PMB definition guideline: Early stage colon and rectal cancer

Disclaimer:

The early 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

APR	Abdominoperineal resection
CMS	Council for Medical Schemes
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
CT	Computed tomographic
DALY	Disability-Adjusted Life Year
DTPs	Diagnosis treatment pairs
EUS	Endo-rectal ultrasound
FBC	Full Blood Count
ICD	International Classification of Diseases
IV	Intravenous therapy
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PMB	Prescribed minimum benefit
RT	Radiation therapy
SDI	Service Level Indicators
TME	Total mesorectal excision
5FU	Fluorouracil
95% UI	"uncertainty interval" replaces the confidence intervals in interpretations
USA	United States of America
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 document serves as a recommendation for the diagnosis, treatment and care of individuals with early stage colon and rectal 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 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 the rectum is collectively known as colorectal cancer (CRC). Colorectal cancer is a major cause of morbidity and mortality throughout the world (Global Burden of Disease Cancer Collaboration, 2016; Haggar & Boushey, 2009; Boyle & Ferlay, 2005). It is the third most common cancer worldwide and the fourth most common cause of death (Cancer Research UK; Global Burden of Disease Cancer Collaboration, 2016; Haggar & Boushey, 2009; Boyle & Ferlay, 2005; Boyle & Langman, 2000; Siegel, DeSantis & Jemal, 2014).

3.2. Worldwide, colorectal cancer represents 9.4% of all cancer incidences in men and 10.1% in women (Haggar & Boushey, 2009). Colorectal cancer is more prevalent in developed countries with a Western culture (Haggar & Boushey, 2009; Cronjé, Paterson & Becker, 2009). Globally, and for countries with high Service Level Indicators (SDI), colon and rectum cancer are ranked third for cancer and second for cancer deaths in 2015. In South Africa, colon cancer is ranked as the fifth most frequent cancer reported (Global Burden of Disease Cancer Collaboration, 2016).

3.3. In 2015, there were 1.7 million (95% UI, 1.6-1.7 million) incidents of colon and rectum cancer, and it resulted in 832 000 (95% UI, 812 000-855 000) deaths. Colon and rectum cancer caused 17 million (95% UI, 16.6-17.5 million) Disability-Adjusted Life Years (DALYs) in 2015. The odds of developing colon and rectum cancer before the age of 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 and medical education on early detection of CRC is essential (Cronjé et al, 2009; Wentink, Räkers, Stupart, Algar, Ramesar & Goldberg, 2010; Coetzee, 2013).

3.5. 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.

3.6. 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 (Cronjé et al, 2009). 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.

4. Investigation, diagnosis and staging

4.1 Diagnosis and workup

4.1.1. Consultations and clinical examinations are covered as PMB level of care.

4.1.2. 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 is considered an important tool. It should however not be relied on alone, to diagnose cancer (Van Cutsem, Cervantes, Nordlinger & Arnold, 2014).

4.1.3. The carcinoembryonic antigen (CEA) test, is recommended as a baseline measure and should be covered as PMB level of care. 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). It is not diagnostic but considered a tumour marker. CEA levels do have value in the follow-up of patients diagnosed with CRC. It aids in surgical treatment planning, post treatment follow-up and in the assessment of prognosis (Macrae, Bendell & Tanabe, 2016).

4.1.4. 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.

4.1.5. CA 19-9 is not indicated for staging of both colon and rectal cancer (Macrae et al., 2016).

4.1.6. Barium enema X-ray exam of the large intestine (colon and rectum) is PMB level of care. This radiological imaging procedure should only be used if the patient does not have access to colonoscopy (Van Cutsem et al., 2014; NICE guidelines, 2011; Agency for Healthcare Research and Quality; Macrae et al., 2016).

4.1.7. Standard (video) colonoscopy is PMB level of care. The rectum and entire colon are examined using a colonoscope. Any abnormal growths in the colon and the rectum can be removed,

including growths in the upper parts of the colon that are not reached by sigmoidoscopy (Klessen, Rogalla & Taupitz, 2007).

4.1.8. Computed tomographic (CT) scan colonoscopy is PMB level of care only if standard colonoscopy has been unsuccessful.

4.1.9. Bowel preparation prior to colonoscopy and CT colonoscopy is PMB level of care.

4.1.10. 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), (Van Cutsem et al., 2014; NICE guidelines, 2011).

Table 2: PMB level of care for diagnosis and workup of early stage colon and rectal cancer

Description	
Clinical assessment	Consultations
Laboratory investigations	Full Blood Count (FBC)
	CEA
Imaging :Procedures	Barium enema
	Colonoscopy
	CT Colonoscopy – On motivation: only if colonoscopy is unsuccessful
Histology assessment	Histology / cytology

4.2. Staging and risk assessment for colon and rectum cancer:

4.2.1. Consultation and clinical examination for staging and risk assessment for both colon and rectal cancer are covered as PMB level of care.

4.2.2. The liver function test, is routinely done for both colon and rectal cancer. Although frequently obtained preoperatively, liver enzymes may be normal in the setting of small hepatic metastases and are not a reliable marker for exclusion of liver involvement (Van Cutsem et al., 2014; NICE guidelines, 2011).

4.2.3. Renal function tests for colon and rectal cancer are routine blood tests to assess organ function (Van Cutsem et al, 2014; NICE guidelines, 2011).

4.2.4. The clinical benefit of routine clinical staging with CT scan of the chest is controversial in colon cancer (Macrae et al, 2016). However, if there is any suspicion of lung involvement, CT scan of the chest is considered PMB level of care.

4.2.5. A CT scan of the abdomen and pelvis is PMB level of care. In patients with newly diagnosed CRC, preoperative abdominal and pelvic CT scans can reveal regional tumour extension, regional lymphatic and distant metastases, as well as tumour related complications, for example, obstruction, perforation and fistula formation (Macrae et al, 2016).

4.2.6. A magnetic resonance imaging (MRI) scan of the pelvis is recommended for rectal cancer because it provides a precise evaluation of the topographic relationship of a tumor to the mesorectal fascia (an important anatomic landmark for the feasibility of total mesorectal excision). An MRI scan is currently the only imaging modality that is highly accurate in predicting whether or not it is likely that a tumor free margin can be achieved, and thus provides important information for planning of an effective therapeutic strategy, especially in patients with advanced rectal cancer (Kijima, Sasaki, Nagata, Utano, Lefor & Sugimoto, 2014; Klessen et al, 2007).

4.2.7. Rectal distension significantly reduces the distance between the rectal wall and the mesorectal fascia contrast might impact on the ability of an MRI scan to predict accurately the distance between the tumor and the potential resection margin, hence an MRI of the pelvis without contrast is used in most circumstances (Slater, Halligan, Taylor & Marshall, 2006).

4.2.8. Endo-rectal ultrasound (EUS) is recommended for rectal cancer only. EUS depicts the anatomic layers of the rectal wall with a high degree of accuracy and thus enables precise determination of the tumor extent in relation to the different wall layers. Reported accuracy rates of trans-rectal ultrasound in assessing the T stage are in the range of 69–97%. EUS is most suitable for evaluating early rectal cancer, however, it is limited in assessing more advanced tumors.

Procedures that are not PMB level of care for the staging and risk assessment of colon and rectal cancer include:

4.2.9. Bone scans for colorectal cancer are not indicated for CRC as it typically metastasizes to bone in less than 10% of patients, and isolated skeletal metastases are found in almost 1% of cases, suggesting a unique clinical and biological behavior in terms of metastatic pathways (Assi, Mukherji, Haydar, Saroufim, Temraz & Shamseddine, 2015).

4.2.10. Positron emission tomography (PET) scans do not appear to add significant information to CT scans in early stage CRC and are therefore not considered PMB level of care for early stage colorectal cancer.

4.2.11. A PET scan is better suited for advanced CRC. The benefit of a PET scan is to detect extrahepatic metastases in patients considered to be candidates for liver resection, and in this situation, it is appropriate to obtain a PET scan prior to initiation of chemotherapy (Van Cutsem et al, 2014; Nahas, Akhurst, Yeung, Leibold, Riedel, Markowitz, Minsky, Paty, Weiser, Temple, Wong, Larson & Guillem, 2008).

Table 3: PMB level of care for the staging and risk assessment of early stage colon and rectal cancer

Description		**Colon cancer**	**Rectum cancer**
Clinical assessment	Consultation	√	√
Laboratory investigations	CEA	√	√
	Liver function test	√	√
	Renal function	√	√
Imaging: radiology	CT chest, abdomen and pelvis only if there is any suspicion of lung involvement	√	√
	MRI pelvis without intravenous (IV) contrast	X	√
	Endo-rectal ultrasound	x	√
Exclusions			
- *Bone scans for early stage colorectal cancer* - *PET scan*			

5. Treatment options for early stage colon and rectal cancer

The severity of the disease determines the treatment options which are used to treat early stage colon and rectal cancer. These include:

- Surgical management
- Chemotherapy and Chemo-radiation
- Radiation therapy

5.1. Surgical management

The type of surgery used depends on the stage (extent) of the cancer, its location, and the goal of the surgery. Treatment is also divided into colon and rectal cancer as the approaches are slightly different.

5.1.1. The following surgical interventions are PMB level of care for colon cancer:

5.1.1.1. Local excision - Stage 0 and some early stage I tumours, or polyps can be removed during a colonoscopy.

5.1.1.2. Polypectomy - the cancer is removed as part of the polyp, which is excised at colonoscopy.

5.1.1.3. Colectomy - in this surgery, all (total colectomy) or part (hemicolectomy, partial colectomy, or segmental resection) of the colon together with surrounding lymph nodes are resected. The colectomy can be done as an open colectomy, through a laparotomy, or via a laparoscopy.

5.1.1.4. Stenting is indicated for obstructing tumours. A self-expanding metal stent (SEMS) is deployed across the tumour to relieve the obstruction allowing time to optimise and adequately stage the patient prior to surgery (Bonin & Baron, 2010; van Hooft, van Halsema, Vanbiervliet, Beets-Tan, DeWitt & Donnellan, 2014).

5.1.1.5. A stoma may comprise of colon (colostomy) or ileum (ileostomy). A Stoma is when the bowel is brought out as an opening onto the abdominal wall. It is indicated in cases of bowel obstruction (with or without resection), perforation or where an anastomosis is not deemed feasible.

5.1.2. The following surgical interventions are PMB level of care for rectal cancer (Van Cutsem et al, 2014; NICE guidelines, 2011; Macrae et al, 2016; Kaplan, Strongin, Adler, Siddiqui, 2014; Bonin & Baron, 2010; van Hooft et al, 2014).

5.1.2.1. Local excision – this is done to remove superficial cancers or polyps, often during a colonoscopy.

5.1.2.2. Polypectomy

5.1.2.3. Trans-anal excision - the procedure can be used to remove some early stage I rectal cancers that are relatively small, and not too far from the anus.

5.1.2.4. Anterior resection entails the excision of cancers in the upper part of the rectum together with its surrounding mesentery and lymph nodes. The remaining colon is then anastomosed to the remaining part of the rectum or brought out as a stoma. The stoma may be temporary or permanent (Kaplan et al, 2014).

5.1.2.5. Low anterior resection with colo-anal anastomosis - this entails the excision of rectal cancers involving the middle and lower third of the rectum. The entire rectum is excised by total mesorectal excision (TME), which is needed to remove the lymph nodes. The colon is then connected to the anus (colo-anal anastomosis). It may be necessary to do a temporary ileostomy (where the end of the ileum is brought out onto the abdominal wall) while the anastomosis heals.

5.1.2.6. Abdominoperineal resection (APR) is reserved for cancers in the lower part of the rectum which are involving the sphincter muscle. It entails an abdominal component to excise the rectum and a perineal component to excise the anus. A permanent colostomy is brought out onto the abdominal wall.

5.1.2.7. In the event of an extra-levator abdomino-perineal resection, which is aimed at achieving a wider tumour clearance, a biological mesh / prosthesis will be required to repair the resultant operative defect to prevent perineal herniation.

5.1.2.8. Diverting colostomy is indicated where the patient presents with obstructive symptoms. It entails bringing out the proximal obstructed colon onto the abdominal wall. This often helps the patient recover enough to start other treatments (such as chemotherapy) prior to definitive surgery. In some instances, the stoma may be permanent.

Table 4: Surgical interventions for PMB level of care for rectum and colon cancer

Rectum cancer	**Colon cancer**
Local excision	Local excision

Polypectomy	Polypectomy
Trans-anal excision	Colectomy
Anterior resection	Stenting
Low anterior resection with colo-anal anastomosis	Stoma
Abdominoperineal resection	
Diverting colostomy	

5.2. Chemotherapy and chemoradiation

Treatment for early stage colorectal cancer includes:

- Adjuvant chemotherapy for colon cancer
- Neo-adjuvant chemoradiation for rectal cancer
- Adjuvant chemotherapy for rectal cancer

5.2.1. Adjuvant chemotherapy for colon cancer:

5.2.1.1. There is no data to support the use of oxaliplatin in stage 2 colon cancer, it is however, recommended for stage 3 patients. FOLFOX4 (combination of fluorouracil, leucovorin and oxaliplatin) shows a 6 year overall survival of 72.9% versus 68.7% when compared to LV5FU2 (leucovorin plus fluorouracil) for stage 3 patients but no difference in overall survival for stage 2 patients (Andre´, Boni, Navarro, Tabernero, Hickish, Topham, Bonetti, Clingan, Bridgewater, Rivera & de Gramont, 2009).

Table 5: PMB level of care for adjuvant chemotherapy for colon cancer

Indication	Description	Medicine details
		Oxaliplatin – *only in high risk not for stage 2*
		Leucovorin

Colon adjuvant	Chemotherapy	Fluorouracil
		Capecitabine

5.2.2. Neo-adjuvant chemoradiation for rectal cancer (Van Cutsem et al, 2014; NICE guidelines, 2011; Macrae et al, 2016).

5.2.2.1. Fluorouracil + Leucovorin with Radiation then surgery.

5.2.2.2. Capecitabine with radiation then surgery.

Table 6: Neo-adjuvant chemoradiation options in early stage rectal cancer

Indication	Description	Medicine details
Rectum: neo-adjuvant	Chemo radiation	Fluorouracil + Leucovorin with Radiation then surgery
		Capecitabine with Radiation then surgery

5.2.3. Adjuvant chemotherapy for rectal cancer (Kachnic, 2007; Mamon, 2011).

5.2.3.1. Leucovorin, Capecitabine and 5FU are PMB level of care.

Table 7: Adjuvant chemotherapy options in early stage rectal cancer

Indication	Description	Medicine details
Rectum : adjuvant	Chemotherapy	Leucovorin
		Fluorouracil
		Capecitabine

5.3. Radiation therapy for colorectal cancer:

5.3.1. Radiation therapy (RT) for colon cancer is not recommended due to the high morbidity (Mamon, 2011). Special motivation would be required prior to any authorisation.

5.3.2. For rectal cancer, the following techniques are PMB level of care.

Table 8: PMB level of care for radiation therapy in early stage rectum cancer

Conventional Radiation therapy – chemoradiation • Radical radiotherapy – 25#: conventional single volume / 3D single volume • Radical radiotherapy – 25# conventional single volume with reduced TV boost + Short Course RT • Radical radiotherapy – 25# 3D single volume with reduced TV boost + Short Course 3D RT • Short course RT – 5# for frail patients. This is an acceptable neoadjuvant approach for early stage rectal cancer and applied to clearly operable disease planned for a total mesorectal excision.

6. Follow up care

Table 9 below shows recommended interventions and the corresponding frequencies up to 10 years post diagnosis.

Table 9: Frequency of interventions considered to be PMB level of care in early stage colon and rectal 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	Consultation	Depends on treatment interventions and supportive care required			
Pathology	Full blood count (FBC)	6	2	1	√
	CEA	2	2	1	√
	Liver function test	2	0	0	√
	Renal function	2	0	0	√
Imaging	CT study of chest and abdomen and pelvis	1	1	1	√
	MRI pelvis without IV contrast	0	0	0	√
Procedures	Colonoscopy	0	At 6 months, at 1 year, at 3 years and then every 3 years in patients with previous colorectal cancer		

Histological assessment	Histology	0	0	0	√

This guideline will be due for update on 31 August 2019

7. References

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