



PMB definition guideline: Metastatic colon and rectal cancer

Disclaimer:

The metastatic stage colon and rectal 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

CMS	Council for Medical Schemes
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
CT	Computed tomography
DALY	Disability-Adjusted Life Year
DTPs	Diagnosis treatment pairs
FBC	Full Blood Count
FDG	Fluorodeoxyglucose
ICD	International Classification of Diseases
LFT	Liver Function Test
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PMB	Prescribed minimum benefit
RT	Radiation Therapy
SDI	Service Level Indicators
5FU	Fluorouracil
95% UI	“uncertainty interval” replaces the confidence intervals in interpretations
WHO	World Health Organization

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). It has been noted however, that in respect of some of the diagnosis treatment pairs (DTPs), medical scheme beneficiaries sometimes find it difficult to know their entitlements in advance. Medical schemes also 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 metastatic colorectal 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 metastatic stage colon and rectal cancer

ICD 10 code	WHO description
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified

C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C26.0	Malignant neoplasm, intestinal tract, part unspecified
C26.8	Malignant neoplasm, overlapping lesion of digestive system
C26.9	Malignant neoplasm, ill-defined sites within the digestive system
D01.0	Carcinoma in situ colon
D01.1	Carcinoma in situ rectosigmoid junction
D01.2	Carcinoma in situ rectum

3. Epidemiology and burden of disease

- 3.1. Cancer of the colon and cancer of the rectum are collectively known as colorectal cancer (CRC). Colorectal cancer is a major cause of morbidity and mortality throughout the world. It is the third most common cancer worldwide, and the fourth most common cause of death (Bowel cancer statistics Cancer Research UK; Global Burden of Disease Cancer Collaboration, 2016; Haggard & Boushey, 2009; Boyle & Ferlay, 2005).
- 3.2. Worldwide, colorectal cancer represents 9.4% of all cancer incidents in men and 10.1% in women. Globally, and for countries with high Service Level Indicators (SDI), colon and rectum cancer are ranked third for cancer incidence, and second for cancer deaths in 2015. In South Africa, colon cancer is ranked as the fifth most frequent cancer incident reported (Global Burden of Disease Cancer Collaboration, 2016; Haggard & Boushey, 2009).
- 3.3. In 2015, there were 1.7 million (95% UI, 1.6-1.7 million) incidents of colon and rectum cancer, and it caused 832 000 (95% UI, 812 000-855 000) deaths. Colon and rectum cancer resulted in 17 million (95% UI, 16.6-17.5 million) Disability-Adjusted Life Year (DALYs) in 2015. The odds of developing colon and rectum cancer before age 79 years at the global level was higher for men than for women (one in every 28 men, one in every 43 women). This pattern followed the developed versus developing countries, patterns (Global Burden of Disease Cancer Collaboration, 2016).

- 3.4. In South Africa the epidemiology of CRC in white South Africans appears to follow the classic Western trend, although the molecular pathology has not been comprehensively investigated. CRC among black South Africans is far less common, but there is evidence that numbers have been increasing in some centres. Furthermore, disproportionately large numbers of young black patients seem to be presenting with CRC, a trend which appears to be common among countries throughout the African continent (Cronje, Paterson, & Becker, 2009).
- 3.5. In a study by Cronje *et. al* in South Africa, of young patients (<50 years) about 41% were black and 10% were white , blacks had predominantly proximal tumours and significantly more poorly differentiated and/or mucinous tumours, and loss of mismatch repair protein expression was more evident than in whites. It seemed likely that CRC in young blacks develops through the accumulation of mutations, most probably via mismatch repair deficiency or promoter methylation, which in turn is linked to poor differentiation and a mucinous architecture (Cronje et al, 2009).
- 3.6. Approximately 20% of patients with CRC already have metastases at diagnosis, and this figure has been stable over the last two decades. Continuous improvement in CRC treatment has led to an improvement in the survival rate of patients.

4. Investigation, diagnosis and staging of metastatic colorectal cancer

- 4.1. Consultation and clinical examination is covered as PMB level of care.
- 4.2. Full blood count (FBC) is part of the laboratory investigations. An FBC measures the number of red cells, white cells and platelets, which are important for measuring the blood status of the patient. FBC is PMB level of care and considered an important tool, but should not be relied on alone, to diagnose cancer.
- 4.3. The carcinoembryonic antigen (CEA) test is recommended as a baseline measure, and is funded as PMB. The test measures the amount of protein that may appear in the blood of some people who have certain types of cancers, especially cancer of the large intestine (colon and rectal cancer).
- 4.4. CEA is not diagnostic, but is considered a tumour marker. CEA levels do have value in the follow-up of patients diagnosed with CRC, and therefore aids in surgical treatment planning, post treatment follow-up, and in the assessment of prognosis (Macrae, Bendell & Tanabe, 2016). A single positive CEA does not equate to a diagnosis of CRC and therefore does not qualify for advanced staging investigations. Further diagnostic studies are warranted (Fleming, Ravula, Tatishchev & Wang, 2012; Compton, 2003).
- 4.5. The Liver function tests (LFT) are part of PMB level of care. There is however no diagnostic role for liver function tests, because they lack sensitivity for detection of liver metastases. Although the tests are frequently obtained preoperatively, it is important to note that liver enzymes may be normal in the setting of small hepatic metastases, as a result, the tests are not a reliable marker for exclusion of liver

involvement. (Fowler, Kaur, Cash, Feig, Gage, Garcia, Hara, Herman, Kim, Lambert, Levy, Peterson, Scheirey, Small, Smith, Lalani & Carucci, 2016).

- 4.6. Renal function test for colon and rectal cancer are routine blood tests, and form part of the pathology investigations to assess organ function (Van Cutsem, Cervantes, Nordlinger & Arnold, 2014).
- 4.7. It is standard practice at most institutions that all patients with stage II, III, or IV colorectal cancer undergo chest, abdomen, and pelvic computerized tomography (CT) scan. It is preferable to obtain these scans prior to, rather than after surgery, as the scan results may occasionally lead to a change in surgical planning (Fowler et al, 2016).
- 4.8. An abdominal ultrasound scan presents high sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the detection of colon cancer. The ultrasound scan may be conducted to see whether bowel cancer has spread to the liver (Martínez-Ares, Martín-Granizo Barrenechea, Souto-Ruzo, Yáñez López, Pallarés Peral & Vázquez-Iglesias, 2005).
- 4.9. Primovist contrast enhanced magnetic resonance imaging (MRI) of the liver can identify more hepatic lesions than can be detected by a CT scan. Liver MRI is generally reserved for patients who have suspicious but not definitive findings on CT scan, particularly if better definition of hepatic disease burden is needed in order to make decisions about potential hepatic resection. An MRI of the liver is used to differentiate between resectable liver disease and non resectable disease which alters the neoadjuvant chemotherapy approach as well as treatment intent. An MRI of the liver with primovist contrast is PMB level of care on specialist motivation only (Klessen, Rogalla & Taupitz, 2007; Fowler et al, 2016; Van Cutsem et al, 2014).
- 4.10. A biopsy is usually done during a colonoscopy or sigmoidoscopy to remove polyps (polypectomy) or small amounts of tissue from the colon or rectum. A core biopsy may be used to collect samples from organs where the cancer may have spread, such as the liver.
- 4.11. A CT-guided or non-CT-guided biopsy is considered as PMB level of care. The biopsy may help determine whether the cancer began at the site of the biopsy, or whether it developed somewhere else and spread to the biopsy site (Tomozawa, Inaba, Yamaura, Sato, Kato, Kanamoto & Sakane, 2011).
- 4.12. A fluorodeoxyglucose (FDG)-positron emission tomography PET scan is inferior to MRI scan for liver metastases, PET scans are considered to be more accurate for distant metastases, and are especially useful in detecting lung metastases. A PET scan is considered PMB level of care only when based on motivation. Simultaneous imaging with a CT scan of the chest and a PET scan is not considered as PMB level of care (Kijima, Sasaki, Nagata, Utano, Lefor & Sugimoto, 2014; Nahas, Akhurst, Yeung, Leibold, Riedel, Markowitz, Minsky, Paty, Weiser, Temple, Wong, Larson & Guillem, 2008).
- 4.13. Colonoscopy with stenting is considered as PMB level of care (de Gregorio, Mainar, Rodriguez, Alfonso, Tejero, Herrera, Medrano & D'Agostino, 2004; Sung & Tae, 2014). Confirmation of

tumour origin includes both histological assessment as well as cytological assay. The confirmation of diagnosis is only given by laboratory analysis of the tumour and tissues affected (histopathology).

Table 2: Summary of PMB benefits for diagnosis and staging of metastatic colon and rectal cancer

Description	
Clinical assessment	Consultation
Pathology	Full Blood Count (FBC)
	CEA
	Liver function tests
	Renal function tests
Imaging: Radiology	CT chest
	CT abdomen and pelvis
	Ultrasound of abdomen
	MRI liver with primovist contrast - on motivation if CT scan shows suspicion or confirmation of liver involvement.
	CT guided biopsy
	Non CT guided biopsy
	PET CT (FDG) – on motivation
Imaging : Procedures	Colonoscopy with stenting
Histology assessment	Histology/ cytology

5. Treatment options for metastatic stage colon and rectal cancer

Several treatment options can be used, depending on severity, to treat advanced/metastatic cancer of the colon and rectum. These include:

- Surgical management
- Chemotherapy
- Radiation therapy

5.1. Surgical management:

5.1.1. Deciding if surgery is an option in metastatic colorectal cancer depends on the severity of the disease (Costi, Leonardi, Zaroni, Violi & Roncoroni, 2014).

5.1.2. The surgical options will be split into palliative procedures and definitive procedures.

5.1.3. The following palliative procedures are part of the PMB level of care:

- 5.1.3.1. Segmental colectomy and primary anastomosis - A colectomy that involves removing a segment of the colon is called a segmental colectomy, and it may be labelled a hemicolectomy to differentiate the right and left halves of the large intestine (American cancer society, 2016).
- 5.1.3.2. Segmental colectomy and end colostomy - End sigmoid colostomy with a Hartmann's pouch is the procedure of choice when permanent fecal diversion is required (Sasaki, Kazama, Sunami, Tsuno, Nozawa, Nagawa & Kitayama, 2012).
- 5.1.3.3. Defunctioning Colostomy - A defunctioning stoma is basically an opening in the bowel which is brought up to the abdominal surface, to divert the contents of the bowel away from its normal passage through the bowel and anus. Waste products will leave the body through a stoma (Sasaki et al, 2012).
- 5.1.3.4. Colonoscopy and Stenting CT Colonography - This is a safe and effective method for preoperative examination of the proximal colon after metallic stent placement in patients with acute colon obstruction caused by cancer. Colonic stent placement is also useful as a palliative treatment for the patient with obstructive carcinoma of the left colon, who is not a surgical candidate (de Gregorio et al, 2004; Cha, Park, Lee, Kim, Yu & Lim, 2010 & Sagar, 2016).

5.1.4 The following definitive procedures are part of PMB level of care:

- 5.1.4.1. Segmental colectomy (with either primary anastomosis or end colostomy) PLUS excision of metastases (this may entail liver or lung resection or both) (Sasaki et al, 2012). This will require special motivation.
- 5.1.4.2. Local ablation therapy for metastatic lesions .This may also be combined with a segmental resection (de Baere, Aupérin, Deschamps, Chevallier, Gaubert, Boige, Fonck, Escudier & Palussière, 2015). The procedure requires specialist motivation.

5.2. Chemotherapy:

5.2.1. Medications and or regimens for metastatic colorectal cancer chemotherapy options are for both the first, and subsequent regimen lines.

5.2.2. Second-Line treatment of metastatic colorectal cancer is indicated if the colorectal cancer continues to grow despite chemotherapy. It is also indicated if the cancer progresses after an initial response to the first-line chemotherapy regimen. The choice of second-line treatment typically depends on the regimen that was given originally. It is probably more important for the person to be exposed to all the available chemotherapy drugs at some point during the course of treatment, than to give the drugs in a specific order. This is because survival may be prolonged by second-line (as well as third-line) therapy (Carrato, 2008; Kachnic, 2007).

Table 3: Chemotherapy options in metastatic colorectal cancer

Indication	Medicine names
Colorectal metastatic first and subsequent lines	Oxaliplatin
	Irinotecan
	Fluorouracil (5FU)
	Leucovorin
	Capecitabine

5.3. Radiation therapy (RT) in metastatic colorectal cancer:

5.3.1. Radiotherapy should be considered (possibly combined with chemotherapy) for patients with metastatic rectal cancer, to alleviate symptoms from the primary tumor (Van Cutsem et al, 2014).

5.3.2. Radiotherapy can also be used to relieve symptoms caused by metastases in the bones.

5.3.3. Radiotherapy can provide safe, cost-effective, efficient palliation of various symptoms of advanced cancer with minimal side effects. Radiotherapy can palliate pain related to bone metastases and growing visceral metastases or primary cancers, neurologic symptoms related to brain and spine metastases, other symptoms including cough and dyspnoea from advanced cancers in the lung, bleeding from various internal and external tumours, and obstructive symptoms (Jones & Simone, 2014; Timmerman, Bizakis, Pass, Fong, Dupuy, Dawson & Lu, 2009).

5.3.4. Radiotherapy should balance the convenience and side effects associated with short, hypofractionated courses of radiotherapy, with the potential of greater durability associated with longer courses of radiotherapy in patients with more prolonged life expectancies (Jones & Simone, 2014; Timmerman et al, 2009).

5.3.5. Radiotherapy at PMB level of care does not include modalities such as stereotactic surgery or SIR-Spheres® Microspheres.

Table 4: Radiation therapy in metastatic colorectal cancer

Conventional Radiation therapy

- Palliation: 1#: conventional single volume / Conventional multiple volumes
- Palliation: 5#: conventional single volume / Conventional multiple volumes
- Palliation: 10#: conventional single volume / Conventional multiple volumes
- Short course palliative RT

6. Follow up care

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 metastatic colon and rectal cancer during therapy, and up to 10 years post diagnosis

Description		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		
Pathology	Full blood count (FBC)	6	2	1	√
	Liver function test	2	2	0	√
	Renal function	2	2	1	√
	CEA#	2	2	1	√
Imaging	CT study of the chest, abdomen and pelvis	1	2	0	√
	MRI – liver or rectum	1	Only if positive CT	0	√
Procedures	Colonoscopy	0	1	0	√

- CEA levels are typically high in people with advanced colorectal cancer; persistently rising CEA levels suggest that disease is progressing and a change in therapy is warranted. However, a rising CEA alone is not sufficient evidence to prompt a change in treatment. Disease progression should be confirmed with radiographic testing (e.g., CT scan) or a biopsy before changing treatment.

This guideline will be due for update on 31 August 2019

7. References

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