Draft PMB definition guideline for non-small cell lung cancer

Disclaimer:

The non-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

CMS	-	Council for Medical Schemes
PMBS	-	Prescribed Minimum Benefits
DTPS	-	Diagnosis Treatment Pairs
NSCLC	-	Non-Small Cell Lung Cancer
AJCC	-	American Joint Committee on Cancer
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
PET	-	Positron Emission Tomography
SUVmax	-	Standardized Uptake Values
MTV	-	Metabolic Tumour Volume
TLG	-	Total Lesion Glycolysis
FDG PET	-	Fluorodeoxyglucose Positron Emission Tomography
EGFR	-	Epidermal Growth Factor Receptor
ALK	-	Anaplastic Lymphoma Kinase
FEV	-	Forced expiratory volume
FVC	-	Forced vital capacity
VATS	-	Video-Assisted Thoracoscopic Surgery
RFA	-	Radiofrequency 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. 31 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 non-small cell lung cancer (NSCLC) 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 non- small cell lung cancer

C33	Malignant neoplasm of trachea
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. Globally, non-small-cell lung cancer (NSCLC) accounts for the majority of lung cancers (85%-90%) while small cell lung cancer accounts for around 10%-15%. There are three major subtypes in NSCLC; the most prevalent is adenocarcinoma (40%) followed by squamous cell carcinoma (25-30%) and then large cell carcinoma (10-15%). About 20% of NSCLC are NOS (Not Otherwise Specified) (Zappa & Mousa,2016).

3.2. In South Africa, the majority of patients with non-small cell lung cancer present with metastatic disease (around 70%) or locally advanced disease (around 20%) (Aubeelack, Koegelenberg, Bolliger, von Groote-Bidlingmaier & Irusen, 2013).

4. Diagnosis, staging and risk assessment of NSCLC

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, 2017). The 8th edition of the American Joint Committee on Cancer (AJCC) / International Union for Cancer Control (UICC) system is used in now used for staging non-small cell lung cancer. The eighth edition includes new tumour stage groupings and refinements of the T and M descriptors (Detterbeck, Boffa, Kim &Tanoue 2017; Lin, Shidan, Yunyun, Sunny, Guanghua, Adi & Yang, 2017). A multi-disciplinary approach is recommended in the diagnosis and staging, as well as determination of optimal treatment and supportive care (Detterbeck, Lewis, Diekemper, Addrizzo-Harris & Alberts, 2013).

There are several similarities between lab, histopathology and imaging investigations in small cell lung cancer (SCLC) and NSCLC.

4.1. Lab investigations / point of care testing

The initial evaluation of patients with newly diagnosed NSCLC 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, serum calcium, 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 tuberculosis (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 NSCLC are recommended as PMB level of care:

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

4.2. **Imaging radiology**

4.2.1. The common imaging modalities used for diagnosis and staging in patients with NSCLC include chest x-ray, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) (Munden, Swisher, Stevens, & Stewart, 2005).

4.2.2. CT of the chest is the most common radiologic study performed after chest radiography to evaluate lung cancer in a patient.

4.2.3. PET is recommended only on motivation in selected patients. A recent meta-analysis showed that patients with surgically resectable NSCLC with aggressive disease had high values of maximum standardized uptake values (SUVmax), metabolic tumour volume (MTV) and total lesion glycolysis (TLG). These patients have a high risk of disease recurrence with high mortality and FDG PET may identify these type of patients, who benefit from aggressive treatments (Liu et al., 2016)

4.2.4. A multi-variate analysis of pooled data from individual patients supports the evidence that a high SUV predicts poor prognosis in early stage disease. This study also showed that SUV has little or no prognostic value among patients with stage IV disease (Paesmans, Garcia, Wong, Patz Jr, Komaki, Eschmann, Govindan, Vansteenkiste, Meert, de Jong, Altorki, Higashi, Van Baardwijk, Borst, Ameye, Lafitte, Berghmans, Flamen, Rami-Porta & Sculier, 2015).

Table 2: Imaging radiology for diagnosis and staging of non-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. Follow up chest x-ray is required if effusion has been drained and a chest drain inserted
CT chest , abdomen and pelvis with contrast	1	CT scan should always be contrast for better definition.
MRI brain	1	MRI brain is recommended over CT scans, especially for adenocarcinomas.
Ultrasound chest	1	Only necessary if there is an effusion that needs drainage. Ultrasound is appropriate to guide the procedure or to assist with therapeutic tap if repeated collection is required.
PET scan	On motivation	Recommended for staging and to facilitate radiotherapy planning in patients receiving radiotherapy with radical intent. Not recommended for diagnosis.
Bone scan	On motivation	Should be done in advanced disease characterised by pleural effusion, mediastinal, hilar nodes and bone symptoms. To be approved 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 for ultrasound in early stage lung cancer.

4.3. **Histology**

4.3.1. Adenocarcinoma, squamous carcinoma, adenosquamous carcinoma, and large cell carcinoma are the four major histological sub-types of NSCLC. Patients with adenocarcinoma have a poorer prognosis than those with squamous cell carcinoma (Suzuki, Nagai,Yoshida, Nishimura, Takahashi & Yokose, 1999).However, the outcome of adenocarcinoma has improved with the availability of targeted treatment agents.

4.3.2. Immunohistochemistry is usually also performed to see if there is squamous or glandular differentiation, and to confirm that the tumour is primary lung cancer.

4.3.3. Adenocarcinoma more commonly manifests metastasis while, in contrast, squamous cell carcinoma metastases tend to occur later in the disease.

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

4.3.5. Although EGFR and ALK targeted treatments (e.g. erlotonib or crizotinib) are not recommended as PMB level of care, molecular testing is recommended as PMB level of care for either the primary tumour, or for a metastasis of epidermal growth factor receptor (EGFR), as a priority, followed by anaplastic lymphoma kinase (ALK) for all patients whose tumour contains an element of adenocarcinoma, regardless of the clinical characteristics of the patient (Lindeman, Cagle, Beasley, Chitale, Dacic, Giaccone, Jenkins, Kwiatkowski, Saldivar, Squire, Thunnissen & Ladanyi, 2013, Leighl, Rekhtman, Biermann, Huang, Mino-Kenudson, Ramalingam, West, Whitlock & Somerfield, 2014).

4.3.6. There are many other molecular markers available, however, insufficient data has been published to establish definitive recommendations as to where, when, and how they should be used (Lindeman et al., 2013, Leighl et al., 2014).

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

4.4.1. Surgery serves an important role in the diagnosis, staging, and management of NSCLC (Lackey & Donington, 2013)

4.4.2. Most patients with suspected lung cancer require a tissue-based diagnosis. The aims of tissue sampling include confirmation of diagnosis (e.g. adenocarcinoma vs squamous cell carcinoma) and molecular testing. The least invasive method of biopsy which yield sufficient tissue for genetic assessment is recommended. Fine needle aspirate is insufficient (Dietel, Bubendorf, Dingemans, Dooms, Elmberger, García, Kerr, Lim, López-Ríos, Thunnissen, Van Schil & von Laffert, 2016).

4.4.3. Baseline pulmonary function is PMB level of care for patients with NSCLC.

4.4.4. The following procedures are recommended as PMB level of care:

- Transthoracic needle aspiration
- Bronchoscopy

- Lymph node biopsy
- Video-assisted thoracoscopy
- Mediastinoscopy or mediastinotomy
- Oesophagoscopy
- Pulmonectomy
- Thoracentesis
- Bone marrow aspiration and biopsy - only where bone metastases are suspected in the absence of adequate of alternative diagnostic means.

5. Treatment options for NSCLC

5.1. Surgery

5.1.1. Surgical resection offers the best opportunity for long-term survival and cure in patients with resectable NSCLC and patients with stage I or II NSCLC should be treated with complete surgical resection whenever possible (West, Vallières & Schild, 2017).

5.1.2. Lobectomy, the surgical resection of a single lobe, is generally accepted as the optimal procedure for early stage NSCLC. Limited resection is associated with worse survival rates compared with lobectomy. The introduction of video-assisted thoracoscopic surgery (VATS) may facilitate the use of limited resections in selected high-risk patients (West et al., 2017).

5.1.3. In patients with early stage NSCLC, video-assisted thoracoscopic surgery (VATS) is an alternative to open thoracotomy for patients undergoing lobectomy.

5.1.4. Segmentectomy (or wedge resection) are also recommended as PMB level of care if a complete resection can be achieved in selected patients with limited disease. This form of surgery may also be preferred for some people who could not tolerate conventional lobectomy, for example, in the case of a person whose lungs do not work well as confirmed by lung function tests (NICE guidelines, 2011).

5.1.5. Surgery is not recommended in metastatic disease with the possible exception of surgery for limited brain metastases (Ettinger, Akerley, Bauman, Chirieac, D'Amico, DeCamp, Dilling, Dobelbower, Doebele, Govindan, Gubens, Hennon, Horn, Komaki, Lackner, Lanuti, Leal, Leisch, Lilenbaum, Lin, Loo, Martins, Otterson, Riely, Schild, Shapiro, Stevenson, Swanson, Tauer, Yang,Gregory & Hughes, 2017b).

5.1.6. The following surgical interventions are the recommended PMB level of care:

- Lobectomy
- Segmental / wedge resection
- Lymph node dissection

5.1.7. Robotic surgery is not PMB level of care.

5.2. Chemotherapy

5.2.1. Stage III is now divided into categories A, B and C.

5.2.1.1. For pathological Stage III diagnosed postoperatively, the recommended treatment includes (Bezjak, Temin, Franklin, Giaccone, Govindan, Johnson, Rimner, Schneider, Strawn , Azzoli, 2015) :

- Radiotherapy to mediastinum if nodes were involved.

- Radiotherapy to tumour bed if resection margins clear.
- Adjuvant chemotherapy.
- Chemotherapy followed by radiotherapy is the preferred sequence if radiotherapy is to be included. Concurrent chemotherapy with RT is of uncertain benefit.

5.2.1.2. Patients with operable stage III (includes T3N1 and T4 N0-1) can undergo surgery followed by chemotherapy.

5.2.1.3. For patients with stage III inoperable (medically) or superior sulcus tumours, the recommended treatment is chemoradiotherapy with adjuvant chemotherapy. Superior sulcus tumours are candidates for surgery after chemoradiotherapy (Rusch, Giroux, Kraut, Crowley, Hazuka, Johnson, Goldberg, Detterbeck, Shepherd , Burkes , Winton , Deschamps , Livingston , Gandara , 2001).

5.2.1.4. For patients with N2 disease, although chemoradiation is a standard option for patients with known mediastinal involvement, the role of surgery after induction chemotherapy or chemoradiation in certain settings is extensively debated. There is a variation in the threshold to offer surgery after induction therapy, given that, while local control may be improved, no randomized studies have demonstrated a survival benefit to this approach. In the setting of limited data, some experts treat essentially all stage III N2 disease with definitive chemoradiation (Pless , Stupp , Ris, Stahel, Weder , Thierstein , Gerard , Xyrafas , Früh , Cathomas , Zippelius , Roth , Bijelovic , Ochsenbein , Meier , Mamot , Rauch , Gautschi , Betticher , Mirimanoff , Peters , 2015).

5.2.2. Cisplatin combinations (including gemcitabine or vinorelbine or taxanes) are recommended as first-line in metastatic disease with poorer outcomes shown with carboplatin. Carboplatin use is recommended in patients where cisplatin is contraindicated, for example patients with renal failure (Novello, Barlesi, Califano, Cufer, Ekman, Levra, Kerr, Popat, Reck, Senan, Simo, Vansteenkiste & Peters, 2016).

5.2.3. Gemcitabine should be considered only in patients who are intolerant to taxanes.

5.2.4. Only the intravenous formulation of vinorelbine is considered PMB level of care for NSCLC. Oral vinorelbine can be considered on a case by case basis especially for elderly patients.

5.2.5. In patients with metastatic disease with performance status of 2 or beyond, alternative treatment with carboplatin doublets or gemcitabine / vinorelbine / taxanes as monotherapy may be considered (Novello et al., 2016; Masters, Temin, Azzoli, Giaccone, Baker, Brahmer, Ellis, Gajra, Rackear, Schiller, Smith, Strawn, Trent & Johnson, 2015).

5.2.6. Clinical evidence does not support recommendations for third-line treatment (Masters et al., 2015).

Table 3: Chemotherapy recommended as PMB level of care for NSCLC

Indication	Medicine names	Comments
Adjuvant	Cisplatin / Carboplatin Vinorelbine - Intravenous Paclitaxel	Only for patients with a resectable tumour.
Neo-adjuvant (chemoradiation)	Cisplatin / Carboplatin Vinorelbine - Intravenous Paclitaxel Etoposide Docetaxel	Gemcitabine is only for patients who are intolerant to paclitaxel or patients with neuropathies.

	Gemcitabine	Only IV vinorelbine is recommended as PMB. Oral vinorelbine to be approved on a case to case basis specifically for elderly patients
Metastatic	Vinorelbine – Intravenous Cisplatin / Carboplatin Paclitaxel Gemcitabine Etoposide Docetaxel	
EXCLUSIONS		
• Pemetrexed - Although it is now an international standard of care, it is not recommended as PMB level of care. • Erlotinib • Bevacizumab		

5.3. **Radiotherapy**

5.3.1. Some patients may have a surgically removable NSCLC, but may not be operable due to poor pulmonary function or comorbidities. Patients with stage I or II disease who are not candidates for surgical resection because of comorbities or refusal of surgery may be candidates for nonsurgical local therapy such as radiation (Ettinger, et al, 2017a; Munden et al, 2005).

5.3.2. All patients should undergo pulmonary function tests (including lung volumes) before having radical radiotherapy or surgical procedures for NSCLC.

5.3.3. Chemoradiation is indicated in stage II or III patients who are not suitable for surgery if the potential benefit in survival outweighs the risk of additional toxicities (NICE guidelines, 2011).

5.3.4. IMRT is recommended as PMB level of care in NSCLC patients.

5.3.5. Other image-guided ablative techniques such as cryoablation, radiofrequency ablation (RFA), laser ablation and microwave ablation have not been proven with adequate long-term data and none of these have an established role in the routine management of stage I or stage II NSCLCs and are not recommended as PMB level of care (West et al., 2017).

5.3.6. Whole brain radiotherapy for confirmed brain metastases is recommended as PMB level care.

5.3.7. Prophylactic radiotherapy has no basis for NSCLC and is therefore not PMB level of care.

5.3.8. Stereotactic radiation is recommended as PMB level of care on motivation for selected patients with limited metastases. The patients are selected based on the recursive partitioning analysis score.

5.3.9. Extracranial stereotactic radiotherapy for metastatic disease or primary is not recommended as PMB level of care.

Table 4: PMB level of care for radiation therapy in NSCLC

Definitive Radiation therapy: 60Gy (30# x 2Gy) / 66Gy (33# x 2Gy) / 70Gy (35# x 2Gy) - any dose between 30 and 35#

Palliative Radiation therapy: 3# to 15# to control pain

6. Best supportive care

Best supportive care guideline is being development and a hyperlink will be added once it is finalised.

This guideline will be reviewed on 31 March 2020

Kindly send any comments to the draft document to pmbprojects@medicalschemes.com by 16 March 2018.

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