Draft PMB definition guidelines for metastatic (including advanced) pancreatic cancer

Disclaimer:

The metastatic 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(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.

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5FU	Fluorouracil
AC	Adenocarcinoma
ASCO	American Society of Clinical Oncology
A-YLLs	Absolute Years of Life Lost
CMS	Council for Medical Schemes
CT	Computed tomographic
DTPs	Diagnosis treatment pairs
EUS	Endoscopic ultrasound
ESPAC	European Study Group on Pancreatic Cancer
FBC	Full Blood Count
GEJ	Gastro-oesophageal junction
ICD	International Classification of Diseases
IMRT	Intensity-modulated radiation therapy
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NCR	National Cancer Registry
OS	Overall survival
PEG	Percutaneous endoscopic gastrostomy
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) are 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 metastatic 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 metastatic 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

3. Epidemiology and burden of disease

3.1. Most pancreatic adenocarcinomas are ductal origin and account for 90% of pancreatic cancers. The remaining 10% are represented by acinar cell carcinomas. With approximately 80% of patients presenting with unresectable disease due to the presence of metastasis or local extension the 5 year overall survival for metastatic pancreatic cancer remains at 2%, with a median life expectancy of < 1 year with current treatments. (1,2) 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.(3)

3.2. The poor prognosis can be attributed to the lack of clinical symptoms and good biomarkers, early metastatic dissemination and an unusually high resistance to targeted and cytotoxic agents.

3.3. Globally, it is the seventh leading cause of cancer mortality in men and women, causing more than 300 000 deaths annually.(4)

3.4. 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 (2010) estimates the lifetime risk of developing pancreatic cancer at about 1 in 1.198 for males and 1 in 2134 for females.(5,6)

4. Investigation, diagnosis and staging

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

4.2. Histopathologic confirmation of pancreatic adenocarcinoma is PMB level of care.

4.3. Cross sectional imaging with a CT scan of the abdomen and pelvis using a pancreatic protocol should be performed to evaluate the extent of disease in all patients with metastatic pancreatic cancer.

4.4. A CT scan of the chest should also be performed to evaluate intrathoracic metastases.

4.5. Tumour marker CA19-9 is a sialylated Lewis A blood group antigen and is a PMB level of care. However, its limitations should be considered as it is not considered 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.(7)

4.6. 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.(8) Preoperative CA 19-9 levels correlate with both AJCC staging and resectability and thus provide additional information for staging and determining resectability.(11) The timing of preoperative measurement of CA 19-9 levels should be after biliary decompression is complete and bilirubin levels are normal.

4.7. A CT scan of the chest, abdomen and pelvis should be performed to assess the extent of disease. Other staging studies should be performed only as dictated by symptoms.

4.8. Endoscopic retrograde cholangiopancreatography (ERCP), and or magnetic resonance (MR) including magnetic resonance cholangiopancreatography (MRCP) are indicated as PMB level of care, as these may help identify an early pancreatic lesion not evident on a conventional CT scan.

4.9. Relief of biliary obstruction by surgical bypass by endobiliary stenting will reduce symptoms and improve the quality of life.

4.10 Surgical decompression should be reserved for patients in whom stenting cannot be accomplished. (9, 10),

4.11 Endoscopic stent placement is a common intervention for management of malignant biliary strictures and is recommended as a PMB level of care.

4.12 Self-expanding metal stents (SEMS) have been found to be more cost-effective than plastic stents for patients whose life expectancy exceeds 6 months.

Table 2: PMB level of care for the diagnosis and staging work-up for metastatic pancreatic cancer

Description	
Clinical assessment	Consultations
Histological Assessment	Histology / cytology
	Biopsy Endoscopic ultrasound (EUS)
Laboratory investigations	Full Blood Count (FBC)
	Liver function test
	CA19-9
	Renal function
Imaging: Radiology	CT study of the chest, abdomen and pelvis
Imaging: Procedures	Endoscopic retrograde cholangiopancreatography (ERCP)
	MRCP
	Biliary and/or duodenal stents

5 Treatment options for metastatic stage pancreatic cancer

Advanced pancreatic cancer is incurable with an average life expectancy after diagnosis of metastatic disease of three to six months. Palliative treatment strategies are therefore important and should focus on improving the quality of life and pain management.

Treatment of advanced pancreatic cancer in patients with adequate performance status involves chemotherapy and/or radiotherapy. Patients with obstructive jaundice may be treated with placement of a plastic stent. In patients who are likely to survive more than 6 months, surgical bypass may be the preferred approach. Endoscopic placement of a biliary stent is a standard palliative measure for patients with metastatic disease, to relieve jaundice and associated pruritus during the last months of life.

5.10 Surgical Management

The PMB level of care for surgical management of metastatic pancreatic cancer includes the following:

- stenting
- bypass +/- stent

5.11 Chemotherapy

5.11.1 The primary goal of treatment for metastatic pancreatic cancer is palliation and lengthened survival.

5.11.2 Fluorouracil (5-FU) was considered the only active chemotherapeutic option for about 20 years until the introduction of gemcitabine.(12)

5.11.3 It is evident from the existing data that there is a significant survival benefit for the intensive chemotherapy treatment regimen, FOLFIRINOX, for metastatic pancreatic cancer.

5.11.4 FOLFIRINOX is a combination of folinic acid, 5-FU, irinotecan and oxaliplatin,

5.11.5 A study by Conroy et al. (2011) of FOLFIRINOX vs gemcitabine showed a survival benefit when compared to gemcitabine. Phase I/II data have supported the efficacy and safety of FOLFIRINOX. The trial included 342 patients from 48 French centres and reported a 48% of patients on FOLFIRINOX being alive after one year. The median survival of patients on the FOLFIRINOX arm was 11.1 months versus 6.8 months in the gemcitabine arm (hazard ratio for death 0.57, $P<0.001$). (16, 17)

5.11.6 However, careful patient selection based on clinical and laboratory findings represents a major challenge for physicians and oncologists in the palliative situation. Currently, no biomarker can reliably predict the response to treatment to FOLFIRINOX. Therefore careful clinical and biochemical follow-up is required to optimise the treatment effects while minimising the side effects.

5.11.7 Gemcitabine is not currently recommended as PMB level of care.

Table 3: Chemotherapy options that are PMB level of care in metastatic pancreatic cancer

Indication	Intervention	Regimen details
Pancreatic: Metastatic	Chemotherapy	Oxaliplatin
		Fluorouracil
		Leucovorin
		Irinotecan

5.12 Radiation therapy

Radiation therapy considered to be PMB level of care for metastatic pancreatic cancer is shown in table 4 below:

Table 4: Radiation therapy for metastatic pancreatic 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 • Palliation : 45# - for locally advanced disease

6 Follow up care

6.10 Although at present there is no evidence based data to inform on the frequency of imaging for patients with metastatic cancer, table 5 provides a guide on recommendations for PMB level of care.

6.11 A CT scan should be offered at least twice from the initiation on therapy to assess the response.

6.12 For the first two years post diagnosis, a CT scan or an MRI scan with IV contrast can be done yearly.

6.13 The routine use of PET scans for the management of patients with pancreatic cancer is not recommended and should only be considered as PMB level of care upon specialist motivation.

This guideline will be reviewed on the 31st of December 2018

Table 5: Frequency of interventions considered to be PMB level of care in metastatic pancreatic cancer during therapy and up to 2 years post diagnosis

		Frequency during therapy	Per year Up to 2 years post diagnosis
Clinical assessment	Consultations	Depends on treatment interventions and supportive care required.	
Pathology	Full Blood Count (FBC)	6	2
	Liver function test	2	2
	CA19-9	2	2
	Renal function	2	0
Radiological Imaging	CT study of the abdomen OR	2	2
	MRI of pancreas with IV contrast	0	2
	PET scan	0	On appeal
Procedures	Endoscopic retrograde cholangiopancreatography	0	0

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