
***Draft PMB definition guideline for small cell lung cancer***

***Disclaimer:***

***The small cell lung cancer benefit definition has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore regulation 15h and 15l may be applied for patients who are inadequately managed by the stated benefits. The procedure codes only serve as an indication of applicable procedure codes, and some significant procedure codes may not have been included. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs, supportive medication and nursing care. However, these interventions form part of care and are prescribed minimum benefits.***

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**Abbreviations**

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|---|---|---|
| PMBs | - | Prescribed Minimum Benefits |
| DTPs | - | Diagnosis Treatment Pairs |
| CMS | - | Council for Medical Schemes |
| SCLC | - | Small Cell Lung Cancer |
| FBC | - | Full Blood Count |
| LFTs | - | Liver Function Tests |
| U&E | - | Urea and Electrolytes |
| CT | - | Computed Tomography |
| MRI | - | Magnetic Resonance Imaging |
| FDG | - | Fluorodeoxyglucose |
| ES | - | Extensive stage |
| LS | - | Limited stage |
| PET | - | Positron Emission Tomography scan |
| VATS | - | Video-assisted Thoracic Surgery |
| EBUS | - | Endobronchial Ultrasound |
| FNA | - | Fine-needle aspiration |
| FEV | - | Forced expiratory volume |
| FVC | - | Forced vital capacity |
| RT | - | Radiation Therapy |
| TRT | - | Thoracic Radiation Therapy |
| PCI | - | Prophylactic Cranial Irradiation |
| RFA | - | Radiofrequency ablation |
| MWA | - | Microwave ablation |

## 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, No.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 aim 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. This is a recommendation for the diagnosis, treatment and care of individuals with small cell lung cancer in any clinically appropriate setting as outlined in the Act.

2.2. The purpose is to provide detailed clarification in respect of benefit and entitlements to members and beneficiaries of medical schemes.

**Table 1: Possible ICD 10 codes to identify small cell lung cancer**

| | |
|---|---|
| C34.0 | Malignant neoplasm, main bronchus |
| C34.1 | Malignant neoplasm, upper lobe, bronchus or lung |
| C34.2 | Malignant neoplasm, middle lobe, bronchus or lung |
| C34.3 | Malignant neoplasm, lower lobe, bronchus or lung |
| C34.8 | Malignant neoplasm, overlapping lesion of bronchus and lung |
| C34.9 | Malignant neoplasm, bronchus or lung, unspecified |
| C38.1 | Malignant neoplasm, anterior mediastinum |
| C38.2 | Malignant neoplasm, posterior mediastinum |
| C38.3 | Mediastinum, part unspecified |
| C76.1 | Malignant neoplasm, thorax |
| D02.1 | Carcinoma in situ, trachea |
| D02.2 | Carcinoma in situ, bronchus and lung |
| D02.3 | Carcinoma in situ, other parts of respiratory system |
| D02.4 | Carcinoma in situ, respiratory system, unspecified |

## 3. Epidemiology

3.1. Tracheal, bronchus and lung cancer has been ranked as having the 4th highest number of incident cases, and the foremost cause of mortality from cancer in South Africa in the recent global cancer burden of disease study (Collaboration, 2016).

3.2. Small cell lung cancer in South Africa accounts for around 15% of all lung cancers. Generally patients present with advanced disease with a low resectability rate (Nanguzgambo, Aubeelack, von Groote-Bidlingmaier, Hattingh, Louw, Koegelenberg & Bolliger, 2011).
3.3. The 5-year survival rate for lung cancers remains below 20% with over 50% of cases diagnosed with distant metastases. In small cell lung cancer the prognosis is even worse with around 90% of patients diagnosed with advanced disease (Chen, Ruiz, Hsieh, Wu, Ries & Lewis, 2014).
3.4. Cigarette smoking remains the primary risk factor for developing lung cancer and is estimated to account for approximately 90% of all lung cancers, although other risk factors such as exposure to environmental toxins, pulmonary fibrosis, HIV infection and genetics have been found to play a role in increased risk of lung cancer (Midthun, 2017).

## 4. Diagnosis, staging and risk assessment of small cell lung cancer

Diagnosis is essential for treatment planning, and tissue diagnosis is required to assess whether the tumour is a primary malignancy, a pulmonary metastasis from another site, or possibly a non-malignant growth (Midthun, 2017a). Currently the 7th American Joint Committee on Cancer (AJCC)/International Union for Cancer Control (UICC) TNM system is used in staging lung cancer, although an 8th Edition is planned for early 2018 (Lin, Shidan, Yunyun, Sunny, Guanghua, Adi & Yang, 2017; Detterbeck, Boffa, Kim & Tanoue, 2017). However, generally small cell lung cancer is classified as 2 stages; limited stage (Stage I-III) or extensive stage (Stage IV) using the Veteran Administration Lung Study Group (VALSG) system to define the extent of disease (NCCN, 2016).

### 4.1. Lab investigations/ point of care testing

The initial evaluation of patients with newly diagnosed SCLC consists of a complete medical history and physical examination, a pathologic review of biopsy specimens, and laboratory studies, including full blood count (FBC), serum electrolytes, renal and liver function tests (LFTs), and serum lactate dehydrogenase (Jett, Schild, Kesler & Kalemkerian, 2013). Sputum cytology might be requested pre-diagnostic to rule out TB or other infections. Sputum cytology is not recommended as a stand-alone diagnostic tool or after a diagnosis has been made.

The following laboratory investigations for small cell lung cancer are recommended as PMB level of care:

- U&E and creatinine
- LFTs
- Renal function tests
- FBC
- Platelets
- Blood gases

### 4.2. Imaging radiology

4.2.1. Contrast-enhanced computed tomography (CT) can be useful in revealing the extent of mediastinal invasion and is routinely used for assessing treatment response, and evaluate

for residual or recurrent disease in patients who are undergoing therapy (Carter, Glisson, Truong & Erasmus, 2014).

4.2.2. Magnetic resonance imaging (MRI) of the brain is recommended as PMB level of care. It is superior to a fluorodeoxyglucose positron emission tomography scan (FDG PET) and FDG PET/ CT in this setting because extensive FDG uptake within the brain parenchyma usually hampers the visualization of metastasis (Carter et al, 2014; Jett et al, 2013)

4.2.3. If a PET scan is obtained for initial staging, pathologic confirmation is required for lesions that result in upstaging. If a patient already has documentation of extensive stage (ES) disease, then a PET scan is not needed because it will not add any useful staging information. At present, available data is insufficient to make recommendations regarding the potential role of PET scans in restaging, response evaluation, or prognostic predictions in patients with SCLC (Jett et al, 2013).

4.2.4. There are no reports to suggest that a bone scan adds useful staging information if a PET scan has already been obtained (Jett et al, 2013).

4.2.5. A multidisciplinary approach is recommended in both the diagnosis and staging as well as in determining optimal treatment and supportive care (Detterbeck, Lewis, Diekemper, Addrizzo-Harris & Alberts, 2013).

**Table 3: Imaging radiology for diagnosis and staging of small cell lung cancer recommended as PMB level of care**

| Description | Frequency | Comment |
|---|---|---|
| Chest X-ray | 1-2 | Needs to be done initially, one test might be necessary |
| CT chest , abdomen and pelvis with contrast | 1 | CT scan should always be contrast for better definition |
| MRI brain | 1 | MRI of brain superior to PET and CT scans for intracranial metastases |
| Ultrasound chest | 1 | Only necessary if there is an effusion that needs drainage.<br>Ultrasound is appropriate only to guide the procedure. |
| PET scan | On motivation | Not recommended for diagnosis<br>In patients with clinically limited-stage (LS)-SCLC<br>more sensitive and specific than conventional imaging for detecting metastatic disease |
| Bone scan | On motivation | Not routine.<br>Only if a PET is not done. |
| Exclusions | | |
| MRI chest | 0 | Not recommended as PMB level of care |
| Ultrasound abdomen | 0 | Inappropriate to do an ultrasound abdomen. No place of ultrasound in early stage lung cancer |

4.3. **Histology**

4.3.1. Small cell carcinoma is a poorly differentiated neuroendocrine carcinoma, so immunohistochemistry might be required, particularly in cases in which histologic features are equivocal. In addition, a proliferation marker may be done to differentiate it from (the less common) well-differentiated neuroendocrine carcinomas ("carcinoids"), because on a biopsy specimen the tumour cells are often crushed, making it difficult to differentiate a small cell carcinoma from a carcinoid on morphology alone (Thunnissen et al., 2017).

4.3.2. Two immunohistochemical stains are recommended as PMB level of care, in addition to routine histology and cytology tests.

4.4. **Procedures for diagnosis and staging of small cell lung cancer**

4.4.1. Evidence for Video-Assisted Thoracotomy (VATS) in small cell lung cancer is very limited. Based on expert opinion, VATS is prevailing state level of care and is recommended as PMB level of care.

4.4.2. Bone marrow aspiration and biopsy can detect metastatic SCLC cells in 15% to 30% of patients at diagnosis. However, about 5% of patients will have bone marrow involvement as the only site of metastatic disease. Therefore, routine bone marrow examination is not indicated as PMB level of care and should be reserved for patients with peripheral cytopenia and no other evidence of metastatic disease (Jett et al, 2013).

4.4.3. Although endobronchial ultrasound (EBUS) has been shown to reduce time to treatment decision (14 days) compared to conventional diagnosis and staging (29 days) in a randomised controlled trial, the study did not measure clinical outcomes as a result of this (Navani, Nankivell, Lawrence, Lock, Makker, Baldwin, Stephens, Parmar, Spiro, Morris, Janes, & Lung-BOOST trial investigators, 2015). EBUS is currently not recommended as PMB level of care.

**Table 4: Procedures for diagnosis and staging of small cell lung cancer recommended as PMB level of care**

| Description | Comments |
|---|---|
| VATS<br><br>(Video-assisted thoracoscopic surgery) | |
| Bronchoscopy | Bronchoscopy is mandatory for diagnosis, staging and surveillance after treatment |
| Fine Needle Aspiration biopsy | Does not give enough sample. It needs good expertise as it is difficult to get a good quality sample. Only to be used where a core biopsy is not feasible |
| Core biopsy | Recommended procedure but if it is not feasible then an FNA can be considered, however limitations of FNA should be noted. |
| Lymph node biopsy (Mediastinal) | |
| Mediastinoscopy via mediastinostomy | |

| | |
|---|---|
| Bone marrow aspiration and biopsy | Not routine unless if there is an abnormality with blood tests indicative of cytopenia. |
| Baseline lung function (pulmonary function) | Spirometry ($FEV_1$, FVC), is recommended<br>Patient might have an anatomically resectable tumour but present as physically unresectable hence lung function test is recommended.<br>Also important in radiation due to radiation pneumonitis and the risk of respiratory failure even if the patient has a small lesion with poor lung function. |
| Exclusions | |
| Endobronchial Ultrasound (EBUS) | Not PMB level of care |

## 5. Treatment Options

Small cell lung cancer is highly sensitive to initial chemotherapy or radiotherapy although disease recurrence is common with a high mortality rate (Detterbeck et al., 2013).

### 5.1. **Surgery**

5.1.1. Surgery should only be considered in stage 1 (T1-2, N0) patients at diagnosis where it is confirmed that mediastinal lymph nodes are not involved. There is no clinical benefit in patients with N2 disease stage or beyond (NCCN, 2016).

5.1.2. There are few randomised controlled trials evaluating surgical resection in limited stage small cell lung cancer and these do not support favourable outcomes, however the trials were found to be of poor quality and further trials are needed, particularly in light of newer staging criteria (Barnes, See, Barnett & Manser, 2017).

5.1.3. In the very early limited stage, resection consists of lobectomy and dissection or comprehensive sampling of mediastinal lymph nodes (Carter et al, 2014).

5.1.4. The following surgical interventions are recommended as PMB level of care:

- Segmental / wedge resection of the lung
- Lobectomy
- Lymph node dissection

Surgical interventions are only recommended in selected cases of patients with early limited stage disease (stage 1 disease) who have a solitary nodule, no hilar or mediastinal involvement based on adequate mediastinal staging, no distant metastases, and no contraindications to surgery (Barnes et al, 2017).

### 5.2. **Chemotherapy**

5.2.1. Although the evidence for adjuvant treatment following surgical resection is limited, data from the National Cancer Database 2016 study has shown adjuvant chemotherapy with or without radiation was associated with significantly improved survival (Yang et al.,

2016). The 2017 updated NCCN guidelines now recommend adjuvant chemotherapy following curative-intent surgical resection (NCCN, 2016).

5.2.2. The most commonly recommended chemotherapy in limited stage disease is etoposide and cisplatin although carboplatin may be used instead of cisplatin to reduce toxicity with no differences seen in survival or response rate (Früh, De Ruysscher, Popat, Crinò, Peters & Felip, 2013; Karam, Jiang, Khaira, Lee & Schellenberg, 2015; Kim, Biswas, Bakaki, Dowlati, Sharma & Machtay, 2016).

5.2.3. The results of studies using irinotecan in combination with etoposide and cisplatin or carboplatin have shown mixed results. Earlier studies suggested a benefit in Japan (Noda, Nishiwaki, Kawahara, Negoro, Sugiura, Yokoyama, Fukuoka, Mori, Watanabe, Tamura, Yamamoto & Saijo, 2002). Whereas more recent studies in North America and Europe studies have failed to show a statistically significant increase in overall survival with irinotecan (Kelley, Bogart, Hodgson, Ansari, Atkins, Pang, Green & Vokes, 2013). Two meta-analyses from China, did not find an improvement in response rate but both showed a statistically significant improvement in overall survival, however the quality of studies was acknowledged to be limited by heterogeneity (Jiang, Liang, Zhou, Huang, Huang, Chu & Zhan, 2010; Shao, Jin & Zhu, 2012).

5.2.4. The benefits of extending chemotherapy beyond 4-6 cycles in first-line treatment have not been proven and increased toxicity is a considerable risk (Früh et al., 2013; NCCN, 2016).

5.2.5. Topotecan or irinotecan have been recommended as second-line treatment, however clinical trial data has shown limited improvements in overall survival benefit, with increased toxicity in small sample sizes (Aktas, Kus, Kalender, Sevinc, Camci & Kul, 2016; Jett et al., 2013; Pelayo Alvarez, Westeel, Cortés-Jofré & Bonfill Cosp, 2013). Topotecan and irinotecan are therefore not recommended as PMB level of care in SCLC.

5.2.6. The medicines given in table 5 are recommended as PMB level of care when used as monotherapy or in combination.

**Table 5: Chemotherapy recommended as PMB level of care for small cell lung cancer**

| **Indication** | **Medicine names** |
|---|---|
| Limited stage - first line | Cisplatin / Carboplatin<br><br>Etoposide |
| Second line | Best supportive care |
| Extensive stage (1st or 2nd line) | Vincristine<br>Etoposide<br>Cisplatin / Carboplatin<br>Cyclophosphamide<br>Doxorubicin |

## 5.3. **Radiation therapy (RT)**

The use of RT for SCLC will be discussed under thoracic radiation therapy (TRT), prophylactic cranial irradiation (PCI), and RT used for the palliation of various metastases (Jett et al,2013).

### 5.3.1. Thoracic radiation therapy (TRT)

5.3.1.1. TRT has been shown to reduce relapses in limited stage disease by 25%-30% with an improvement in survival rate. If TRT is initiated early, it is associated with improved survival rate compared to later treatment, although this may be at the expense of increased toxicity (De Ruysscher, Lueza, Le Péchoux, Johnson, O'Brien, Murray, Spiro, Wang, Takada, Lebeau, Blackstock, Skarlos, Baas, Choy, Price, Seymour, Arriagada, Pignon & RTT-SCLC Collaborative Group, 2016).

5.3.1.2. TRT is typically administered with systemic chemotherapy in patients with LS-SCLC. Studies suggest that concurrent treatment is more effective than sequential therapy (Carter et al, 2014).

5.3.1.3. For patients with LS-SCLC, early chemoradiotherapy, with accelerated hyper-fractionated radiation therapy (twice-daily treatment) concurrently with platinum-based chemotherapy, is recommended. In patients with ES-SCLC who have completed chemotherapy and achieved a complete response outside the chest and complete or partial response in the chest, a course of consolidative TRT is suggested (Jett et al,2013).

5.3.1.4. No difference in survival outcomes or toxicity has been shown between twice-daily and once-daily concurrent chemoradiotherapy in patients with limited-stage small-cell lung cancer (Faivre-Finn, Snee, Ashcroft, Appel, Barlesi, Bhatnagar, Bezjak, Cardenal, Fournel, Harden, Le Pechoux, McMenemin, Mohammed, O'Brien, Pantarotto, Surmont, Meerbeeck, Woll, Lorigan, Blackhall & CONVERT Study Team, 2017).

5.3.1.5. In limited stage disease, the use of three-dimensional conformal radiation therapy (3DCRT) is PMB level of care.

5.3.1.6. Intensity modulated radiation therapy (IMRT) is recommended as PMB level of care on motivation.

5.3.1.7. In extensive stage disease, there is no role of radical thoracic radiation therapy (Carter et al, 2014).

### 5.3.2. Prophylactic Cranial Irradiation

5.3.2.1. The incidence of brain metastases is high (around 50%) in patients with small-cell lung cancer and therefore Prophylactic Cranial Irradiation (PCI) should be considered in patients who have achieved a partial or complete response to treatment to reduce the risk of cerebral metastases and improve overall survival (Zhang, Jiang, Luan, Wang, Zheng & Wang, 2014).

5.3.2.2. PCI is recommended as PMB level of care for patients with both LS and ES SCLC who demonstrate a good response to chemotherapy or chemoradiation therapy (Carter et al, 2014).

5.3.2.3. In patients with LS- or ES-SCLC who achieve a complete or partial response to initial therapy, PCI is recommended

5.3.2.4. Stereotactic radiation is recommended as PMB level of care on motivation for selected patients.

5.3.3. Palliative radiation

5.3.3.1. Radiation is established and recommended as an effective palliative therapy for various metastases for the management of other lung cancer related symptoms (Jett et al,2013).

5.3.3.2. Palliative radiation is PMB level of care in both LS and ES disease.

**Table 6: PMB level of care for radiation therapy in small cell lung cancer.**

| Radiation therapy | Indication | Recommended dose |
|---|---|---|
| TRT | Limited stage disease | 45Gy (1.5# x 2x daily) / 60Gy (30# x 2Gy) / 66Gy (2.0Gy x33#) |
| PCI | Limited and extensive stage disease | 24 Gy (10# x 2.4gy) / 25.2Gy (14# x 1.8Gy) |
| Palliative Radiation therapy | Limited and extensive stage disease | 1# to 15# to control pain |

## 6. Exclusions

The following interventions are **not recommended** as PMB level of care for small cell lung cancer

- Radiofrequency ablation ((RFA)
- Microwave ablation (MWA)
- Alternative medicine e.g. acupuncture, massage
- Targeted therapy
- Robotic surgery

**This guideline will be reviewed on 31 March 2020**

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