PMB definition guideline for early stage pancreatic cancer

Disclaimer:

The early stage pancreatic 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
CT	Computed tomographic
DTPs	Diagnosis treatment pairs
ERCP	Endoscopic retrograde cholangiopancreatography
ESPAC	European Study Group on Pancreatic Cancer
FBC	Full Blood Count
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
OS	Overall survival
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 pancreatic 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 pancreatic cancer

ICD 10 code	*WHO description*
C25.0	Malignant neoplasm, head of pancreas
C25.1	Malignant neoplasm, body of pancreas
C25.2	Malignant neoplasm, tail of pancreas
C25.3	Malignant neoplasm, pancreatic duct
C25.4	Malignant neoplasm, endocrine pancreas
C25.7	Malignant neoplasm, other parts of pancreas
C25.8	Malignant neoplasm, overlapping lesion of pancreas
C25.9	Malignant neoplasm, pancreas, unspecified
D01.7	Carcinoma in situ other specified digestive organs

3. Epidemiology and burden of disease

Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms across the world (Ferlay, Soerjomataram & Dikshit, 2015). Globally it is the seventh leading cause of cancer mortality in men and women, causing more than 300 000 deaths annually (Torre, Bray & Siegel, 2015. In South Africa, cancer of pancreas is the 12th most frequent cancer, with breast and cervical cancer ranked first and second respectively. The National Cancer Registry (2012) estimates the lifetime risk of developing pancreatic cancer at about 1 in 698 for males and 1 in 1211 for females (National Cancer Registry, 2012).

4. Diagnosis and Staging:

4.1. **Pre-diagnostic work up**

4.1.1. The work up of a suspected pancreatic cancer patient ideally should not only focus on the establishment of the diagnosis, but also on the potential for fitness to undergo curative treatment. The nature of pancreatic cancer is complex and thus, evaluation of all patients with pancreatic cancer should be managed by a multidisciplinary team, including gastroenterologists, radiologists, oncologists, surgeons, pathologists and palliative care specialists.

4.1.2. There is a number of investigations that should be conducted as part of a pre-diagnosis work up for early stage pancreatic cancer (see table 2).

4.1.3. Imaging remains the primary means through which the stage of pancreatic cancer is determined. For many patients presenting with the common symptoms of pancreatic cancer, ultrasound of the abdomen should be the first imaging test to be conducted. With a reported sensitivity of 80 – 95%, ultrasound of the abdomen can identify the pancreatic tumour as well as dilated bile ducts. Sensitivity is however reduced in the evaluation of the body and tail of the pancreas and provides less accurate staging information (Cotton, Lees & Vallon, 1980; Taylor, Buchin & Viscomi, 1981).

4.1.4. Tumour marker CA19-9 is a sialylated Lewis ^{A} blood group antigen. As the CA19-9 biomarker is commonly expressed and shed in pancreatic and hepatobiliary disease in many malignancies, it is therefore considered not tumour specific. Individuals who are jaundiced with cholestasis will induce false positive results, as CA19-9 levels correlate with high levels of bilirubin levels and do not necessarily indicate cancer or advanced disease (Kim, Y., Kim, H. & Park, 2009).

4.1.5. The degree of increase in CA 19-9 levels, however, may be useful in differentiating pancreatic adenocarcinoma from inflammatory conditions of the pancreas and CA 19-9 therefore remains a good marker, with sensitivity of 79 to 81% and specificity of 82 – 90% in symptomatic patients (Kondo, Murakami & Uemura, 2010). Preoperative CA 19-9 levels correlate with both AJCC staging and resectability and thus provide additional information for staging and determining

resectability (Oettle, Post & Neuhaus, 2007). The timing of preoperative measurement of CA 19-9 levels should be after biliary decompression is complete and bilirubin levels are normal.

Table 2: Pre-diagnosis work-up for early stage pancreatic cancer

Description		**Frequency**
Clinical assessment	Consultations with primary care practitioner, gastroenterologist, oncologist, surgeon	2 consultations per speciality
Imaging: Radiology	Ultrasound of abdomen	1
Laboratory investigations	Full Blood count	1
	Liver function tests	1
	Renal function	1
	CA 19-9	1

4.2. Diagnostic work up for early stage pancreatic cancer

4.2.1. The diagnostic work up for pancreatic cancer is shown in table 3 below.

4.2.2. When the diagnosis of pancreatic cancer is suspected from clinical symptoms and/or abdominal ultrasound findings, computerised tomography (CT) of the abdomen and pelvis is the standard for diagnosis and staging and is PMB level of care (American Gastroenterological Association, 1999; Karlson, Ekbom & Lindgren, 1999). CT can reliably demonstrate the primary tumour as well as evidence of extrapancreatic spread, particularly in the presence of liver metastasis (Steiner, Stark & Hahn, 1989; Vellet, Romano & Bach, 1992; Warshaw and Del Castillo, 1992). Contrast enhanced CT accurately predicts resectability in 80 – 90% of cases (Schima, Ba-Ssalamah & Goetzinger, 2007).

4.2.3. CT study of the chest is only a PMB level of care on specialist motivation, if there is a confirmed adenocarcinoma.

4.2.4. If CT is not possible either from lack of availability or allergy to contrast media, magnetic resonance imaging (MRI) with IV contrast media can be used to diagnose and stage pancreatic cancer. MRI can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for the characterisation of CT-indeterminate liver lesions and when suspected pancreatic tumours are not visible on the CT or in cases of contrast allergy (Vachiranubhap, Kim & Balci, 2009).

4.2.5. MRI detects and predicts resectability with accuracies similar to the CT. Identification of a pancreatic mass may be followed by endoscopic ultrasound and fine-needle aspiration if required (Bret and Reinhold, 1997; Ichakawa, Haradome & Hachiya, 1997; Megibow, Zhou & Rotherdam, 1995).

4.2.6. If no mass is identified on cross-sectional imaging and no evidence of metastatic disease is present, further endoscopic ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), and/or magnetic resonance (MR) including magnetic resonance cholangiopancreatography (MRCP) are indicated. These may help identify an early pancreatic lesion not evident on a conventional CT.

4.2.7. MRCP provides detailed ductal images without the risk of ERCP induced pancreatitis and may clarify diagnostic uncertainties (chronic pancreatitis versus cancer), as well as being informative on intraductal tumours. MRCP does not have the sensitivity and specificity of ERCP and therefore does not have a central role in assessing the pancreatic duct. ERCP is important in the diagnosis of ampullary tumours by direct visualisation and cytology (Vitellas, Keagan & Spritzer, 2000).

4.2.8. ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions (Nallamothu, Hilden, & Adler, 2011). ERCP remains the gold standard for diagnosing biliary obstruction (which occurs in pancreatic cancer). MRCP is used as a secondary tool in cases where ERCP is unsuccessful or contraindicated (Kaltenthaler et al, 2006)

Table 3: PMB level of care for diagnosis and staging work- up for early pancreatic cancer

Description		**Frequency**
Clinical assessment	Consultations with primary care practitioner, gastroenterologist, oncologist, surgeon	2 consultations per speciality
Histological Assessment	Histology / cytology	1
Imaging: Radiology	CT study of the chest –On specialist motivation, if confirmed adenocarcinoma	1
	Contrast CT study of the abdomen and pelvis OR	1
	MRI of the pancreas with IV contrast	1
	Endoscopic ultrasound with needle biopsy	1

Imaging: Procedures	Endoscopic retrograde cholangiopancreatography (ERCP)	1
	MRCP – on specialist motivation, only if ERCP is unsuccessful or contraindicated.	1

5. Treatment options for early stage pancreatic cancer

5.1. Surgical Approach

5.1.1. The treatment of resectable pancreatic adenocarcinoma requires a multidisciplinary approach. Although radical surgery offers a low cure rate, it is the only potentially curative treatment of pancreatic adenocarcinoma for mainly stage I and some stage II patients. Complete tumour removal in patients undergoing resection is the cardinal rule for improving the prognosis (Wagner, Redaelli & Lietz, 2004).

5.1.2. Appropriate radiological staging allows for the selection of patients who will have the best chance for curative intent resection (R0) and only patients with high probability of R0 resection are good candidates for upfront surgery.

5.1.3. The following surgical interventions are PMB level of care:

- pancreaticoduodenectomy (with or without pylorus preservation)
- distal pancreatectomy with splenectomy to resect disease with macroscopic clear margins.

The long-term survival after surgery remains low due to high rate of systemic recurrence.

5.2. Chemotherapy

5.2.1. In cases of resectable pancreatic cancer neoadjuvant chemotherapy, radiotherapy or chemoradiation should only be performed within clinical trials, as there is no data that clearly demonstrates improved resectability or survival with neoadjuvant treatment compared with initial surgery followed by adjuvant therapy.

5.2.2. Adjuvant treatment has been shown to improve survival as demonstrated in studies such as the European Study Group on Pancreatic Cancer (ESPAC-1) (Neoptolemos, Stocken & Dunn, 2001) CONKO-001 (Oettle, Neuhaus & Hochhaus, 2013) ESPAC-3 (Neoptolemos, Moore & Cox, 2012), RTOG 9704 (Regine, Winter, & Abrams, 2011) and GITSG (Boyle, Czito, & Willett, 2015).

5.2.3. A Phase III randomised trial on combination of capecitabine to gemcitabine in adjuvant treatment of pancreatic cancer reported by the ESPAC4 outperformed gemcitabine alone in terms of overall survival (OS), reflecting a 28.8% vs 16.3% 5 year survival rate (Neoptolemos,

Palmer, Ghaneh, Valle, Cunningham, Wadsley, Meyer, Anthoney, Glimelius, Falk, Segersvard, Izbicki, Middleton, Ross, Wasan, Mcdonald, Crosby, Psarelli, Hammel & Buchler, 2016).

5.2.4. In the adjuvant setting, fluorouracil, leucovorin, capecitabine and gemcitabine are PMB level of care

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

Table 4: PMB level of care chemotherapy options in early stage pancreatic cancer

Indication	Medicine details
Chemotherapy: adjuvant	Fluorouracil Leucovorin Gemcitabine Capecitabine

6. Follow up after surgical resection:

Follow up investigations should be tailored based on stage of cancer, adjuvant treatment provided, performance status and clinical signs and symptoms.

- In patients treated with curative intent, follow up clinical visits should be up to 4 times for the first 2 years and annually for 3 to 10 years thereafter;
- Laboratory tests should include full blood count, serum chemistry, liver and renal function tests, as clinically indicated;
- CA19-9 is a useful tumour marker to monitor for possible recurrence (Bauer, El-Rayes & Li, 2013).

Table 5: Frequency of interventions considered to be PMB level of care in early stage pancreatic 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
			Frequency per year		
Clinical assessment	Consultations	Depends on the treatment intervention	Every 6 months for the first 2 years	Once per annum	
Laboratory investigations	Full Blood Count (FBC)	6	4	1	√
	Liver function test	2	2	1	√
	CA19-9	2	2	1	X
	Renal function	2	0	0	X
Imaging: Radiology	CT study of the chest, abdomen Or	1	2	1	√
	MRI of pancreas with IV contrast	1	2	1	√
Imaging: Procedures	Endoscopic retrograde cholangiopancreatography	0	0	0	√

This guideline will be due for update on 31 December 2018

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