PMB definition for early stage oesophageal cancer

Disclaimer:

The early stage oesophageal cancer 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

AC	Adenocarcinoma
ASCO	American Society of Clinical Oncology
CMS	Council for Medical Schemes
CT	Computed tomographic
DTPs	Diagnosis treatment pairs
FBC	Full Blood Count
GEJ	Gastro-oesophageal junction
ICD	International Classification of Diseases
IMRT	Intensity-modulated radiation therapy
NCR	National Cancer Registry
OC	oesophageal cancer
PMB	Prescribed minimum benefit
SCC	Squamous cell carcinoma
SEMS	self-expanding metal stents

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). In respect of some of the diagnosis treatment pairs (DTPs), medical scheme beneficiaries find it difficult to know 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 coordinated by the Council for Medical Schemes (CMS) and aims to define 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 early stage oesophageal cancer in any clinically appropriate setting as outlined in the Act.

2.2. The purpose is to improve clarity in respect of funding decisions by medical schemes, taking into consideration evidence based medicine, affordability and in some instances cost-effectiveness.

Table 1: Possible ICD10 codes for identifying early stage (including resectable) oesophageal cancer

ICD 10 code	*WHO description*
C15.0	Malignant neoplasm, cervical part of oesophagus
C15.1	Malignant neoplasm, thoracic part of oesophagus
C15.2	Malignant neoplasm, abdominal part of oesophagus
C15.3	Malignant neoplasm, upper third of oesophagus
C15.4	Middle third of oesophagus
C15.5	Malignant neoplasm, lower third of oesophagus
C15.8	Malignant neoplasm, overlapping lesion of oesophagus
C15.9	Malignant neoplasm, oesophagus, unspecified
D00.1	Carcinoma in situ, oesophagus

3. Epidemiology and burden of disease

3.1. Worldwide oesophageal cancer (OC) has been the 6th leading cause of cancer mortality and the 8th most common cancer with the majority of cases occurring in less developed countries (Ferlay, Soerjomataram, Ervik, Dikshit, Eser, Mathers, Rebelo, Parkin, Forman & Bray, 2012). The recent

Global Burden of Cancer study places oesophageal cancer in 6th place for incident cases in South Africa (Global Burden of Disease Cancer Collaboration, 2016).

3.2. The South African National Cancer Registry (NCR) report for 2011 (most recent publication) shows that oesophageal cancer is the 7th most common cancer in males (5.56 per 100 000 age standardised incidence rate) and 9th in females (3.06 per 100 000 age standardised incidence rate) however it is responsible for the highest number of cancer related deaths in Southern Africa (Ferlay et al, 2012; National Cancer Registry. Cancer in South Africa, 2011).

3.3. Globocan data for 2012 indicates that in Southern Africa, the incidence of oesophageal cancer is nearly double in males (13.7 per 100 000 age standardised incidence rate) compared to females (6.7 per 100 000 age standardised incidence rate) (Ferlay et al, 2012).

3.4. Squamous cell carcinoma (SCC) is by far the most common type of OC in Asian and African countries with a strong association to cigarette smoking and alcohol consumption. Adenocarcinoma (AC) aetiology appears to be more linked to chronic gastro-oesophageal reflux. Both SCC and AC have a higher prevalence in the African population in South Africa compared to non-African populations (Gould, Morgan, Motha, Makda, Domingo, Tiedt, Wing, Munanga, Tembo, Hale & Bizos, 2015).

3.5. The prognosis for oesophageal is poor, with a 5 year survival of around 15% often because it is diagnosed in the advanced stages of disease (Arnal, Arenas, & Arbeloa, 2015). The most common presenting symptom of oesophageal cancer is persistent, progressing dysphagia (Varghese, Hofstetter, Rizk, Low, Darling, Watson, Mitchell & Krasna, 2013).

3.6. Gastro-oesophageal junction (GEJ) carcinoma will be defined in the Gastric Cancer benefit definition.

4. Investigation, diagnosis and staging

4.1. Staging of OC is conventionally as per the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system (7th Edition), however this has recently been updated to the 8th Edition which is published as 3 separate recommendations for staging (Rice, Ishwaran, Hofstetter, Kelsen., Apperson-Hansen, & Blackstone, 2016: 897-905; Rice et al, 2016: 913-919; Rice et al, 2016: 906-912).

4.2. Chest x-ray may be used to detect lung metastases, pleural effusion, and aspiration and is included as control in Barium study.

4.3. Computed tomographic (CT) of the chest and abdomen is recommended as the optimal test for staging early oesophageal cancer (Lordick, Mariette, Haustermans, Obermannová & Arnold, 2016; Varghese et al, 2013).

4.4. Barium studies can be utilised to assess the anatomical extent of the tumour, as well as assess for strictures and fistulae. It may assist with surgical planning and the presence of other pathology (Varghese et al, 2013).CT remains the optimal staging test.

4.5. Upper gastrointestinal endoscopy with multiple biopsies is the recommended method for diagnosis of early oesophageal cancer (Lordick, et al, 2016; NCCN Guidelines Version 2, 2016; Varghese et al , 2013).

4.6. A meta-analysis showed that the sensitivity and specificity for detecting distant metastases were 71% and 93%, respectively, for FDG PET and 52% and 91%, respectively, for CT. A The superior ability of FDG PET in detection of occult distant metastasis during the initial staging process may provide sufficient evidence to avoid unnecessary surgery in up to 20% of patients. A multicentre prospective cohort study of 491 patients showed that PET/CT led to clinically significant changes in stage for 24% of patients. Although a PET-CT is recommended as an optional test for staging, there are limitations to the use of PET due to avid uptake of 18-FDG in the primary tumour and confounding factors resulting in false positive FDG uptake (Cuellar, Carter, Macapinlac, Ajani, Komaki, Welsh, Lee, Swisher, Correa, Erasmus & Hofstetter, 2014; NCCN Guidelines Version 2, 2016; Schmidt, Lordick, Herrman & Ott, 2015; Varghese et al, 2013).

4.7. PET-CT is PMB level of care for staging in selected cases only on specialist motivation.

4.8. Endoscopic ultrasound, performed prior to initiation of treatment, is recommended for accurate assessment of depth of tumour invasion and lymph node status (American Society for Gastrointestinal Endoscopy Standards of Practice Committee, 2013; NCCN Guidelines Version 2, 2016; Varghese et al, 2013).

4.9. Full blood count, liver function tests and renal function tests are PMB level of care.

Table 2: Summary for PMB level of care for diagnosis and staging work-up for early stage oesophageal cancer

Description		**Frequency**
Clinical assessment	Consultations with primary care practitioner, gastroenterologist, oncologist, surgeon	2 consults per speciality
Imaging: Radiology	Chest x-ray	1
	CT study of chest and abdomen	1
	PET-CT (FDG) – on specialist motivation for staging	1
	Barium swallow with contrast	1

Imaging procedures	Upper gastro-intestinal endoscopy	1
	Endoscopic ultrasound	1
Histological assessment	Histology/ Cytology	1
Laboratory investigations	Full blood count	1
	Liver function test	1
	Renal function	1

5. Treatment options for early stage oesophageal cancer

The mainstay treatment options for early oesophageal cancer include:

- endoscopic therapy,
- surgical oesophagectomy and
- chemoradiation.

Treatment options are influenced by histological subtype: squamous cell carcinoma or adenocarcinoma; stage, tumour location and patient clinical status. Clinical trial data favouring one modality over another is unavailable and therefore all three treatment options are PMB level of care. Therapeutic modalities may be combined as in the case of chemo-radiotherapy or chemotherapy before or after surgery in resectable disease.

5.1 Surgical management

5.1.1. Endoscopic resection is recommended in T1a tumours and may be considered as an alternative to oesophagectomy in patients without lymph node involvement (T1b) (American Society for Gastrointestinal Endoscopy Standards of Practice Committee, 2013). There is limited evidence (only retrospective cohort studies) comparing survival and mortality outcomes with endoscopic modalities to surgery in early lesions with surgery showing superiority in 3 and 5 year survival in a recent meta-analysis (Bustamante, Hourneaux, Moura, Bernardo, Sallum, Ide & Baba, 2016).

5.1.2. Oesophagectomy and lymph node removal is standard level of care for surgical treatment of oesophageal cancer (NCCN Guidelines Version 2, 2016). This can be done using conventional open access or laparoscopic surgical techniques (Yibulayin, Abulizi & Sun, 2016).

5.1.3. Minimally invasive oesophageal (MIE) surgical resection may be considered an appropriate and evidence-based treatment option compared to open oeseophagectomy (NICE, 2011). Laparoscopy has been associated with reduced peri-operative complications and in-hospital mortality (Lv, Hu, Ren & Wei, 2016). However, this is only based on low quality evidence from

observational studies and therefore a laparoscopic approach cannot be recommended as PMB level of care (Gurusamy, Pallari, Midya & Mughal, 2016).

5.1.4. In locally advanced disease, surgical resection is recommended in patients eligible for surgery without metastatic disease following neoadjuvant therapy. Surgery alone is not recommended in non-metastatic locally advanced disease and should be preceded with neoadjuvant chemo-radiation or chemotherapy in squamous cell carcinoma or perioperative chemotherapy or neoadjuvant or adjuvant chemotherapy in adenocarcinoma (Lordick, Mariette, Haustermans, Obermannová & Arnold, 2016; Oppedijk, Van der Gaast, Van Lanschot, Van Hagen, Van Os, Van Rij, Van der Sangen, Beukema, Rütten, Spruit, Reinders, Richel, Van Berge Henegouwen & Hulshof, 2014).

5.1.5. Endoscopic stenting with self-expanding metal stents (SEMS) is recommended for palliation of dysphagia due to tumours or fistulas although this is more likely to occur in late stage, metastatic disease (Dai, Li, Xie, Liu, Zhang, Zhou, Pan & Yang, 2014; Spaander, Baron, Siersema, Fuccio, Schumacher, Escorsell, Garcia-Pagán, Dumonceau, Conio, de Ceglie, Skowronek, Nordsmark, Seufferlein, Van Gossum, Hassan, Repici & Bruno, 2016).

5.2. Chemotherapy and chemoradiation

Table 3: PMB level of care chemoradiation options in early stage oesophageal cancer

Indication	Treatment description	Medicine details
Oesophageal cancer: Definitive and Neo – adjuvant	Chemoradiation	Fluorouracil Cisplatin Carboplatin Paclitaxel Capecitabine

5.2.1. The medicines listed as PMB level of care above may be used in recognised combinations.

5.2.2. Definitive chemoradiation is only indicated in the case of proximal oesophageal cancer (cervical oesophagus) and patients who are unfit for surgery (NCCN Guidelines Version 2, 2016).

5.2.3. Definitive chemoradiation has similar short-term and long-term mortality outcomes to surgery in squamous cell carcinoma. The levels of evidence for definitive chemoradiation compared to surgery in adenocarcinoma are very low and therefore no conclusions can be determined (Best, Mughal & Gurusamy, 2016).

5.2.4. Neoadjuvant chemotherapy or chemoradiation with a platinum based agent (cisplatin or carboplatin) is recommended in patients with surgically resectable cancer (Lordick et al ,2016; Mariette, Dahan, Mornex, Maillard, Thomas, Meunier, Boige, Pezet, Robb, Le Brun, Bosset, Mabrut, Triboulet, Bedenne & Seitz, 2014). Histologic response rates and rates of margin-negative resections favor neoadjuvant chemoradiotherapy over chemotherapy in adenocarcinoma, but no trial demonstrates that these benefits translate into an improved survival rate. Thus, the relative benefits of preoperative chemotherapy versus chemoradiotherapy remain uncertain. Nevertheless, given the higher rates of complete (R0) resection seen in all three trials and the high rates of local failure with chemotherapy alone in the PreOperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma (POET) trial, preoperative chemoradiotherapy, rather than perioperative chemotherapy is recommended for most patients with T3 or higher, or node-positive or borderline resectable EGJ tumors who can tolerate the combined modality approach (Van Hagen et al, 2012).

5.2.5. The most recent and largest meta-analysis in squamous cell carcinoma included 12 randomized comparisons of neoadjuvant chemoradiotherapy (either concurrent or sequential) versus surgery alone for esophageal or EGJ cancer, including the FFCD 9901, CALGB 9781, and CROSS trials. The HR for all-cause mortality for neoadjuvant chemoradiotherapy was 0.78 (95% CI 0.70-0.88), and this translated into an absolute survival benefit of 8.7 percent at two years and a number needed to treat to prevent one death of 11 (Mariette et al, 2014; Markar, Gronnier & Pasquer, 2016; Oppedijk et al, 2014).

5.2.6. Therefore, international guidelines continue to recommend neoadjuvant chemoradiation (Malthaner, Wong, Spithoff, Rumble & Zuraw, 2008; NCCN Guidelines Version 2, 2016).

5.2.7. Neoadjuvant chemotherapy has been shown to have improved long-term (5-years) survival benefits in resectable thoracic oesophageal cancer over surgery alone in a 2015 Cochrane review including both squamous cell and adenocarcinoma. Cisplatin plus another agent (typically 5-fluorouracil in the more recent trials) was the most commonly used regimen in the trials. No single agent or combination showed superiority over another. Increased toxicity was observed in the chemotherapy arm (Vellayappan, Soon, Ku, Leong, Lu & Tey, 2015).

5.2.8. Evidence for pre-operative chemotherapy is uncertain, however patients who have not received neoadjuvant therapy prior to surgery, adjuvant or post-operative therapy is required in completely resected adenocarcinoma.

5.3. Radiation therapy

Table 4: Radiation therapy in early stage including resectable oesophageal cancer

Neo-adjuvant or adjuvant conventional radiation therapy is offered with concurrent chemotherapy. Neo-adjuvant - 25-28 # conventional radiation single volume /multiple volumes Adjuvant - 25 – 33# conventional radiation single volume /multiple volumes Brachytherapy

5.3.1. Whilst it may allow for shorter treatment times, the evidence supporting use of increased doses of radiotherapy is still lacking in terms of improved survival or tolerability or safety (Brower, Chen, Bassetti, Yu, Harari, Ritter & Baschnagel, 2016; Lordick et al, 2016).

5.3.2. Radiotherapy as monotherapy before surgery is not recommended and not considered to be PMB level of care (Little, Lerut, Harpole, Hofstetter, Mitchell, Altkori & Krasna, 2014).

5.3.3. Radiotherapy should be given in combination with chemotherapy for locally advanced, resectable cancer (Little et al, 2014).

6. Follow up care

6.1. Interruptions to radiation treatment should be avoided where possible with optimal patient monitoring and management. A weekly patient assessment should be carried out during radiation therapy (NCCN Guidelines Version 2, 2016).

6.2. Routine follow-up is recommended with endoscopy and CT after neoadjuvant treatment (Lordick et al, 2016).

6.3. Follow-up with EUS after chemotherapy or chemoradiation is not routinely recommended. Specialist motivation would be required as it may be required to assess response to neoadjuvant therapy in locally advanced N1 or T3-4 disease (Little et al, 2014; NCCN Guidelines Version 2, 2016; Varghese et al, 2013).

6.4. Endoscopy surveillance may be required at 3 months in patients who have not had surgery but have shown a complete response following chemoradiation (Lordick et al, 2016).

6.5. The evidence for use of barium esophagram with contrast to detect anastomotic leaks following oesophagectomy is limited and does not appear to improve patient management (Cools-Lartigue, Andalib, Abo-Alsaud, Gowing, Nguyen, Mulder & Ferri, 2014). This is not PMB level of care.

6.6. The American Society of Clinical Oncology (ASCO) recommends in its Choosing Wisely campaign of 2013 to "avoid using positron emission tomography or positron emission tomography–computed tomography scanning as part of routine follow-up care to monitor for cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome" (Schnipper, Lyman, Blayney, Hoverman, Raghavan, Wollins & Schilsky, 2013).

6.7. The use of PET as a follow-up to detect recurrence in oesophageal does not improve survival outcomes at 2 years (Healy, Yin, Reddy & Wong, 2016).

Table 5 below shows recommended interventions and the corresponding frequencies up to 10 years post diagnosis

Table 5: Frequency of interventions considered to be PMB level of care in early stage oesophageal cancer during therapy and up to 10 years post diagnosis

		Frequency during therapy	Up to 2 years post diagnosis	3-10 years post diagnosis	Recurrent work up – **only if there is suspicion of disease recurrence**
			Frequency per year		
Clinical assessment	Consultations	Depends on the treatment intervention	Every 6 months for the first 2 years	Once per annum	
Laboratory	Full Blood Count (FBC)	6	2	1	√
	Liver function test	2 (Capecitabine requires LFT before each cycle)	2	1	√
	Renal function	2 (renal monitoring each cycle in cisplatin treatment)	0	0	√
Imaging	Chest x-ray	If clinically indicated	1	1	√
	CT study of chest and abdomen OR	1 (follow-up scan required in neoadjuvant approach)	1	1	√
	PET scan – only on specialist motivation	1	0	0	√

Procedures	Swallow with contrast	0	0	0	√
	Upper GI endoscopy	1 (post neoadjuvant and pre-surgery to assess treatment response)	1	0	√

This guideline will be due for update on 31 December 2018

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