Draft Benefit Definition-Prostate Cancer

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Disclaimer:

The prostate cancer benefit definition has been developed for majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore regulation 15h may be applied for patients who are inadequately managed by the stated benefits.

The procedure codes are just an indication of applicable procedure codes however some significant procedure codes may not have been included.

The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs, supportive medication nursing care. However these interventions form part of care and are prescribed minimum benefits.

1. Introduction

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. 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.

The benefit definition project is coordinated by the Council for Medical Schemes and aims to define condition-specific treatment guidelines, which will serve to guide the interpretation of the PMB provisions by relevant stakeholders.

The guidelines are based on the available evidence of clinical and cost effectiveness taking into consideration affordability constraints and financial viability of medical schemes in South Africa.

2. Epidemiology

Cancer is an under-emphasised issue in Africa, partly because of the overwhelming burden of communicable diseases. Prostate cancer is one of the commonest cancers in African men, estimated to constitute 9.5% of all male cancers (1). The increasing prevalence of prostate cancer is partly due to earlier diagnosis from screening. In South Africa, the incidence of histologically diagnosed prostate cancer is 40.1 per 10^5 males in the white population and 14 per 10^5 males in the black population; however, the black population has poorer access to diagnostic and screening facilities, and the reported rates may therefore underestimate the true burden of disease. NHLS is in the process of implementing a cancer surveillance system based on histological data from both private and public sector. This data would assist in quantifying burden of prostate cancer.

3. Scope

This is a recommendation for the diagnosis, treatment and care of individuals with prostate cancer in any clinically appropriate setting as outlined in the Medical Schemes Act of 131. The purpose is to improve clarity in respect of funding decisions by medical schemes, taking into considerations evidence medicine, affordability and in some instances cost-effectiveness.

PMB and ICD10 Codes

C61	Malignant neoplasm of the prostate
D07.5	Carcinoma in situ, prostate

4. Diagnostic Procedures

The cornerstone of prostate cancer diagnosis is biopsy. Work-up in prostate cancer is mainly to stage the disease, which includes the identification of metastasis. Most patients in the private sector may be detected from screening, some patients may however present with symptoms. Patients presenting with elevated PSA should be offered biopsy and digital rectal examination. Abnormal PSA is non- specific in diagnosing cancer -PSA may be elevated in non-cancerous conditions such as benign prostate hypertrophy and prostatitis (2). Therefore, diagnosis of a prostate cancer is only considered PMB level if the histology confirms cancer. The schemes should pay for all diagnostic work-up retrospectively in patients with confirmed histology.

Table 1: Diagnostic work-up for prostate cancer

	Procedure	***Procedure code***	***Comment***
Histopathology	Transrectal or transurethral biopsy with or without ultrasound	3610,3627,3628,5100	PMB level of care include local anaesthetic, general anaesthesia, hospitalisation where necessary and prophylactic antibiotic (including out of hospital antibiotics)
	Lymph node biopsy		If CT scan or MRI shows involvement of Lymph nodes.
Biochemical and haematological test	Full blood count (FBC)	3755	Standard pre-operative assessment and as screening for possible bone marrow metastasis
	Liver function test	4130-4134; 4009-4010	As baseline when ADT is required and possible liver involvement
	Urea, creatinine and electrolytes	4171; 4032	Pre-operative bloods and assessment of possible obstructive renal symptoms
	Prostate specific antigen (PSA)	4524	PSA screening for asymptomatic patients is not a PMB level of care
Imaging	Bone scan	10090,10093	Limited to patients with Gleason scores of more than 7 to detect possible bone metastasis
	Chest X-RAY	1241	To exclude possible lung metastasis
	CT scan or MRI scan	140320	To assess nodal spread and metastatic spread in patients with locally advanced disease and beyond. In patients with localised cancer, MRI or CT scan should be limited to patients with high risk disease as probability of detecting LN metastasis is < 1% in low risk patients (3) The CT scan to assess distant metastasis should be guided by clinical findings.
	PET scan		Not routinely recommended in Prostate cancer screening (4)
	Transrectal ultrasound	40200, 42200, 43200, 43210	For T- staging.

5. Management of prostate cancer

Treatment selection in patients with localized prostate cancer should be guided not only by patient-related factors (e.g. age and co-morbidities), but also by cancer-related parameters (clinical stage, biopsy grade and preoperative PSA levels) that enable patients to be classified as low, intermediate, or high risk for unfavourable outcomes. Treatment for prostate cancer does not only involve one mode of treatment, many patients may require multimodal treatment. Treatment of prostate cancer is a multidisciplinary process involving generalists, urologist, radiologist and oncologists. Patients need to be adequately counselled of treatment choices.

6.1 Management of localised disease

6.1.1 Deferred treatment

Deferred treatment for management of prostate cancer include watchful waiting and active surveillance

i. Watchful waiting

Watchful waiting is also known as 'deferred treatment' or 'symptom-guided treatment, this term was coined in the pre-PSA screening era (before 1990) and referred to the conservative management of prostate cancer until the development of local or systemic progression, at which point the patient would be treated palliative with resection of the prostate (TURP) or other procedures for urinary tract obstruction and hormonal therapy or radiotherapy for the palliation of metastatic lesions (5). The rationale behind watchful waiting is the observation that prostate cancer often progresses slowly, and is diagnosed in older men in whom there is high incidence of co-morbidity and related high competitive mortality (2).

In a Scandinavian study with a median follow up time of 8 years, outcomes of watchful waiting were compared to radical prostatectomy (RP). Patients who had RP had significantly higher cancer free survival rates, low disease specific mortality rates and low metastatic progression rates (6). However this study was done in early stages of routine asymptomatic PSA screening.

The results of the Prostate Cancer Intervention vs. Observation Trial (PIVOT) may provide better evidence and outcomes of active surveillance or watchful waiting as compared to radical prostatectomy. To date only preliminary results are available on PIVOT. Since PIVOT is a randomised trial, it would provide a higher level of evidence as compared to existing observational studies.

Watchful waiting was previously recommended in men with life-expectancy of less than 5-10 years and existing severe medical condition.

It is recommended that men who are candidates for watchful waiting be offered active surveillance to treat progressive disease early as studies have reported higher progression rate.

ii. Active surveillance

Active surveillance (AS) was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined low-risk prostate cancer, without giving up radical treatment, as happened with the watchful waiting strategy.

Only data from non-mature randomised clinical trials of AS with follow-up < 10 years are currently available (2).

The best available evidence is from observational studies, (level 2a) with a follow-up time of less than 5 years in majority of studies. Only Klotz et al had median follow-up time of 8 years (7). All the observational studies reviewed were a cohort follow-up of patients who mainly self selected into treatment without any comparison arm. The authors evaluated disease specific mortality and disease progression that required intervention.

Table 2: The summary statistics and outcomes of observational studies for active surveillance in patients with organ confined prostate cancer (2)

Authors	n	Median follow-up	Overall survival	Cancer specific survival	Progression/ intervention	Inclusion criteria
Klotz et al (7)	453	6.8 (1-13)	78.6%	97.2%	30%	PSA < 10 Gleason score < 6
Van der Bergh (8)	616	3.9 (0-11)	91%	99.8%	32% intervention; only 14% due to progressive PCA	PSA <10, PSA-density < 0.2, cT1C/T2, Gleason score < 6, < 2 biopsies positive
Soloway et al (9)	99	4 (1-14.9)		100%	9%	< 80 years, Gleason score < 6, PSA < 0,15 ng/mL, cT < 2, < 50% cancer in < 2 biopsies
Dall" Era et al (10)	321	3.6 (1-17)	100%	100%	24%	PSA < 10 ng/mL, Gleason score < 6, no Gleason grade > 3, < 33% positive biopsies, cT 1-2a
Berglund at al (11)	104	3 (1-6)	No data	100%	27%	PSA < 10, cT1-2a, Gleason grade < 3, < 3 positive biopsies, < 50% cancer in biopsy
Al Otaibi (12)	186	6.4(2.5-14)	No data	100%	36%	< cT2a, < 2 positive biopsies, < 50% cancer in biopsy, no Gleason grade 4
Kakehi et a L (13)	134	4.5	97.5%	100%	17.7%	cT1cN0M0, 50-80 years, PSA < 20ng/mL, < 2 positive out of 6-12 biopsies Gleason score < 6, < 50% cancer

Indications for deferred treatment with active surveillance is indicated in patients who meet the following criteria as recommended in European guidelines supported by evidence in Table 2

a. In younger patients with life expectancy of more than 10 years: Stage T1a well and moderately differentiated tumours. With PSA < 10 ng/ml, biopsy Gleason score < 6, < 2 positive biopsies cores, < 50% cancer per biopsy core.
b. In asymptomatic patients with life expectancy of < 5-10 years, stage T1b-T2b well and moderately differentiated tumours with PSA < 10 ng/ml, biopsy Gleason score < 6, < 2 positive biopsies cores, < 50% cancer per biopsy
c. Deferred treatment is not recommended in patient with Intermediate and high risk localised disease (any prostate cancer with T stage > T2, Gleason score ≥7 and PSA > 10 ng/ml
d. In patients who are candidate for active treatment however wishes to defer treatment

Active surveillance benefits should include the following:

a. Care with a specialist urologist
b. Digital rectal examination (DRE) and clinical examination every 6 months until disease progression or a lifetime
c. PSA every 6 months for a lifetime or until disease progression
d. Biopsy of the prostate annually or if the PSA is increasing or DRE findings are suspicious of progression

Although active surveillance resulted in 17% -30% of patients progressing to needing treatment, the treatment outcomes are unknown. In van der Berg et al, 18% of patients wished not to continue with the study and needed active treatment whilst 14% continues with the study (8). It is not clear what factors resulted in patients choosing to switch to active treatment without any progressive disease.

Whilst deferred treatment with active surveillance may improve quality of life, it needs to be noted that there is lack of long term information regarding safety of AS and that rates of progression of disease may increase as the year progresses.

Both NICE and European guidelines emphasise on patients well informed choices when choosing treatment option, and American guidelines do not recommend watchful waiting with surveillance in patients with life expectancy of > 10 year.

Therefore, active surveillance must be voluntarily accepted by the patient with alternative treatment offered as this intervention is supported by level 2a evidence. This modality will be reviewed when PIVOT results becomes available.

6.1.2 Radical Prostatectomy:

Radical prostatectomy is indicated in:

a. Patients with low and intermediate risk disease (cT1a-Ct2b, PSA < 20 ng/Ml, and Gleason score of 2-7) (4) (2).
b. Radical prostatectomy can be offered in selected patient with high-risk localised disease when multimodal treatment is considered (2).

Care elements of radical prostatectomy include assessment for fitness of surgery and prostatectomy. Care should include in-hospital admission as well as surgical follow-up post prostatectomy.

PMB level of care includes retropubic, transperineal and trans-urethral prostatectomies with or without Lymph node dissection. However, ***laparoscopic prostatectomy and robot assisted radical prostatectomy are not at PMB level of care, and will only be considered after economic evaluation has shown that this modality is cost effective and affordable.***

Lymph node dissection: Lymph node dissection is not recommended in patients with low risk localised disease as probability of nodal involvement is around 7%. However it is indicated in intermediate and high risk disease. Besides being useful for staging extensive lymph node dissection may have disease control functions. Joslyn et al, reported better survival rates in patients who received lymphadenectomy as compared to those (Level 2c evidence) (14)**. Therefore lymph node dissection is at PMB level of care for high risk disease.**

6.1.3 Radiotherapy

a) *External Beam radiation therapy*

External Beam Radiation therapy (EBRT) is indicated for the following

i. Localised cancer (cT1c-cT2c) with adjuvant androgen deprivation therapy in high risk localised cancer.
ii. As post-operative radiation therapy in patient with tumour stage T3 N0 M0
iii. In locally advanced prostate cancer with concomitant androgen deprivation therapy

Patients need to be assessed for suitability for EBRT and risks and benefits discussed. Although EBRT can be used for localised disease, brachytherapy has higher predicted probability of maintaining erectile function as compared to EBRT. (15). Generally, patients with previous obstructive bowel disease or diabetes are not good candidates for EBRT due to increased risk of complications. This risk-benefit ratio is higher for patients with localised disease than for patients with locally advanced disease.

There are 3 types of EBRT: 3d conformal radiation therapy (3d-CRT), conventional radiotherapy and intensity modulated radiotherapy.

- *Conventional radiotherapy* is a form of radiotherapy where the whole pelvis is irradiated. This has been replaced by 3 d-CRT but can still be used when pelvic irradiation is required.
- *3-dimensional conformal radiotherapy (3D-CRT*), the radiation beam is shaped to include a 3-dimensional anatomic configuration of the prostate and any specified adjacent tissue. Adjacent structures include the seminal vesicles and periprostatic adventitial tissues. 3D-CRT allows for more precise delivery of therapy to the target organ or organs
- *Intensity modulated radiotherapy (IMRT*) enables radiation oncologists to increase radiation doses homogeneously, up to as much as 86 Gy within the target volume, while respecting the tolerance doses in organs at risk. IMRT may require image guiding.

IMRT is a new intervention and is **not** at a PMB level of care until evidence on cost-effectiveness as compared to 3d-CRT is available. Both conventional radiotherapy and 3d CRT are PMB level of care.

b) *Brachytherapy*

Brachytherapy is more suitable for localised characterised by the following (16):

i. cT1–T2a
ii. Gleason score <6
iii. PSA ≤10 ng/ml,
iv. prostate volume ≤50 ml without a previous resection of the prostate
v. < 50% of the biopsy involved with cancer

Two modalities of brachytherapy are used. Permanent low-dose radiation is at a PMB level of care, but temporary high-dose radiation, which is more recently developed intervention, may have to be subjected to economic evaluation before it is considered to be at PMB level of care.

6.1.4 Androgen blockade

i. Patient with localised disease may be offered androgen deprivation therapy as first line of treatment if contraindications to (17) radiotherapy and radical prostatectomy are present (Table 2).
ii. Androgen Deprivation therapy (androgen deprivation therapy) can be offered in patients with intermediate and high risk localised prostate cancer as an adjuvant to radiotherapy (18; 19). In the Phase II trial of EORT Androgen deprivation provide better disease control when taken for 3 years from the time RT was commences (20; 17).
iii. In a Cochrane systematic review neo-adjuvant ADT prior to prostatectomy had significantly improved pathological outcomes (Reduction in positive margins, organ confinement and lymph node invasion) but no effect on overall or disease-free survival. Therefore this treatment combination is not recommended in localised cancer survival (19).
iv. Adjuvant ADT is not recommended prior to prostatectomy (20) (17) (19).

PMB level of care include both surgical and medical ADT, however surgical ADT is unacceptable to most men. ADT include both surgical and medical therapy

6.1.5 Triple therapy

Triple therapy should be subject to evaluation before it could be considered a PMB level of care. Triple therapy consists of EBRT, radical prostatectomy and brachytherapy.

6.1.6 Exclusions for treatment of localised disease

i. Image modulated radiotherapy due to additional high costs
ii. Cryotherapy
iii. Proton beam and carbon ion beam therapy
iv. High Intensity Focused ultrasound

Table 3: Procedure codes for management of prostate cancer

Treatment Modality	*Procedure code*
Watchful waiting with Active Surveillance	0190,0191,0192
Radical prostatectomy	
Retropubic	2257, 2259,1408, 1451, 1453, 1455
Perineal	2251, 2253
Transrectal	
Laparoscopic/ Robotic assisted (Not considered PMB level of care)	2496, 2499 (Not considered PMB level of care)
Radiotherapy	
Prostate brachytherapy	2260
External beam radiotherapy	5801, 5601, 5802, 5602, 5803, 5603, 5808, 5608, 5809,5609

6.2 Management of locally advanced disease:

Locally advanced prostate cancer is defined as cancer that has perforated the prostate capsule. Treatment of locally advanced prostate cancer can be multimodal.

6.2.1 Watchful waiting

Watchful waiting is **not** recommended in patients with advanced prostate. In a study by the medical research council prostate cancer working party investigators group in United States patients who had deferred treatment had higher cancer specific mortality rates and higher rates of disease progression (21)**.**

6.2.2 Radical prostatectomy

Radical prostatectomy (with post-operative radiotherapy) as a treatment of locally advanced prostate cancer has a well demonstrated 5 years survival rates of between 85% and 100%.

Radical prostatectomy may be option patients with

- Tumour stage T3 N0 M0
- Gleason of < 8
- PSA < 20ng/ml and
- life expectancy of > 10 years

Over the years there is some retrospective evidence that indicate that surgery may be beneficial in patient with locally advanced prostate cancer. Management of locally advanced disease is multi-modal and can include a combination of hormonal treatment, EBRT and radical prostatectomy. See table 2 for suitable procedure codes

6.2.3 Radiotherapy

a. External Beam Radiation Therapy

External beam radiation therapy is the preferred mode of treatment in patients with locally advanced cancer. The Radiation oncology Group (RTOG STUDY 10 86) did not report any significant differences in survival in patients receiving only EBRT as compared to those who received neo-

adjuvant therapy prior to EBRT (34% vs. 43%; p =0.12) however the group that received ADT and radiotherapy had higher rates of disease free survival and metastatic free survival as compared to the group that received only ADT (22). The Australian Trans-Tasman Radiation Oncology Group 96.01 trial was designed to determine whether 3 months or 6 months of androgen deprivation given before and during radiotherapy improves outcomes for patients with locally advanced prostate cancer. Compared with patients assigned no androgen deprivation, those assigned 3 months treatment had significantly improved local failure, biochemical failure-free survival, disease-free survival, and freedom from salvage treatment as illustrated in previous trials. Similarly, compared with no ADT, 6 months of androgen deprivation significantly improved similar outcomes. However, no difference in outcome was seen between the 3 and 6 month groups (23). Since there was no difference in outcome between 3 and 6 months group ADT should be limited to 3 months prior to radiotherapy. Neo-Adjuvant ADT with Radiotherapy may be suitable for patients who do cannot tolerate long term ADT to slow down the progression.

In the EORTC study, concomitant and adjuvant ADT or radiotherapy only were given to patients with locally advanced cancer. ADT was given 1 week prior to EBRT and continued throughout the trials. With a median follow-up of 66 months, the group receiving adjuvant ADT with radiotherapy had better overall (78% vs. 62%; p=0.0002) and cancer specific survival rates (94% (90-98) vs.79% (72-86) 62%; p = 0.001) (20).

Analysis of the EORTC was conducted at 10 years with a median follow-up period was 9.1 years. The group receiving ADT plus radiotherapy had better overall survival rate (58.1% vs. 39.8%; $p < 0.0001$) and clinical progression-free survival (47.7% vs. 22.7%; $p < 0.0001$). The cumulative incidence of cancer mortality was 11.1% versus 31% ($p < 0.0001$) at 10 years with no significant difference in cardiovascular mortality rate (11.1% vs.8.2%; p=0.75) (24).

Whole pelvis radiation plus hormonal treatment was reported to have better survival results as compared to Prostate only radiation therapy. Therefore external beam radiation therapy plus ADT is a PMB level of care.

b. Brachytherapy

High dose brachytherapy with EBRT has been recommended in management of locally advance disease however this would not be a PMB level of care in South African setting until cost-effectiveness studies are conducted.

6.2.4 Androgen deprivation therapy

In a randomised phase III study by Widmark et al, men with locally advanced prostate cancer randomised to ADT and radiotherapy had better outcomes as compared to men receiving hormonal therapy alone (25).
Androgen deprivation therapy alone without radiotherapy maybe indicated in patients who have contraindications to radiotherapy.

6.3 Management of metastatic disease

With improving technology and wide availability of PSA, prostatic cancer is detected early therefore reducing the incidence of metastatic disease. Management of metastatic prostate cancer is a prescribed minimum benefit and care aims at improving quality of life and minimising the acute effects of cancer.

In the explanatory notes of the Act, solid organ tumour will be regarded as treatable where

i. They involve only organ of origin and have not spread to adjacent organs
ii. There is no evidence of distant metastatic spread
iii. They have not, by means of compression, infarction, or other means brought about irreversible and irreparable damage to the organ which they originated or another vital organ or
iv. If points I-III do not apply, there is a well demonstrated five years survival rates.

6.3.1 Survival rates in patients with metastatic prostate cancer

Points i to iii are not applicable for metastatic prostate cancer however the survival rates amongst prostate cancer patients have been reported to be well above 10%.

Soloway et al analysed 166 patients with bony metastasis receiving ADT. Patients were categorised into 5 groups depending on the number of bony metastasis, with group 0 having no bony metastasis, group I fewer metastasis and group IV with > 75% of the rib and vertebrae involved. At the end of 48 months, 35% of the patients were alive (there is no data beyond 48 months for this group). Survival rates at 5 years for group II to IV were between 30% and 85% with patients with lesser extend of disease having higher survival rates (9).

In a collaborative analysis of 27 trials by Prostate Cancer Collaborative group examining the outcomes of prostate cancer in men with advanced (18% of men) and metastatic (82%) prostate cancer received single agent androgen suppression or combined androgen therapy. Both treatment modalities have a five year survival rates of 25% and 26% respectively (26).

6.3.2 Watchful waiting

The MRC trial highlighted the risk of developing symptoms (pathological fractures, spinal cord compression), and even death from prostate cancer, without receiving the possible benefit from hormone treatment (21). Deferred treatment can be offered in patients who have strong will to avoid side effects of treatment however this patients need to be closely monitored. (2)

6.3.3 Radiotherapy

Brachytherapy should not be given in metastatic prostate cancer. Radiotherapy in metastatic prostate cancer is given as a palliative treatment to distant metastasis.

6.3.4 Radical prostatectomy:

This is not a treatment options for this group as the cancer has already extended beyond the pelvis. RP does not improve survival benefits in these patients.

6.3.5 Hormonal therapy

When prostate cells are deprived androgen, they undergo apoptosis therefore reducing cancer growth and size of metastasis. Hormonal therapy in metastatic cancer is given to reduce the amount of testosterone in the blood stream.

i. To palliate symptoms and to reduce the risk for potentially catastrophic consequences of advanced disease (spinal cord compression, pathological fractures, urethral obstruction, extra-skeletal metastasis)
ii. to defer progression to symptomatic stage and prevent serious disease progression-related complications in patients who are asymptomatic

Hormonal therapy can be achieved by:

i. Suppressing testicular androgens through medical or surgical castration
ii. inhibiting the action of the circulating androgens at the level of their receptor in prostate cells using anti androgens
iii. Combination of castration and inhibition of circulating androgens (complete androgen blockade).
iv. Intermittent androgen blockade: where androgen deprivation therapy is given with treatment breaks to minimise side effects and recently thought to reduce resistance of prostatic cancer cells to ADT.

Selection of treatment depends on the individual patient circumstances, response to disease and development of side effects. Patients may be able to tolerate adverse effect of one treatment as compared to the other.

a. <u>Monotherapy</u>

All monotherapy treatments for androgen deprivation therapy (orchidectomy, estrogens LHRH analogues and non-steroidal anti-androgens) were reported to have similar efficacy (27). Monotherapy treatment include the following

i. **Orchidectomy**: although still a gold standard of care, is not psychologically acceptable to most men
ii. **Oestrogens**: Although Estrogens were initially used for treatment of prostate cancer, their use has declined due to increased cardiovascular event. Estrogens may be used where LHRH agonists are contraindicated or if patients develop severe side effects. Although oestrogens are equally as effective as orchidectomy and LHRH agonist and cheaper, they should not be used as first line therapy due to increased risk cardiovascular events (2) (28) (29).
iii. **Luteinising hormone Releasing agonists**: These are synthetic analogues of luteinizing hormone given as depot injections or subcutaneous injection at 1,2, 3 and 6 months and thereafter every 6 months. Flare-up occurs in the first 2-3 days up to a week. Castration levels of should be achieved within 2-4 weeks. In order to minimise flare-ups LHRH antagonist can be offered with anti-androgens for 2 weeks if a patient is to be maintained only on LHRHa. LHRH agonists have become the preferred treatment in prostate cancer due

to lack oestrogen associated cardiotoxicity and they are acceptable to men as compared to orchidectomy.

iv. LHRH antagonist: LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. This seemingly more desirable mechanism of action has made LHRH antagonists very attractive. However, practical shortcomings have limited clinical studies. Many LHRH antagonists have been associated with serious and life threatening histamine-mediated side-effects and, until recently, no depot formulation was available. (2) The 2 existing LHRH antagonist (Degarelix and Aberalix) are not registered at MCC and therefore not considered PMB level of care.

v. Anti-androgens (Steroidal and non-steroidal:
Steroidal antiandrogens are synthetic derivatives of hydroxyprogesterone. In addition to peripherally blocking androgen receptors, Seroidal anti-androgens have progestational properties and inhibit the release of gonadotrophins (LH and FSH) and suppress adrenal activity. Since steroidal antiandrogens lower testosterone levels, the main pharmacological side-effects are loss of libido and erectile dysfunction, while gynaecomastia is quite rare. The non-pharmacological side-effects are cardiovasculartoxicity (4-40% for CPA) and hepatotoxicity.

Non-steroidal anti-androgens (bicalutamide, flutamide, nilutamide) competitively inhibit the binding of androgens to the androgen receptor; the serum testosterone levels are not suppressed and may even be raised. Compared to steroidal anti-androgens and LHRH agonist NSAA may spare some sexual function.

b. Combination treatment

Combined androgen Blockade consists of anti-androgen (long term) and LHRH agonist. Currently there is conflicting evidence on effectiveness of combined androgen deprivation therapy vs. monotherapy.

Prostate cancer trialist group reanalysed individual patient data from 27 RCT. Re-analysed data consisted of 8275 men and 88% had metastatic cancer and 12% locally advanced cancer. Men were randomised to combined androgen blockade or single agent. Five-year survival rates were 25% in men receiving CAB and 23% in men receiving single agent. The difference was not statistically significant (26).

A meta-analysis of 27 RCT by Samson et al, reported that CAB did not provide statically significant improvement in survival at 2 years, however at 5 years it provided statistically significant improvement in survival. The results at 5 years were based on 66% of the patient and 10 RCT. The study could be biased towards inflating the results as studies that did not report any significant statistical results were likely to be terminated early (30).

A study by HQAA indicated that compared to other monotherapy treatments, CAB is the least cost-effective. For it to be cost-effective it needs to be 20% more effective than monotherapy (31). Bayoumi et al also concurred with AHRQ that CAB is the least cost-effective of all androgen deprivation therapies ((32).

Combined androgen therapy cost far more than the 4 types of monotherapy treatments (DES, orchidectomy, LHRH agonist or NSAA).

Based on the above, CAB would not be considered a PMB level **of care for first line treatment of metastatic prostate cancer as it is not supported by strong evidence and is not cost-effective.** However, it may be provided as second line in a form of intermittent androgen blockade when a patient is not tolerating monotherapy due to side effects or when the patient progresses despite monotherapy.

Table 4: Procedure and ATC codes for management of prostate cancer

Clinical Category	***Description***	***Procedure / ATC code***	***Comment***
Hormonal therapy (Hormone sensitive disease)			
Androgen Blockade	LHRHa	L02AE	Advantages include intermittent use. Less cardio toxicity and more acceptable amongst men
	Anti-androgens	L02BB	
	Combined androgen blockade(CAB) (LHRHa plus antiangrogens)		Possible use for intermittent androgen blockade or if patient is not responding adequately to single agent blockade
	Triple Androgen Blockade		Not enough evidence that it is beneficial as compared to monotherapy
	Oestrogens	L02AA	Less favoured due to cardio-toxic effect, however may be considered when LHRHa are contraindicated
Intermittent Androgen blockade	Drugs as CAB regimen given intermittently		Used to minimise Side effects of androgen blockade. This is a PMB level of care provided patients provides patients did not respond to single agent and IAB is provided to minimise Side effects.
Surgical	Bilateral orchidectomy	2193	Unacceptable to most men, alternative interventions must be available
	Corticosteroids	H02	

Symptomatic management of cancer complication should aim at relieving acute symptoms and chronic symptoms that may result in distress as well as adequate pain management. Below is a list of symptoms of advanced disease and recommended management:

Table 5: Management of side effects associated with ADT

Hormonal therapy	Side-effects	Management
Non-steroidal Anti-androgens	Gynaecomastia and breast tenderness incidence of hot flushes, loss of libido and impotence was significantly lower than expected for luteinising hormone-releasing hormone (LHRH) agonists and CAB Liver abnormalities Androgen spare bones better as compared to LHRH analogues	If on monotherapy, change to LRHR analogues if not contraindicated Liposuction/ Breast tissue excision (**This is not PMB level of care)** Analgesia for pain Irradiation for pain ALT should be monitored at 3 monthly interval and complete liver function tests only done when ALT is abnormal-(ALT has been shown to be a good predictor of liver dysfunction and is cost-effective for screening of liver

		disease).
LHRH analogues	sexual desire, impotence, hot flashes and the development of osteoporosis	May provide intermittent androgen deprivation therapy or consider non-steroidal anti-androgen monotherapy.

Table 6: Side effects associated with Hormonal replacement therapy and management

Side -effect	**Hormonal therapy**	**Treatment**
Sexual dysfunction	Prevalence of sexual dysfunction is higher in patients receiving LHRH agonist as compared to those receiving anti-androgens	Treatment is non-specific. Monotherapy with NSAA may be initiated however provider need to do a risk benefit analysis as LHRH offer better survival rates than NSAA monotherapy
Hot-flushes	The incidence of hot flushes is lower in patients receiving anti-androgen monotherapy as compared to LHRH agonist and CAB	Hormonal therapy: Oestrogen receptor modulators (DES) and progesterone-based treatment (e.g. megestrol acetate, medroxy-progesterone acetate, and CPA
		Antidepressant: Selective-Serotonin reuptake inhibitors have been shown to reduce hot-flashes. This is based on observational studies. (33) (34) (35)
Non-metastatic bone fractures		All patients on ADT must receive prophylactic biophosphonates Denosumab is a new monoclonal antibody and not registered with MCC therefore not a PMB level of care
Obesity and metabolic syndrome	ADT is associated with obesity and increased risk of metabolic syndrome.	Men must be encouraged to modify lifestyles to prevent metabolic syndromes associated with ADT. Please note that referral to dietician or biokineticist are not a PMB level of care. Screening for hyperglycaemia and hypercholestrolaemia is a PMB level of care at a primary health care setting when provided by a community health nurse or GP. Hypercholesterolemia, hypertension and Diabetes mellitus type 2 will be managed as per published regulations in the medical scheme act.

Table 7: Complications of metastatic prostate cancer and recommended treatment

Local symptoms	***Treatment modality***
Local pain	External beam radiotherapy analgesia (opiods plus adjuvant antidepressant; anti-seizure and NSAIDS)
Spinal cord compression	This is an emergency condition and patients must have an MRI , steroidal treatment and Surgery and/or radiotherapy
Urethral compression	Urethral catheter or TRUP
Diffuse pain	Hormonal therapy/chemotherapy
Inflammatory syndrome	Steroids and NSAIDS
Bone metastasis	Biophosphonates can be used in patients with osseous masses to prevent complication. The benefits of biophosphonates must be weighed against the risk of side-effects.

6. Level o f care of follow-up post prostate cancer treatment

7.1 Follow-up post radical prostatectomy:

Once the patients are stable from all surgery related complications and have reached desirable PSA levels, patients may be referred back to GP for routine laboratory and clinical monitoring. Patients are to be referred back to specialist once the PSA increases and when they develop physical symptoms suggestive of progressive disease

7.2 Follow-up post radiotherapy:

It may take as long as 3 years for PSA to reach nadir levels post radiotherapy. In patients whom PSA is satisfactory, patients may be managed at the Primary health care level by general practitioner.

Since the risk of failure is high in the first year, it is recommended that patients remain with the urologist for first year and all stable patients be referred to PHC from 2nd year on wards.

Please note that the scheduled follow-up may not be suitable for patients with undifferentiated tumours, positive margins and high risk localised tumours.

Table 8: Procedure codes for follow-up of prostate cancer

	Description	***Procedure code***	***Comment and frequency***
Consultation	General practitioner, Oncologist , Urologist	0190,0191,0192	With urologist at 6 weeks post-treatment, 3,6 and 12 months in the first year. Every 6 months until end of Year 2. Stable patient with localised prostate should be referred for continuous monitoring with GP when they are stable after 2 years however patients with advanced and metastatic cancer should be followed up by a urologist. A standard of
Examination	Digital rectal examination		As part of consultation
Blood test	PSA	4524	At 6 weeks, and thereafter every 6 months for 2 years then annually for a life-time.
	Alkaline phosphate	3240	As a first line to screen for possible metastasis. When metastasis are suspected
	Creatinine	4001	As a first line to screen for possible obstructive renal symptoms
Imaging	MRI, CT scan, Bone scan	4032	Not routinely recommended for stable but may be requested to diagnose suspected local spread or bone metastasis

7.3 Follow-up after hormonal treatment

This follow-up is recommended to a typical patient with advanced or metastatic disease. Patients with hormone refractory disease may require individualised follow-up plan.

Action		**Comments**	**Frequency**
Clinical follow-up	Urologist (this patients should never be referred to PHC)	Patients on ADT for advanced and metastatic disease should never be managed at PHC setting. There is no need to attend specialist for injections. This	Monthly for the first 3 months, then 3- 6 monthly for the first year. Patients with Stage M0 disease can be reviewed every 6 months and patients with stage M1

		can be provided at PHC or by a professional nurse based at the pharmacy provided the skills exist. However if the injection is due at the same date as urologist, then urologist can provide depot injections to minimise patient movement	disease every 3 months
PSA	4524	PSA is still a good marker to follow response to treatment. In patients with Metastatic cancer trends in PSA values indicate response to treatment. There is no cut-off point to indicate when the treatment is not working however an increase trend may indicate poor response to treatment whilst decreasing PSA indicate good response to treatment	At 6 weeks, 3 months, 6 and 12 months
Creatinine	3629	When a patient has urinary tract obstruction	6 monthly
ALT	4131	As a screening test for liver related side effects. When ALT is abnormal liver function tests may be requested. Should be done every 6 months or when patient symptomatic	6 monthly
Haemoglobin	3705	This is done to assess disease progression or side effects of hormonal treatment.	6 monthly
Bone scan		Bone scan should not be routinely offered to asymptomatic patients. When patient present with symptoms X-rays may be requested for each specific site	
Alkaline Phosphatase	3789	This can be requested in patient with M1b as it is not affected by PSA	
Testosterone	4501		Can be done at 4 weeks post ADT and then at 6 months. There after it can only be requested if PSA is rising to confirm that cancer is castrate

			resistant
Monitoring of metabolic complications		Fasting Blood glucose, Fasting total cholesterol, weight measurement , BP measure Glucose tolerance tests if indicated	6 monthly

7. Management of relapsed cancer after intention to cure treatment

Treatment failure is defined as

i. Progression to metastatic disease or
ii. Recurrence on digital rectal examination or
iii. two consecutive values of PSA > 0.2 ng/mL in patients post radical prostatectomy or PSA increase is **>** 2 ng/mL higher than the PSA nadir (post-radiotherapy value)

Definition of local and systemic failure (2)

- Local failure following RP is predicted with an 80% probability by PSA increase > 3 years after RP, a PSA DT **>** 11 months, a Gleason score **<** 6, and stage **<** pT3a pN0,.
- Systemic failure following RP is predicted with > 80% accuracy by a PSA increase < 1 year after RP, a PSA DT of 4-6 months, a Gleason score of 8-10, and stage pT3b, pTxpN1.
- Local failure after radiotherapy is documented by a positive prostatic biopsy and negative imaging studies.
- Prostatic biopsy after radiotherapy is necessary only if local procedures such as salvage prostatectomy are indicated in an individual patient.

8.1 Work-up after intention to cure treatment

Investigation	Comment
Prostatic biopsy or prostatic bed biopsy	Omit prostate biopsy post radiotherapy
CT scan or MRI scan	To exclude metastasis. However due to low predictive values as low PSA scans are recommended when PSA level is more than 20ng/ml (2)
Endorectal MRI	Ideally this procedure should only provided in men who have had radiotherapy and have no metastasis. It is done to assess whether a patient is a candidate for radical prostatectomy with an intention to cure. This treatment is **not** PMB level of care until it can be shown that it is more sensitive and cost-effective as compared to the biopsy of the prostate.
Bone scan	To exclude metastasis. However due to low predictive values as low PSA scans are recommended when PSA level is more than 20ng/ml (2)
Positron emission tomography	Not PMB level of care. Not sufficient data and the uptake of 11C-choline is not specific for Prostate Cancer and may sometimes be due to inflammatory intraprostatic lesions.
Immunoscintigraphy	Not a PMB level of care as the diagnostic modality is still experimental.

8.2 Treatment options for treatment failure

8.2.1 Treatment options post radical prostatectomy

i. Salvage radiotherapy: Salvage radiotherapy to the prostatic bed may be offered to patients with local recurrence post radical prostatectomy.

ii. Androgen blockade: This can be offered as neo-adjuvant or adjuvant to External beam radiation in local recurrence. Androgen blockade can be offered to patients with systemic spread to improve survival and disease progression.

iii. Watchful waiting: This is an option in patients who have contraindications to radiotherapy OR with in asymptomatic patients with suspected systemic spread with an intention of delaying hormonal therapy.

8.2.2 Treatment options for treatment failure post Radiotherapy

i. *Salvage Brachytherapy*: use of salvage brachytherapy in patients who received EBRT is not supported by evidence; therefore this is not a PMB level of care.
ii. *Radical prostatectomy*: RP can be offered in carefully selected patients with local recurrence. It is especially suitable in patients with a low co-morbidity, a life expectancy of at least 10 years, an organ-confined cancer < T2, Gleason grade < 7, and pre-surgical PSA < 10 ng/mL
iii. *Watchful waiting:* This is an option in patients who have contraindications to radiotherapy OR with in asymptomatic patients with suspected systemic spread with an intention of delaying hormonal therapy
iv. *Androgen blockade:* This can be offered as neo adjuvant to Radical prostatectomy as there is evidence that it reduces positive margins. Androgen blockade can be offered to patients with systemic spread to improve survival and disease progression. The median survival time for Androgen Blockade is 6 years –meaning that 50% of patients survived up to 6 years.

8.3 Management of hormone refractory prostate cancer

Hormone refractory prostate cancer is defined as disease progression evidenced by a progressively rising PSA (three consecutive rises of at least 10% each or three rises that involve an increase of 50% over the nadir PSA) or an increase in tumor mass on bone scan, X-ray, CT scan or MRI despite a castrate level of testosterone (T<20 ng/dl)

Treatment options for hormone refractory cancer

i. Hormonal approaches which may include combination therapy
ii. Antiandrogen substitution
iii. Antiandrogen removal
iv. Secondary hormonal manipulation
v. Chemotherapy

8. Management of side effects associated with prostate cancer treatment

Table 9: Management of side effects of treatment for prostate cancer

Clinical Category	*Description*
Radiation induced Gastro-intestinal injury	Steroid enema
Erectile dysfunction: nerve sparing surgery, penile rehabilitation	PDE5 inhibitors in early post-recovery period including Intracarvenous therapy (Maximum 3 months) a Nerve sparing surgery-PMB should not attract extra cost as compared to standard prostatectomy Vacuum constriction device (Non-PMB Penile prosthesis as a last resort (Non-PMB)
Stricture	Dilatation, Urethretomy
Incontinence	Pelvic floor exercise Injection Bulking agents Alpha stimulants, anticholinergics Urethral occlusion devices, artificial sphincter
Urinary retention	Alpha blockers, TURP could be performed 6-8 months post brachytherapy
Gynecomastia due to hormonal treatment	Sub-areolar mastectomy or radiotherapy
Hot flushes	Cyproterone acetate, Bicalutamide monotherapy, Intermittent (Androgen deprivation Therapy (ADT), Clonidine
Depression	Antidepressants as per scheme formulary
Osteoporosis related to ADT	Biphosphonates
Bone metastasis	Biphosphonates
Lymphoedema	Occupational therapy and/or physiotherapy

Annexure A: Possible procedure codes for diagnosis and management of prostate cancer

NHRPL	NHRPL Description
0190	New and established patient: Consultation/visit of new or established patient of an average duration and/or complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on
0191	New and established patient: Consultation/visit of new or established patient of a moderately above average duration and/or complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with
0192	New and established patient: Consultation/visit of new or established patient of long duration and/or high complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on
2565	Implantation hormone pellets (excluding after-care)
3001	Implantation of pellets (excluding cost of material) (excluding after-care)
5033	Percutaneous cystostomy in radiology suite
5035	Urethral balloon dilatation in radiology suite
5037	Urethral stenting in radiology suite
1945	Instillation of radio-opaque material for cystography or urethrocystography
1989	Cystometrogram
1993	Voiding cysto-urethrogram
3610	Transrectal ultrasonographic prostate volume study for prostate brachytherapy (own equipment)
3627	Ultrasound examination includes whole abdomen and pelvic organs, where pelvic organs are clinically indicated (including liver, gall bladder, spleen, pancreas, abdominal vascular anatomy, para-aortic area, renal tract, pelvic organs)
3628	Renal tract ultrasound
5100	Pelvic organs ultrasound: Transvaginal or trans rectal probe

Annexure B : In-Hospital Diagnostic procedure codes

NHRPL	NHRPL Description
0305	Needle biopsy - soft tissue
1441	Excision of lymph node for biopsy: Groin
1945	Instillation of radio-opaque material for cystography or urethrocystography
1949	Cystoscopy: Hospital equipment
1963	With fulguration or treatment of minor lesions, with or without biopsy
1969	And cold biopsy
1971	With cryosurgery for bladder or prostatic disease
2235	Biopsy prostate: Needle or punch, single or multiple, any approach
2237	Biopsy prostate: Incisional, any approach
2493	Diagnostic laparoscopy (excluding after-care)
2499	Laparoscopy: Plus biopsy (excluding after-care)
5094	Cutting needle biopsy with image guidance

Annexure B: In-Hospital treatment procedures

0109	Hospital follow-up visit to patient in ward or nursing facility - Refer to general rule G(a) for post-operative care) (may only be charged once per day) (not to be used with items 0111, 0145, 0146, 0147 or ICU items 1204-1214)
0173	First hospital consultation/visit of an average duration and/or complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on behalf of the patient (not appropriate for
0174	First hospital consultation/visit of a moderately above average duration and/or complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on behalf of the patient (not
0175	First hospital consultation/visit of long duration and/or high complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on behalf of the patient (not appropriate for p
0151	Pre-anaesthetic assessment: Pre-anaesthetic assessment of patient (all hours). Problem focused history and clinical examination and straightforward decision making for minor problem. Typically occupies the doctor face-to-face with the patient for between
0152	Pre-anaesthetic assessment: Pre-anaesthetic assessment of patient (all hours). Detailed history and clinical examination and straightforward decision making and counselling. Typically occupies the doctor face-to-face with the patient for between 20 and 35
0153	Pre-anaesthetic assessment: Pre-anaesthetic assessment of patient or other consultative service. Consultation with detailed history, complete examination and moderate complex decision making and counselling. Typically occupies the doctor face-to-face for
0316	Fine needle aspiration for soft tissue (all areas)
1408	Placement of Hickman catheter or similar
1451	Radical excision of lymph nodes of groin: Ilio-inguinal
1453	Radical excision of lymph nodes of groin: Inguinal
1455	Retroperitoneal lymph adenectomy including pelvic, aortic and renal nodes
1809	Laparotomy
1927	Uretero-neo-cystostomy: Unilateral
1929	Uretero-neo-cystostomy: Bilateral
1931	Uretero-neo-cystostomy: With Boariplasty
1951	And retrograde pyelography or retrograde ureteral catheterisation: Unilateral or bilateral
1955	And bilateral ureteric catheterisation with differential function studies requiring additional attention time
1964	And control of haemorrhage and blood clot evacuation
1976	Optic urethrotomy
1981	Internal urethrotomy: Male
1986	Transurethral resection of bladder neck: Male
1999	Percutaneous cystostomy

2001	Total cystectomy: After previous urinary diversion
2003	Total cystectomy: With conduit construction and ureteric anastomosis
2005	Cystectomy with substitute bowel bladder construction with anastomosis to urethra or trigone
2006	Cystectomy with continent urinary diversion (e.g. Kocks Pouch)
2009	Radical total cystectomy with block dissection, ileal conduit and transplantation of ureters
2015	Suprapubic cystostomy
2021	Vesico-plication (Hamilton Stewart)
2035	Cutaneous vesicostomy
2037	Cystoplasty, cysto-urethraplasty, vesicolysis
2049	Evacuation of clots from bladder: Other than post-operative
2050	Evacuation of clots from bladder: Post-operative
2053	Bladder neck plasty: Male
2063	Dilatation of urethra stricture: By passage sound: Initial (male)
2065	Dilatation of urethra stricture: By passage sound: Subsequent (male)
2067	Dilatation of urethra stricture: By passage sound: By passage of filiform and follower (male)
2083	Reconstruction or repair of prostatic or membranous urethra: First stage
2085	Reconstruction or repair of prostatic or membranous urethra: Second stage
2086	Reconstruction or repair of prostatic or membranous urethra: If done in one stage
2088	Peri-urethral teflon injection: Male or female - fee as for cystoscopy (item 1949) plus 42,00 clinical procedure units
2093	Total urethrectomy: Male
2191	Orchidectomy (total or subcapsular): Unilateral
2193	Orchidectomy (total or subcapsular): Bilateral
2243	Trans-urethral cryo-surgical removal of prostate
2245	Trans-urethral resection of prostate

2247	Trans-urethral resection of residual prostatic tissue 90 days post-operative or longer
2251	Prostatectomy: Perineal: Sub-total
2253	Prostatectomy: Perineal: Radical
2254	Pelvic lymph adenectomy
2255	Supra-pelvic, transversical
2257	Retropubic: Sub-total
2259	Retropubic: Radical
2260	Prostate brachytherapy
2496	Laparoscopy: Plus aspiration of a cyst (excluding after-care)
2499	Laparoscopy: Plus biopsy (excluding after-care)
2551	Laparotomy
2802	Procedures for pain relief: Peripheral nerve block
2803	Alcohol injection in peripheral nerves for pain: Unilateral
2805	Alcohol injection in peripheral nerves for pain: Bilateral
1995	Percutaneous aspiration of bladder
1996	Bladder catheterisation: Male (not at operation)
2051	Simple bladder lavage: Including catheterisation
2063	Dilatation of urethra stricture: By passage sound: Initial (male)
2065	Dilatation of urethra stricture: By passage sound: Subsequent (male)
2067	Dilatation of urethra stricture: By passage sound: By passage of filiform and follower (male)
1995	Percutaneous aspiration of bladder
1996	Bladder catheterisation: Male (not at operation)
2051	Simple bladder lavage: Including catheterisation
2063	Dilatation of urethra stricture: By passage sound: Initial (male)

2065	Dilatation of urethra stricture: By passage sound: Subsequent (male)
2067	Dilatation of urethra stricture: By passage sound: By passage of filiform and follower (male)
43215	Ultrasound transrectal prostate volume for brachytherapy

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