PMB definition guideline for early stage gastric/ gastro-oesophageal junction cancer

Disclaimer:

The early stage gastric / gastro-oesophageal junction (GEJ) 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(I) 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

Table of Contents

Abbreviations

5FU	Fluorouracil
CMS	Council for Medical Schemes
CT	Computed tomographic
DTPs	Diagnosis treatment pairs
EMR	Endoscopic mucosal resection
EGC	Early gastric carcinomas
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasound
FBC	Full Blood Count
GEJ	Gastro-oesophageal junction
PMB	Prescribed minimum benefit

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 gastric/gastro-oesophageal junction (GEJ) 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 gastric / gastro-oesophageal junction cancer

ICD 10 code	*WHO description*
C16.0	Malignant neoplasm, cardia
C16.1	Malignant neoplasm, fundus of stomach
C16.2	Malignant neoplasm, body of stomach
C16.3	Malignant neoplasm, pyloric antrum
C16.4	Malignant neoplasm, pylorus
C16.5	Malignant neoplasm, lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm, greater curvature of stomach, unspecified
C16.8	Malignant neoplasm, overlapping lesion of stomach
C16.9	Malignant neoplasm, stomach, unspecified
D00.2	Carcinoma in situ, stomach

3. Epidemiology

3.1. Despite the marked decline of incidences of gastric cancer over the past decades, approximately 990 000 people globally are diagnosed with gastric cancer, and gastric cancer is reported to be the 4th most common incident cancer (Ferlay, Shin, Bray, Forman, Mathers & Parkin, 2008; Jemal, Center & DeSantis, 2010).

3.2. In Africa, gastric cancer is ranked the twelfth most common cancer (Ferlay, Shin & Bray, 2010). Southern Africa has an incidence rate of 11.9/100 000 (Ferlay, Autier, Boniol, Heanue, Colombet & Boyle, 2007). In South Africa, gastric cancer is the 7th most frequent cancer and is ranked the 9th leading cause of death amongst the cancers (Global Burden of Disease Cancer Collaboration, 2016).

3.3. In most countries, gastric cancer is reported to show a constant declining trend (Parkin, Bray, & Ferlay, 2005; Singh and Ghoshal, 2006) and part of the decline may be due to the recognition of risk factors such as H. pylori and other dietary and environmental risks (Lunet and Barros, 2003). The mechanism by which H. pylori contributes to gastric carcinogenesis is still largely unknown.

4. Diagnostic and staging investigations

4.1. Adenocarcinomas account for 95% of all gastric carcinomas (Howson, Hiyama & Wynder, 1986) and based on the level of invasion, early gastric carcinomas (EGC) by definition is an invasion that is confined to the mucosa and submucosa, irrespective of lymph node metastasis (Angelelli, Lanora & Scardapane, 2001). As prognosis of gastric carcinoma is closely correlated with stage of disease at the time of diagnosis, early detection and treatment of gastric cancer is vital improving the survival rate at 5 years to greater than 90% (Jung, Won, & Kong, 2014; Onodera, Tokunaga & Yoshiyuki, 2004).

4.2. Histology, full blood count (FBC), liver and renal function tests are routine tests and recommended as PMB level of care.

4.3. Chest x-ray may be used to detect lung metastases, pleural effusion and aspiration.

4.4. CT chest, abdomen and liver is PMB level of care and is useful in identifying the primary tumor, assessing for local spread as well as detection of lymph node involvement and distant metastasis.

4.5. Upper gastrointestinal endoscopy remains the gold standard to detect and diagnose gastric cancer. It is performed so as to assess for macroscopic appearance of the stomach as well as the morphology and location of the lesion(s) in question (Russell, Hsu & Mansfield).

4.6. Endoscopic ultrasound (EUS) is a useful staging tool in gastric cancer, specifically to determine pre-therapy T and N stages so as to guide the sequence of therapy as well as enhance the information on the extent of disease (Fairweather, Jajoo, Sainani, Bertagnolli & Wang, 2015; Yoshinaga, Oda, Nonaka, Kushima & Saito, 2012). It is also used preoperatively to assess the submucosal vasculature in order to predict intraoperative bleeding during endoscopic therapy. Apart from the utility of EUS for diagnosing invasion depth, EUS can be used preoperatively to assess the submucosal vasculature in order to predict intraoperative bleeding during endoscopic therapy (Kikuchi, Lizuka & Hoteya, 2011).

4.7. The depth of mural invasion and the presence of extragastric lesions can be determined with endoscopic ultrasonography (US) and computed tomography (CT).

4.8. To overcome the limitations of contrast-enhanced imaging, diagnostic laparoscopy is strongly recommended as an additional staging tool to avoid nontherapeutic laparotomy. Staging laparoscopy can detect radiographically occult peritoneal metastases and prevent futile laparotomy in patients with gastric adenocarcinoma. This is evidenced by reports of up to 30% of patients with no preoperative evidence of metastatic disease that harbor occult intra-abdominal metastases that cannot be detected radiographically by modern imaging techniques (Kriplan and Kapur, 1991; Possik, Franco & Pires, 1986; Sarela, Lefkowitz, Brennan & Karpeh, 2006).

4.9. Given the relatively low sensitivities for detection of gastric cancer, the value of PET/CT in diagnosis and evaluation remains controversial (Dassen, Lips, Hoekstra & Pruijt, 2009; Filik, Kir & Aksel, 2015; Kim, Kang & Lee, 2006). PET scan is not recommended as PMB level of care.

Table 2: PMB level of care for the diagnosis and staging work up of early stage gastric cancer / gastroesophageal junction

Description		**Frequency**
Clinical assessment	Consultations with primary care practitioner, gastroenterologist, oncologist, surgeon	2 consultations per speciality
Imaging: Radiology	CT chest	1
	CT abdomen, pelvis	1

	Chest x-ray	1
Laboratory investigations	Full blood count	1
	Liver function test	1
	Renal function	1
Imaging: Procedures	Gastroscopies: upper GI	1
	Contrast meal – only if indicated	1
	Diagnostic laparoscopy	1
	Endoscopic ultrasound	1
Histology assessment	Histology/ cytology	1

5. Treatment options for early stage gastric / gastro-oesophageal junction cancer

Involvement of a multidisciplinary strategy for the treatment of patients with newly diagnosed gastric / gastro-oesophageal junction cancer is strongly recommended. Several factors such as the patient's underlying comorbidities, performance status and electrolyte imbalances are some of the factors that should be considered in the evaluation of such as a patient for surgical treatment. The potential beneficial effects on survival and quality of life from a short period of preoperative rehabilitation to optimise their operative course, is increasingly recognised (Gill, Baker & Gottschalk, 2003; Shimada, Okazumi & Koyama, 2011; Sawatzky, Kehler & Ready, 2014).

5.1. Surgical management

Surgery has traditionally been regarded as the standard of care for EGC and surgical resection has long been the primary treatment for gastric cancers.

The following surgical interventions of early stage gastric cancer are PMB level of care:

5.1.1. Endoscopic resection

Endoscopic resection for EGC is indicated in patients with negligible risk of lymph node metastasis and is a minimally invasive treatment that allows the patient to preserve the entire stomach and maintain a good quality of life. The main endoscopic techniques used are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) (Balmadrid and Hwang, 2015; Oka, Tanaka & Kaneko,2006; Probst, Pommer & Golger, 2010).

5.1.2. Total gastrectomy with lymph node resection

The surgical treatment options for gastric cancer include laparoscopic gastric resection, or open gastrectomy. A multicentre case series of 1294 patients undergoing laparoscopic surgery,

reported 5 year disease free survival to be 99.8% for stage IA disease, 98.7% for stage IB disease, and 85.7% for stage II disease (Kitano, Shiraishi & Uyama, 2007).

5.1.3. Esophagogastrectomy with lymph node resection

Patients with proximal tumours usually require an esophagectomy or extended gastrectomy, with the stomach or jejunum used for intestinal continuity.

5.1.4. Subtotal gastrectomy with lymph node resection

Comparisons disease-free survival between total and subtotal gastrectomy for distal gastric cancer has shown no significant difference in overall or disease free survival. The 5-year overall survival rate is 41% for total gastrectomy and 43% for subtotal gastrectomy is 41% and 43% respectively (Brancato and Miner, 2008). Subtotal gastrectomy has been associated with better nutritional outcomes and better quality of life when compared with total gastrectomy (Bozzetti, Marubini & Bonfanti, 1999).

5.2. Chemotherapy

The following perioperative chemotherapy agents are used only for gastric carcinoma of the distal esophagus or gastroesophageal junction (Cunningham, Allum & Stenning, 2006; Macdonald, Smalley & Benedetti, 2001; Sumpter, Harper-Wynne & Cunningham, 2005).

- Epirubicin,
- 5FU
- Cisplatin
- Capecitabine

5.2.1. The MAGIC trial involved random assignment of 503 patients with resectable stage IB-IV gastric cancer to either perioperative chemotherapy of epirubicin cisplatin, 5-FU (ECF)] and surgery or surgery alone. The 5-year survival rate, following a median follow up of years, was 36% in the perioperative chemotherapy group vs 23% in the surgery alone group (HR = 0.75; 95%CI: 0.6-0.93; P = 0.009) (Cassidy, Saltz, Twelves, Van Cutsem, Hoff, Kang, Saini, Gilberg & Cunningham, 2011).

5.2.2. Adjuvant therapy for gastric cancer has been investigated in a number of clinical trials to improve outcomes for gastric cancer and to define the appropriate adjuvant regimen. A major survival benefit from postoperative adjuvant chemoradiotherapy has been demonstrated by the INT0116 trial.

5.2.3. Following surgery, 556 patients stage IB-IV gastric cancer were randomly assigned to either observation or adjuvant therapy with 4 monthly cycles of bolus 5-fluorouracil (5-FU) and leucovorin combined with radiation to 45 Gray in 25 fractions. The 3-year survival rate was 50% in the CRT group vs 41% in the surgery alone group (P = 0.005) (Van Hagen, Hulshof & Van Lanschot, 2012).

5.2.4. Capecitabine is recommended as an alternative to 5FU. Capecitabine is at least equivalent to 5-FU in terms of overall survival in patients with gastrointestinal cancers (Cassidy et al, 2011).

5.2.5. The medicines listed below may be used in recognised combinations.

Table 3: Chemotherapy and chemoradiation options in early stage gastric cancer

Indication	Treatment description	Medicine details
Gastric - peri-operative	Chemotherapy	Epirubicin
		Cisplatin
		Fluorouracil
		Capecitabine (alternative to 5FU)
Gastric - adjuvant	Chemoradiation	Fluorouracil
		Levofolinic acid
		Capecitabine

5.3. Radiation therapy

Table 4: Radiation therapy in early stage gastric / GEJ-junction cancer

Conventional Radiation therapy

Definitive Chemoradiation

- 25 – 28# over 5 weeks, TD 45 -50.4 Gy

Neo-adjuvant chemoradiation

- 23# over 5 weeks, TD 41.4 Gy
- 25# over 5 weeks, TD 45 Gy

Adjuvant chemoradiation

- 25 – 28# over 5 weeks, TD 45 – 50.4 Gy

6. Follow up care

The table below provides a guide on recommendations for follow up of gastric/ GEJ cancer as PMB level of care.

Table 5: Frequency of interventions considered to be PMB level of care in early stage gastric / GEJ 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	
Imaging : Radiology	CT chest, abdomen, pelvis	1	1	1	√
	Chest x-ray	1	1	1	√
Pathology	Full blood count	6	2	1	√
	Liver function test	6	2	1	√
	Renal function	6	0	0	√
Imaging : Procedures	Gastroscopies	1	1	1	√
	Contrast meal	0	0	0	√
	Diagnostic laparoscopy	0	0	0	√

	Endoscopic ultrasound	0	0	0	√
Histology assessment	Histology/ cytology	0	0	0	√

This guideline will be due for update on 31 December 2018

7. References

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