, 2014). The impact of cigarette smoke as well as numerous other fibrous materials such as glass fibres and mineral glass wool is, however, excluded. Recently, a germline mutation in the BAP1 gene has been linked to predisposition in some cases of MPM (Testa, Cheung, Pei, Below, Tan, Sementino, Cox, Dogan, Pass, Trusa, Hesdorffer, Nasu, Powers, Rivera, Comertpay, Tanji, Gaudino, Yang, & Carbone, 2011). Somatic mutations may also play a role in developing MPM.

4. DIAGNOSIS OF MESOTHELIOMA

4.1 Clinical Symptoms

Patients typically present with complaints of shortness of breath, chest pain, fatigue and weight loss. These symptoms can occur over many months. During physical examination, unilateral effusions are often observed. It is important that a detailed occupational history be obtained. Shortness of breath is often initially caused by a pleural effusion and later by extensive restriction due to pleural and pulmonary tumour masses in the thoracic cavity. Patients describe the chest pains as diffuse, sometimes radiating into the shoulders, arms, or abdomen. Tumour ingrowth into the neural structures of the brachial plexus and the intercostal or paravertebral structures can also cause neuropathic pain. Weight loss is a symptom of the advancement of the disease. Typically, MPM occurs initially unilaterally. The tumour can, however, spread to the other pleural cavity or into the peritoneum in the further course of disease. Compared with lung cancer, distant metastases in the extrathoracic lymph nodes or in other parenchymal organs are usually rare, although they do occur in advanced stages (Finn, Brims, Gandhi, Olsen, Musk, Maskell, & Lee, 2012).

4.2 Imaging radiology for diagnosis of mesothelioma

4.2.1. Chest x-ray- The typical finding on chest X-rays of patients with MPM is pleural effusion or pleural thickening, which, however, is not specific (Geltner C et al. 2016).

4.2.2. CT chest abdomen and pelvis - CT chest is the imaging modality of choice to evaluate MPM and elegantly demonstrates the extent of primary tumour, local invasion, intrathoracic

lymphadenopathy, and extrathoracic spread (Nickell, Lichtenberger III, Khorashadi, Abbott & Carter, 2014).

- 4.2.3. MRI scan - There is no consensus on the role of MRI in diagnosis on mesothelioma and it is not recommended as PMB level of care (Nickell, et al, 2014; Van Zandwijk, Clarke, Henderson, Musk, Fong, Nowak, Loneragan, McCaughan, Boyer, Feigen, Currow, Schofield, Pavlakis, McLean, Marshall, Leong, Keena, & Penman, 2013).
- 4.2.5. PET-CT – there is no role for PET-CT in the diagnosis of mesothelioma and is therefore not PMB level of care.

Table 2: PMB level of care imaging radiology interventions for the diagnosis of mesothelioma

Description	Frequency	Comment
Chest X-ray	2	Recommended by consensus as the initial diagnostic work up
CT chest, abdomen and pelvis	1	Both in initial diagnosis and follow up. Depends on the diagnosis whether it's a pleural or peritoneal mesothelioma.

When an occupational history indicates considerable asbestos exposure, or the radiology is suggestive of mesothelioma, cytology can be used to detect malignant cells but histological specimens must often be obtained.

4.3. Imaging procedures for diagnosis of mesothelioma

- 4.3.1. A thoracoscopy is recommended to obtain adequate histology, to optimally stage, and to allow pleural fluid evacuation (with or without pleurodesis) (Maskell et al 2003, Greillier et al 2007). This can be performed as a pleuroscopy or as video-assisted thoracic surgery (VATS). VATS is not only the gold standard for securing biopsy tissue for the pathological diagnosis, but it also allows effective drainage of pleural effusion and talc pleurodesis.
- 4.3.2. Image-guided core biopsy, either by ultrasound or CT, is suitable for cases where pleural thickening or a nodular/ mass lesion has been demonstrated. Ultrasound biopsy has an equivalent yield and less exposure to radiation (Sconfienza LM et al., 2013).
- 4.3.3. Fine needle aspiration (FNA) biopsy has a low diagnostic yield (about 30%) and is not routinely recommended for mesothelioma. Likewise, percutaneous pleural biopsy also has a low diagnostic yield and is not recommended for routine diagnosis (Van Zandwijk et al., 2013). These procedures are not recommended as PMB level of care.
- 4.3.4. Thoracotomy should probably be restricted to a small incisional biopsy into the chest wall for those cases where the pleural space has been obliterated.

4.3.5. Mediastinoscopy and mediastinotomy can be performed where indicated for tissue diagnosis.

4.3.6. Laproscopic guided biopsy of peritoneum is recommended as PMB level of care if it is peritoneal mesothelioma.

Table 3: PMB level of care of imaging procedures and procedures for obtaining tissue for the diagnosis of mesothelioma.

Description	Comment
CT- or ultrasound-guided needle biopsy	CT-guided core biopsy or VAT-guided pleural biopsy is recommended – depending on the clinical circumstances – to obtain adequate tissue for histological analysis including immunohistochemistry, and has high sensitivity and specificity for the diagnosis of malignant pleural mesothelioma
Thoracoscopy / Thoracentesis	
Thoracotomy	
Mediastinoscopy	
Mediastinotomy	
Laprosopic guided biopsy of peritoneum	Important if its peritoneal mesothelioma

4.4. Histopathology

4.4.1. Standard practice is to subtype mesotheliomas into three categories, epithelioid, sarcomatoid and biphasic types (mixed epithelioid and sarcomatoid). Determining the histological subtype of malignant mesothelioma is a factor that influences prognosis in this disease. Epithelioid subtype is the most common (50-70%) and associated with the best prognosis. Sarcomatid tumours (5-20% prevalence) have the poorest prognosis with a 5months median survival (Van Zandwijk et al., 2013).

4.4.2. A panel of immunohistochemical markers should be used for pathologic diagnosis of malignant pleural mesothelioma. The immunohistochemical panels should contain positive (mesothelial) and negative (carcinoma-related) markers for malignant mesotheliomas with an epithelioid component and include at least one cytokeratin marker, at least two mesothelial markers and at least two carcinoma related markers. For pleural mesothelioma-like tumour with an epithelial component, it is recommended that immunolabelling for both calretinin and TTF-1 is routinely carried out. Additional markers should be added when tumour other than lung cancer enter into the differential diagnosis (Van Zandwijk et al., 2013).

4.4.3. Full-thickness biopsies are required to separate invasive from non-invasive growth patterns and a panel of numerous immunohistochemical markers is needed for the differentiation of epithelioid MPM from adenocarcinoma (Scherpereel et al., 2010).

4.5. Lab investigations

The laboratory tests indicated in table 4 below are PMB level of care for mesothelioma

Table 4: PMB level of care laboratory investigations for mesothelioma

Description	Frequency	Comments
U+E and Creatinine	1	
LFT's	1	
FBC	1	
Blood gases	1	
Cytology pleural fluid	1	The test is actually pre-diagnostic and should not be repeated if already done.

4.6. Staging and risk assessment of mesothelioma

- 4.6.1. Once cancer is diagnosed, the treating doctor will need to establish the staging and risk factors in order to suggest treatment options and for therapeutic planning.
- 4.6.2. Computed tomography (CT) of the chest and abdomen is the preferred radiological method to assess patients with MPM. Plain chest radiography lacks sufficient sensitivity for routine staging because small malignant pleural effusions are not detected and large pleural effusions can obscure pleural/chest lesions (Van Zandwijk et al., 2013).
- 4.6.3. Ultrasound abdomen and chest is recommended as PMB level of care as it is more sensitive than CT in detecting nodal involvement and distant metastasis, and in differentiating tumour activity from benign disease. In comparison to CT, it both downstages some disease by excluding lesions potentially significant by CT, and upstages disease by detecting tumour sites not detected by CT.
- 4.6.4. A potential candidate for surgical treatment should undergo PET-CT scanning to rule out distant metastasis and involvement of the abdomen and the mediastinal lymph nodes.
- 4.6.5. If nodes are negative, patients can proceed to induction treatment and should be re-staged with CT or PET-CT.
- 4.6.6. MRI is not recommended as PMB level of care based on the fact that a CT and PET are sufficient for the staging of a mesothelioma patient.
- 4.6.7. Although malignant mesothelioma has been rarely reported in the bone, when clinically indicated in specific patients, a bone scan is PMB level of care (Collins, Constantinidou, Sundar, Chenard-Poirier, Yap, Banerji, De Bono, Lopez & Tunariu, 2017).

Table 5: PMB level of care for imaging radiology and procedures for staging and risk assessment of mesothelioma

Description	Comments
Ultrasound abdomen and chest	CT or ultrasonography should be used to guide biopsy and drainage of pleural effusion
PET-CT	On motivation for staging and re-staging; <ul style="list-style-type: none"> - if surgery is required in selected patients it might be necessary - if there are any procedures that involve the pleura, a PET-CT might also be warranted - no role for baseline PET
Bone scan	Only if clinically indicated on a case by case basis.
CT Chest and abdomen	Chest CT alone is often sufficient for disease staging and treatment planning. CT is the radiological standard used for staging of disease, identifying possible resectability of primary tumour and baseline pre-chemotherapy assessments.
Thoracoscopy / VATS	

5. TREATMENT OPTIONS

5.1. Surgical Treatment

- 5.1.1. Surgical interventions include procedures for diagnostic, staging and palliative purposes.
- 5.1.2. MPM patients are not suitable for resection with curative intent (Kondola, & Mannners 2016).
- 5.1.3. Mesothelioma patients should be followed up with surgeons rather than oncologists because majority of long term palliative interventions are surgical.
- 5.1.4. The surgical interventions listed below are recommended as PMB level of care for malignant pleural mesothelioma (Scherpereel, Astoul, Baas, Berghmans, Clayson, de Vuyst, Dienemann, Galateau-Salle, Hennequin, Hillerdal, Le P  choux, Mutti, Pairon, Stahel, van Houtte, van Meerbeeck, Waller & Weder, 2010).
 - Pleurectomy
 - Extra pleural pneumonectomy
 - VATS
 - Pericardial Biopsy
 - Partial pericardectomy
 - Insertion of pleural catheter

5.2. Chemotherapy

Chemotherapy requests can be considered on a case by case basis and when reviewing the literature for evidence, it should be noted that the sample sizes of clinical trials will be small as the prevalence of mesothelioma is low. There is currently no chemotherapy recommended as PMB level of care for mesothelioma.

5.3. Radiotherapy

5.3.1. Radiotherapy only has a palliative role for patients with mesothelioma (Jenkins et al. 2011). Systematic reviews have not shown evidence that radiotherapy prolongs survival in patients with MPM (Ung et al. 2006); however, this is not unexpected given the palliative context in which it is usually used (Kondola Manners, D. & Nowak, A.K & Manners 2016).

5.3.2. For palliative radiotherapy, 3# to 15# are recommended as PMB level of care to control pain.

5.3.3. The administration of adjuvant radiotherapy using specialised IMRT techniques has not shown any benefit and is not recommended as PMB level of care (Van Zandwijk et al., 2013).

This guideline will be due for update on 31 March 2020

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