

SOUTH AFRICAN PROSTATE CANCER GUIDELINES

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INTRODUCTION

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Disclaimer

This document is a holistic outline of clinical, screening and evaluation recommendations in the management of prostate cancer to be utilised in a South African context. The document has been compiled by members of The Prostate Cancer Foundation's Medical and Scientific Advisory Board. It is not to be used as a reference for any academic publications or dissertation purposes and is loosely based on summaries of the latest EAU, NCCN, AUA, NICE and ABS guidelines. Additional references are listed at the end of each section for convenience.

International guidelines used as references

EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

Available at: <https://uroweb.org/guidelines/prostate-cancer/summary-of-changes/2023>

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Prostate Cancer, Version 4.2023 — September 7, 2023. Available at:

https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

American Urological Association Guidelines:

Available at: <https://www.auanet.org/guidelines-and-quality/guidelines/oncology-guidelines/prostate-cancer>

Prostate cancer: diagnosis and management

NICE guideline [NG131] Published: 09 May 2019 Last updated: 15 December 2021.

Available at: <https://www.nice.org.uk/guidance/ng131>

American Brachytherapy Society prostate low-dose rate task group guidelines.

Available at: <https://www.americanbrachytherapy.org/consensus-statements/brachytherapy-guidelines-and-consensus-statements/>

List of abbreviations

ARPI – androgen receptor pathway inhibitor
 ASAP – atypical acinar proliferation
 5ARI – 5 alpha reductase inhibitors
 BS – 99mTc-methylene diphosphonate - (MDP) bone scan
 BT – brachytherapy
 BMD – Bone mineral density
 CAT – computed axial tomography
 CLD – clinically localised disease
 CRPC – castrate resistant prostate cancer
 DRE – digital rectal examination
 ERBT – external beam radiation therapy
 GS – Gleason score
 HRPc – high risk prostate cancer
 HSPC – hormone-sensitive prostate cancer
 HRPc - hormone-resistant prostate
 IB – interstitial brachytherapy
 IRPc – intermediate risk prostate cancer
 LHRH – luteinizing hormone releasing hormone
 LND – lymph node dissection
 LRPc – low risk prostate cancer
 nmHSPC – non metastatic hormone sensitive prostate cancer
 mHSPC – metastatic hormone sensitive prostate cancer
 MRI – magnetic resonance imaging
 OS – overall survival
 PCa – prostate cancer
 PCA3 – prostate cancer antigen 3
 PET/CT – positron emission tomography/computed tomography
 PSA – prostate specific antigen
 RP – radical prostatectomy
 RALP – robotic assisted laparoscopic prostatectomy
 RS – risk stratification for localised prostate cancer
 RT – radiation therapy
 SI – staging investigations
 SPCa – castrate sensitive prostate cancer
 T – tumour stage
 TTP – time to progression
 TRUS – trans rectal ultrasound scan
 WW – watchful waiting

Background

Prostate cancer (PCa) is the commonest non cutaneous cancer in men worldwide with an estimated annual incidence between 39-300/100 000 men.

PCa is the most common cancer affecting South African men and has the second highest mortality rate after lung cancer (Globan 2020) with incidence rates of 61.8 per 100 000 although this probably underestimates the incidence as it is based on outdated data from a pathology based National Cancer Registry. Actuarial predictions forecast that PCa will be the most common cancer in South Africa by 2030.

South African males are in the highest quartile of incidence and are more likely to develop metastases and less likely to be cured of low stage prostate cancer. Black South African males also present with higher PSA levels and histopathological tumour grade compared with Black Americans, which is further escalated in men from rural localities.

Compared to white males, Black African males have a 60% higher risk for PCa and are 2.5 times more likely to die from the disease.

Research shows that many South African men living in rural areas have never heard of PCa. This is of concern as this is the highest risk group in SA for aggressive PCa.

Dramatic developments in diagnostic and therapeutic modalities have led to significant changes in the diagnosis and treatment of PCa in the past twenty years.

Aims, Scope and Usage of these guidelines

The management of PCa is complex and these guidelines serve as a framework for the diagnosis and treatment of the disease in South Africa with reference to internationally accepted norms. Whilst these guidelines have been based on the best international evidence available, they include reference to South African studies and to treatments modalities that may no longer appear in major society guidelines where they have been replaced by newer superior treatments. Many of these older treatments are still applicable to clinical practise in South Africa as they are often the only treatments available in resource constrained settings.

The highest possible Levels of Evidence (LOE) and Grades of Recommendation (GOR) currently available have been strived for in the preparation of this document. However, due to the dynamic nature of cancer research in general some LOE and GOR may not be the highest due to lack of data. To make the document less cumbersome the exact LOE and GOR are not always listed.

Whilst Guidelines can never replace clinical expertise when making treatment decisions for individual patients, they can help focus decision making. The Individual needs and preferences of patients and their families should always be considered. Patients have a right to be involved in discussions about their care and they should be provided with sufficient information to make an informed decision.

Conclusions & Recommendations

PCa is the commonest cancer in men in South Africa (SA) and causes a significant amount of morbidity and mortality. A lack of awareness about PCa and a lack of access to screening are the most likely reasons for the high rates of South African men who present with de novo metastatic PCa in South Africa. To attempt to offset the health risks of PCa, knowledge on the condition needs to be expanded, not just to health care providers but also to the general public. Information about the benefits of age and risk appropriate screening needs to be freely available. The current lack of urological and oncological resources at state healthcare facilities needs to be addressed to ensure

that a reasonable standard of care can be provided to South African men who are diagnosed with PCa.

Patient participation in clinical trials constitutes good clinical practice. Treating physicians should therefore not allow preconceived opinions or other biases to prevent them from encouraging their patients to participate in clinical trials.

Concepts in PCa are continually evolving as new evidence becomes available, so these guidelines and recommendations should be a living document with regular revision and updates.

PREVENTION AND RISK FACTORS

A healthy lifestyle is the backbone of prevention for the vast majority of cancers and must be given as generic advice. ^[3,4,5,6]

Race

Black African men have a 60% higher risk for PCa and are approximately 2.5 times more likely to die from their disease than white males. They are also more likely to develop metastases and less likely to be cured of low stage PCa. Black South African males also present with higher PSA levels and histopathological tumour grade compared to Black Americans males, which is further escalated in men from rural localities.

Family history/hereditary prostate cancer and Genetic Testing Guidelines

Men with a family history of PCa have a higher incidence of PCa compared to men from the general population. Evidence suggests a spectrum of risk, with at least a two-fold increase and worsening risk with the number and closeness (i.e., first degree) of relatives affected.

There is also an inherent relation between PCa and breast cancer. An incident of one in a family increases the risk of developing the other. So, men with a family history of breast cancer have an increased risk of PCa.

Genetic testing guidelines for prostate cancer:

Genetic testing should be considered in appropriate individuals where it is likely to impact the prostate cancer treatment, including use of targeted therapies, management of risk of other cancers, and/or management of potential risk of cancer in family members. Locally, genetic testing is funded by medical aids if a strong motivation is provided. Pre- and post-test genetic counselling is an integral part of the process to ensure the appropriate genetic test is requested, as well as the accurate interpretation and understanding of results.

Men who have not been diagnosed with prostate cancer should be cautioned that undergoing genetic testing and testing positive for a mutation in a cancer-associated gene, may have an impact on certain insurance policy premiums and/or exclusions. Therefore, these policies should ideally be in place prior to undergoing genetic testing. Genetic testing is unlikely to have an impact on the insurance policies of men who have been diagnosed with prostate cancer.

There are two types of genetic tests, germline and somatic. Germline testing is performed on blood or saliva samples and identifies inherited genetic mutations. Somatic testing is performed on the tumour tissue and identifies genetic mutations that occur in the cancer cells. These somatic genetic mutations can either occur in the cancer cells only or can be inherited.

If germline testing indicates a therapeutic target, somatic testing is not indicated. If germline genetic testing is normal (no gene variants identified), somatic genetic testing is still indicated to identify possible therapeutic targets. Germline genetic testing should be considered if there is a suspicion of an inherited prostate cancer syndrome, regardless of somatic test results.

It is important to refer to a genetic counsellor if a germline and/or somatic mutation (pathogenic/likely pathogenic variant) is identified to facilitate cascade testing for family members. If there is a strong family history of cancer, but no pathogenic variant or a variant of uncertain significance (VUS) is identified, a referral to a genetic counsellor is recommended to ensure the accurate understanding of familial implications and to review indications for additional genetic testing and/or cancer surveillance and/or follow-up.

Germline genetic testing:

Germline genetic testing should be considered for men that meet one or more of the following criteria (adapted from NCCN and EAU guidelines):

- Unaffected men with:
 - A strong family history of prostate cancer, especially metastatic prostate cancer and/or prostate cancer diagnosed at an age younger than 60 years and/or family members who died from prostate cancer
 - A strong family history of cancer, especially the following: female and male breast, endometrial, melanoma, colorectal, ovarian, pancreatic, upper tract urothelial, glioblastoma, biliary tract and small intestinal cancer
 - A family member(s) with a known high-risk germline mutation
- Men diagnosed with prostate cancer who:
 - Are diagnosed at the age of 60 years or younger
 - Are diagnosed with metastatic, regional (node positive), very-high-risk localised, high-risk localised, intermediate-risk with intraductal/cribiform histology prostate cancer at any age
 - Have a history of other primary cancer(s)
 - Have a strong family history of males diagnosed with metastatic prostate cancer at any age or who died from prostate cancer
 - Have a strong family history of cancer, especially the following: female and male breast, endometrial, melanoma, colorectal, ovarian, pancreatic, upper tract urothelial, glioblastoma, biliary tract and small intestinal cancer
 - Are of Ashkenazi Jewish and/or Afrikaner ancestry
 - Have a family member(s) known to have a high-risk germline mutation

If germline genetic testing is requested, it is recommended that the gene panel includes at least the following genes: BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6 and PMS2. Additional genes may be appropriate depending on the clinical context and family history of the patient. The HOXB13 gene will not lead to any therapeutic benefit but is important to determine the risk of prostate cancer for family members.

If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional (genetic counsellor and/or medical geneticist) is recommended. Individuals who carry germline mutations in prostate cancer risk genes may have an elevated lifetime risk of prostate cancer. Certain genes also lead to an elevated risk for early onset and/or potentially lethal prostate cancer (like the BRCA2 gene). Such risk genes include, but are not limited to BRCA2, BRCA1, ATM, CHEK2, PALB2, HOXB13, MLH1, MSH2, MSH6, PMS2, EPCAM, and TP53 (NCCN prostate screening guidelines). It is recommended that men who carry these mutations commence with prostate cancer screening at an earlier age depending on the gene and family history (NCCN prostate screening guidelines). See table no 1 with regards to prostate-cancer associated genes/inherited cancer syndromes, the associated cancer risks as well as the current prostate cancer screening recommendations for each.

Table 1: Prostate-cancer associated genes/inherited cancer syndromes and current prostate cancer screening recommendations

Gene/Inherited cancer syndrome	Lifetime risk for prostate cancer	Prostate cancer screening recommendations	Risk for other cancers
HOXB13	22-52% by age 80 yrs 10-fold risk for early onset	Baseline PSA level blood test at the age of 40 years (or 10 years prior to the youngest age of onset of prostate cancer in the family). PSA level blood testing every year (or as dictated by the baseline PSA). To consider digital rectal examination if PSA level of concern.	Currently no conclusive evidence to suggest increased risk for other cancers. One study that suggests a possible slight increased risk for basal cell carcinoma as well as rectal and sigmoid colon cancer in men, but findings have not been reproduced by other researchers (PMID: 32830201).
BRCA1	21% by age 74 yrs 29% by age 85 yrs	Consider annual PSA screening starting from the age of 40 years (or 10 years younger than youngest age of onset). Consider digital rectal examination when PSA testing done.	Female breast: 53-78% Male breast: 1-2% Ovarian: 39-65% Pancreatic: 1-4% Possible risk: melanoma
BRCA2	27% by age 75 yrs 60% by age 85 yrs	Consider annual PSA screening starting from the age of 40 years (or 10 years younger than youngest age of onset). Consider digital rectal examination when PSA testing is done.	Female breast: 44-80% Male breast: 6-8% Ovarian: 11-46% Pancreatic: 3-9% Melanoma: elevated

Lynch syndrome: MLH1 MSH2 MSH6 PMS2 EPCAM	By age 80 yrs: MLH1: 4.4-13.8% MLH2: 3.9-23.8% MSH6: 2.5-11.6% PMS2: 4.6-11.6% EPCAM: 3.9-23.8%	Consider risk based on LS gene and family history. Consider beginning shared decision-making about prostate cancer screening at age 40 years and consider screening at annual intervals rather than every other year.	Gene dependant: Colorectal: 12-75% Endometrial: 12-57% Ovarian: 2-38% Renal pelvis/ureter: 5-28% Stomach/ small bowel: 2-16% Bladder: 1-13% Brain: 1-8% Female breast: 8-11% Pancreatic: 1-6% Possible risk: benign skin tumours
ATM	26-44% by age 80 yrs	Consider annual PSA screening starting from the age of 40 years (or 10 years younger than youngest age of onset). Consider digital rectal examination when PSA testing is done.	Ovarian: elevated Female breast: 17-52% Pancreatic: 5-10% Possible risk: colorectal, stomach and melanoma
CHEK2	Elevated	Consider annual PSA screening starting from the age of 40 years (or 10 years younger than youngest age of onset). Consider digital rectal examination when PSA testing done.	Female breast: 25-39% Male breast: 0.4-1% Colorectal: elevated Possible risk: melanoma and thyroid
NBN	Elevated	Consider annual PSA screening starting from the age of 45 years (or 10 years younger than youngest age of onset).	Possible risk: ovarian

		Consider digital rectal examination when PSA testing done.	
PALB2	Elevated	Family history dependent.	Female breast: 17-53% Male breast: 1% Ovarian: 5% Pancreatic: 2-3%
BRIP1	Elevated	Family history dependent.	Female breast: 20% Ovarian: 8% Possible risk: pancreatic
RAD51C	Elevated	Family history dependent.	Ovarian: 5-9% Possible risk: female breast
RAD51D	Elevated	Family history dependent.	Ovarian: 7-12% Possible risk: female breast
Li-Fraumeni syndrome: Tp53	Elevated	Consider risk based on family history. Consider annual PSA screening starting from the age of 40 years. Consider digital rectal examination if PSA is raised.	Predisposition to all neoplasms Overall cancer risk by 70 yrs: - Male: 79-95% - Female: 82-100%

Somatic genetic testing:

Due to the availability of targeted therapies; tumour molecular and biomarker analysis is important for treatment decision-making. About 89% of metastatic castration-resistant prostate cancer tumours will contain a potentially actionable genetic mutation, of which only 9% will occur in the germline. Therefore, somatic genetic testing is recommended for all men with metastatic prostate cancer regardless of germline genetic test results, age of diagnosis and family history.

It is recommended to include the following in somatic testing:

- Tumour testing for mutations in homologous recombination DNA repair genes, such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12. If pathogenic/likely pathogenic variant identified, refer for post-test genetic counselling to assess presence in germline and risk for other associated cancers for patient and cancer risk for family members.

- Tumour testing for microsatellite instability (MSI) or deficient mismatch repair (dMMR) is recommended. If MSI-H or dMMR found, refer for post-test genetic counselling to assess possibility of Lynch syndrome.

Other Risk Factors

Obesity

Obesity is associated with lower risk of low-grade PCa, but an increased risk of high-grade PCa and mortality.

Dietary factors

There is insufficient high-level evidence to make dietary recommendations, however there is strong evidence between certain dietary factors and the risk for other cancers and health problems. Men should be encouraged to follow a healthy eating plan.

Table 2. Dietary factors and their association with prostate cancer, other cancers and other common diseases affecting men

Food type	Association with prostate cancer
Alcohol	High alcohol intake and no alcohol intake have been associated with a higher risk of PcA and PCa-specific mortality. This is similar to the risk for cardiovascular disease. Alcohol intake increases the risk for colorectal cancer
Coffee	Coffee consumption may be associated with a reduced risk; with a pooled RR of 0.91 for the highest category of coffee consumption
Dairy products	There is some weak evidence between the high intake of protein from dairy products and the risk of PCa
Fat	Consumption of long-chain omega-3 poly-unsaturated fatty acids has not been shown to increase the risk for PCa. A relation between intake of fried foods and the risk of PCa may exist. Many fried foods contain hydrogenated fats which increase the risk for cardiovascular disease
Meat	Meta-analyses show a potential association between the consumption of red meat, the total amount of meat consumed and the consumption of processed meat. The consumption of red meat and processed meat are associated with an increased risk for colorectal cancer.
Soy (Phytoestrogens [isoflavones/ coumestans])	There is conflicting evidence. In one meta-analyses Phytoestrogen intake was significantly associated with a reduced risk of PCa. Total soy food intake has been associated with a reduced risk of PCa, but also with an increased risk of advanced disease
Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease
Vitamin E Selenium	Taking Selenium and Vitamin E supplements have not been shown to affect PCa incidence

Adapted from EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

5-alpha-reductase inhibitors (5-ARIs)

In the initial results of the Prostate Cancer Prevention Trial (PCPT) released in 2003 finasteride was shown to reduce the risk for PCa by 25%. Additional analyses published in 2013 showed that this increased to a 30% risk reduction, however this risk reduction was only for low-grade cancers. Although men who developed prostate cancer while taking finasteride were more likely to have high-grade cancers, the increase is thought to be due to better detection of disease rather than being caused by the drug.

In the PCPT, men taking finasteride reported more sexual side effects than men on the placebo. However, men on finasteride were also less likely to experience urinary symptoms such as urgency/frequency of urination or incontinence and were less likely to need surgery for prostate enlargement.

Finasteride is effective in the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia but is not currently be indicated for the prevention of PCa.

Adapted from Prostate Cancer Prevention Trial (PCPT): Questions and Answers. Available at: <https://www.cancer.gov/types/prostate/research/prostate-cancer-prevention-trial-qa>

Testosterone

Men with hypogonadism receiving testosterone supplementation therapy do not have an increased risk of PCa.

Cigarette smoking

Current cigarette smoking increases the risk of death from PCa and the likelihood of having an aggressive tumour type with a worst prognosis, even after smoking cessation.

Exposure to sunlight

Ultraviolet radiation exposure decreases the risk of PCa but prolonged exposure increases the risk for basal cell and squamous cell cancers.

Ejaculation Frequency

Men who ejaculate more than 21 times throughout adult life have a 20% reduced risk for PCa vs men who ejaculate 4 to 7 times a month.

Screening for Prostate Cancer (PCa)

Screening of asymptomatic men in the primary care setting

Screening of asymptomatic men reduces PCa mortality rates and reduces the number of men presenting with advanced metastatic disease.^{1a} However, this is at the cost of increasing the diagnosis of mainly low risk disease which may lead to the unnecessary treatment of these, with the resultant morbidities associated with active treatments.^{1a} Population based screening is therefore not currently recommended. However, In South Africa the majority of men are not aware of screening and/or do not have access to screening, resulting in the underdiagnosis and undertreatment of localised prostate cancer, and high rates of men presenting with locally advanced or advanced disease.²

Screening of symptomatic men and men with factors that may affect PSA accuracy

Patients with lower urinary tract symptoms (LUTS) and/or clinical suspicion of PCa, regardless of age group should have a PSA test and a digital rectal examination (DRE).

Educating men about prostate screening to enable shared decision making

Overdiagnosis and overtreatment of PCa can be avoided by using biopsy risk calculators and/or MRI targeted biopsies and by properly educating patients with low-risk disease about active surveillance as a treatment option.^{1b}

Given that the majority of South African men are black, and therefore fall into a high-risk category for PCa, all men from the age of 40 should be made aware of their risk for PCa and the advantages and disadvantages of screening.^{3a} This allows for shared decision-making regarding screening between men and primary care practitioners.^{3b}

The serum prostate specific antigen (PSA) blood test

The serum prostate specific antigen (PSA) blood test is currently the best available screening test to detect PCa. Although the PSA test is not a cancer specific test and has limitations, it is currently the best screening test available and should therefore be the first screening test used for PCa.^{3c}

The digital rectal examination is not recommended as a first-line screening test for prostate cancer in asymptomatic men

There is insufficient evidence to support the addition of a digital rectal examination (DRE) to a PSA test to improve PCa detection rates in asymptomatic men.^{3d} The positive predictive (PPV) of a suspicious DRE at 50 years was 0.87% in the PROBASC trial.^{3e} The DRE appears to be most useful for detecting clinically significant PCa in men with an elevated PSA.^{3f}

Screening men with a life expectancy of less than 10 years

Screening patients with a life expectancy of less than 10 years is not recommended as screening is unlikely to provide a benefit in terms of disease-specific or overall mortality.^{3g} If a man is screened by a healthcare practitioner who is not familiar with the patient's medical history and comorbidities, a life expectancy calculator is a useful aid to assist with estimating life expectancy.^{3h}

Guidelines for screening based on age and risk

Informed patient-based screening is recommended in males with a life expectancy of more than 10 years in the following situations:

From the age of 40 in Black African men and in those with a positive family history of prostate and/or breast cancer in a first degree relative³ⁱ

From the age of 45 years in all other males^{3k}

In men who have undergone genetic testing and who are carriers of prostate cancer risk germline mutations, screening should be done at age 40 or at 10 years younger than the age of onset of the youngest affected family member if this is before 40⁴

Germline mutations that increase the risk for prostate cancer include: BRCA2, BRCA 1, HOXB13, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, PMS2, EPCAM and TP53 genes.⁴

Recommended screening intervals

There is no agreement on the optimal screening interval, however serial PSA testing increases the overall sensitivity. In view of this, men with a low initial PSA level (PSA ≤ 1.0 ng/mL) can screen every two years and those with higher levels should screen annually.^{3l}

Due to their increased risk for PCa, Black African men should consider screening annually.^{3m}

Men with a mutation in a PCa-associated gene, or a strong family history of PCa should screen annually.^{3m}

Age at which screening should be discontinued

There is no agreement on a specific age at which screening should be discontinued. However, in line with other international guidelines we recommend that men with a life expectancy of less than 10 years should not be screened. The decision to continue screening men over the age of 70 should be based on shared decision-making with the patient to balance the detection of aggressive cancers with the potential of over diagnosis. Factors such as previous PSA levels, comorbid conditions, and the reduced risk/benefit ratio of curative treatments should be discussed with the patient.^{2g}

Interpretation of PSA levels

Certain factors can affect PSA levels and provide an inaccurate result. The following guidelines can be utilised to determine when PSA testing should be delayed, or levels adjusted to ensure an accurate result.

Factors affecting the PSA level	Recommended action
In men with symptoms of prostatitis due to an infection	Delay PSA testing until 6 to 8 weeks after symptoms resolve ⁵
In men with acute urinary retention	Delay PSA testing for at least 2 weeks ^{6,7}
In men with chronic urinary retention	Delay PSA testing for at least 4 to 6 weeks ⁸
In men who have undergone urethral instrumentation	Delay PSA testing for at least 2 weeks ⁵
In men who have undergone a transurethral resection of the prostate (TURP) or a prostate biopsy	Delay PSA testing for at least six weeks ⁵
In men taking 5-alpha reductase inhibitors (ARI's) for more than one year	A correction factor must be applied in order to obtain an accurate score as these medications reduce the PSA score ⁹
In men who have been taking an ARI for 1 to 2 years	Multiply the PSA result by 2 ⁹
After 2 or more years of ARI therapy	Multiply the PSA result by 2.5 ⁹
After a urinary tract infection	Delay PSA testing for at least six weeks ⁵

PSA levels and urology referral

The most common threshold used to define a high PSA is ≥ 4 ng/mL.^{3j} The use of age-related references improves detection rates and it is therefore recommended rather than using the traditional threshold of 4 ng/mL.^{3j}

If men have a PSA close to the cut-off for their age group, the PSA can be retested using the same laboratory and assay before a urology referral, with the proviso that they avoid ejaculating or perineal trauma for 48 hours before retesting as these can cause an elevation in the PSA level. If the second PSA remains high, patients should be referred to a urologist for further investigation.⁵

Recommended age-related total PSA reference ranges:

Age Group	Reference Range
40 - 50 years	0 - 2.5 ng/mL
50 - 60 years	0 - 3.5 ng/mL
60 - 70 years	0 - 4.0 ng/mL*

*Although most international guidelines use 4.5 ng/mL as the normal upper limit for men between the ages of 60 – 70, we recommend repeat testing and then referral to a urologist for a urological assessment and ongoing monitoring if the PSA is ≥ 4.0 ng/mL. This is particularly relevant for black African males who are more at risk for an aggressive early onset prostate cancer.²ⁿ

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UROLOGICAL ASSESSMENT AND PRE-BIOPSY WORK UP

Most men will be referred for an assessment because of an elevated PSA or an abnormal DRE. A focused urological history and clinical examination form the basis of all assessments. A Definitive diagnosis of PCa can only be made based on pathology results from a prostate biopsy.

Digital Rectal Examination (DRE)

A digital rectal examination must be performed by the examining urologist irrespective of whether this was performed by a primary care physician or not. An abnormal DRE is suggested by the presence of nodules, asymmetry, irregularity, and tethering of the overlying mucosa. A normal DRE does not exclude PCa. DRE should include palpation of the rectum and inspection of the faeces on the glove. An abnormal DRE in combination with an elevated PSA doubles the likelihood of a positive biopsy ((48.6% vs. 22.4%) and biopsy is recommended for these patients. In men with a DRE that is very suspicious of PCa but with a normal PSA, a biopsy should be considered based on the clinical judgement of the urologist.

Prostate Specific Antigen (PSA)

Repeat PSA Testing

The PSA should be repeated in men referred based on an elevated PSA using the same assay and ideally the same laboratory. Patients should be advised that they must avoid ejaculation and activities such as cycling that cause perineal trauma for 48 hours before testing, as these can cause an elevation in PSA. There should be no active urinary tract infection. PSA has low reliability for detecting clinically significant PCa and a limited raise in PSA is alone is insufficient reason for an immediate biopsy. Clinicians should therefore utilise the PSA together with other diagnostic modalities to determine the need for a prostate biopsy.

Prostate-specific antigen density (PSA-D)

Calculation: $\text{PSAD (ng/ml/cm}^3\text{)} = \text{PSA (ng/ml)} \div \text{Prostate vol (cm}^3\text{)}$

PSA-density (PSA-D) is the strongest predictor in risk calculators of clinically significant PCa. The higher the PSA-D, the more likely it is that the PCa is clinically significant.

The likelihood of clinically significant prostate cancer at different PSA densities.

Adapted from Yusim I, Krenawi M, Mazor E et al. The use of prostate specific antigen density to predict clinically significant prostate cancer. Scientific Reports. (2020) 10:20015.

PSA Density	Likelihood of clinically significant PCa
< 0.09 ng/ml ²	4%
0.091 – 0.193*	8.5%*
0.193 – 0.349	31.5%
> 0.340	56.4%

* the risk of clinically significant PCa in this “grey zone is dependent on prostate size

Prostate volume ≤ 33ml risk = 16.5%

Prostate volume > 33 ml risk = 6.8%

The higher the PSA-D the more likely it is that the cancer is clinically significant. Several studies show that PSA-D over 0.1 - 0.15 ng/mL/cc is predictive of prostate cancer.

A South African study by Maher et al found that a PSA-D cut-off of ≥ 0.11 ng/ml had the optimum sensitivity and specificity.

Free/total PSA ratio (f/t) PSA

Calculation: $fPSA (\%) = \text{free PSA (ng/ml)} \div \text{total PSA (ng/ml)} \times 100$

Free/total PSA can only be used when PSA is < 10 ng/mL. Results should be interpreted with caution as the test can be adversely affected by a number of factors including the storage of whole blood samples for more than 2 hours at room temperature (WHO), and the presence of benign prostatic hyperplasia (BPH).

Free to total PSA less than 20% indicates a higher risk of the possibility of PCa. Age reference ranges provide a useful means of interpreting the results.

Based on free PSA : total PSA ratio - the percent probability of finding prostate cancer on a needle biopsy by age in years:

Free/total PSA ratio	50-59 years	60-69 year	70 year and older
≤0.10	49%	58%	65%
0.11-0.18	27%	34%	41%
0.19-0.25	18%	24%	30%
>0.25	9%	12%	16%

Ref: Mayo Clinic Laboratories Neurology Catalog: "Prostate-Specific Antigen (PSA), Total and Free, Serum. Available at: <https://neurology.testcatalog.org/show/PSAFT>

PSA velocity and doubling time (ref EAU guidelines)

Prostate-specific antigen velocity and PSA-DT has a prognostic role in monitoring patients who have undergone treatments for localised disease and who have a rising PSA or in patients who are currently undergoing treatment for advanced disease. It has limited use for diagnosing PCa due to various confounding factors.

Biomarker testing

Various biomarkers are available to assist clinicians and patients to assess the risk for clinically significant cancer before deciding on whether to proceed with a biopsy. None are currently available in South Africa.

Risk-stratification for a prostate biopsy

It is recommended that a risk calculator such as the the Rotterdam Prostate Cancer Risk Calculator be used prior to deciding on whether to proceed with magnetic resonance imaging (MRI) and/or prostate biopsy. This simple inexpensive tool can assist with identifying men at higher risk of having clinically significant PCa and can avoid unnecessary MRI's and biopsies in up to 37% of men.

<https://www.prostatecancer-riskcalculator.com/assess-your-risk-of-prostate-cancer>

Magnetic resonance imaging (MRI) and the decision to biopsy

MRI has been shown to have good sensitivity for the detection and localisation of ISUP grade > 2 cancers, especially when their diameter is larger than 10 mm. However, the use of MRI should be viewed against potential factors that affect the accuracy of MRI reporting. Inter-reader reproducibility remains moderate, which limits its accuracy when interpretation is performed by

non-dedicated radiologists. To improve this, multidisciplinary meetings with pathological feedback should be encouraged.

Recommendations for the use of MRI pre-biopsy

It is recommended that an MRI is performed before a biopsy.

It is recommended that the PI-RADSv2 scoring system guidelines be used.

Biopsy recommendations based on PI-Rads score

EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

PI-RADS Score	Recommendation
PI-RADS > 3	Combine targeted and systematic biopsy
PI-RADS < 2 and clinical suspicion of PCa is low	Consider no biopsy based on shared decision making with the patient

Biopsy recommendations based on PI-Rads score combined with PSA-Density risk groups

By linking PI-RADS scores to PSA density the ability to determine the risk of clinically significant PCa can be better assessed and used to decide on whether to perform a biopsy or not.

PI-RADS risk categories	PSA-density risk groups			
	Low < 0.10	Intermediate-low 0.10–0.15	Intermediate-high 0.15–0.20	High > 0.20
PI-RADS 1–2	No biopsy	No biopsy	No biopsy	Consider biopsy
PI-RADS 3	No biopsy	Consider biopsy	strongly consider biopsy	Perform biopsy
PI-RADS 4–5	Perform biopsy	Perform biopsy	Perform biopsy	Perform biopsy

EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

PROSTATE BIOPSY

Biopsy technique

Ultrasound guided systemic biopsy

Sextant biopsy is no longer considered adequate.

Sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland regardless of the approach used.

Recommended number of cores

Prostate Size and suspected lesions	Number of biopsy cores
In prostates of approximately 30cc	8
In prostates > 30cc	10 to 12
Suspect areas identified by DRE or lesions detected on MRI	3 to 5 per MRI-visible lesion

MRI-directed targeted biopsy

A combination of systematic and targeted biopsy is currently recommended in men with a positive MRI as it increases the number of ISUP grade ≥ 2 and grade ≥ 3 PCa's detected by approximately 20% and 30%, respectively. Suspicious lesions can be targeted through cognitive guidance, Ultrasound/MR fusion software or direct in-bore guidance. No one image guided technique has been shown to be superior to another.

Biopsy approach

Transperineal biopsy is recommended over transrectal biopsy due to the lower risk of infections and complications. However, it should be noted that the transperineal approach is significantly more painful for patients and appropriate pain control measures should be implemented.

Transperineal biopsy

This approach avoids rectal flora. A single oral dose of either cefuroxime or cephalexin is required for antibiotic prophylaxis for skin commensals.

Prior negative mid-stream urine test is required.

Routine surgical disinfection of the perineal skin is required.

Transrectal Biopsy

Transrectal biopsies should only be performed when transperineal biopsies are not feasible. Due to the risk of infection, the following protocols should be adhered to when performing a transrectal biopsy as they have been shown to significantly reduce the risk of infection.

- Use rectal cleansing with povidone-iodine
- Use antibiotic prophylaxis based on local resistance patterns and in accordance with responsible antibiotic stewardship.

Seminal vesicle biopsy

At a PSA of > 15 ng/mL, the odds of tumour involvement of the seminal vesicles are 20-25%. The added value of a seminal vesicle biopsy is questionable if an MRI has been done.

Biopsy core labelling

Biopsy cores from different sites must be submitted separately for processing and pathology reporting.

Pathology reporting

Prostate core biopsies from different sites must be processed separately.

Before processing, the number and length of the cores are recorded.

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2014 grade.

For MRI targeted biopsies consisting of multiple cores per target the aggregated (or composite) ISUP grade and percentage of high-grade carcinoma should be reported per targeted lesion

Mandatory elements to be reported for a carcinoma-positive prostate biopsy

- type of carcinoma
- primary and secondary/worst Gleason grade (per biopsy site and global)
- International Society of Urological Pathology grade (global) (ISUP Grading)
- percentage high-grade carcinoma (global)
- extent of carcinoma (in mm or percentage) (per biopsy site)
- if present: EPE, SV invasion, LVI, intraductal carcinoma/cirriiform pattern, peri-neural invasion
- For MRI-targeted biopsies with multiple cores report aggregate (or composite) ISUP grade and percentage high-grade carcinoma per targeted site
- For carcinoma-negative MRI-targeted biopsy report specific benign pathology, e.g., fibromuscular hyperplasia or granulomatous inflammation, if present

Recommended terminology for reporting prostate biopsies:

Benign/negative for malignancy; if appropriate, include a description. Strong
Active inflammation.
Granulomatous inflammation.
High-grade prostatic intraepithelial (PIN).
High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP).
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern.
Intraductal carcinoma.

The International Society of Urological Pathology (ISUP) grading system

(Grade group is prognostic for PSA recurrence and PCa mortality - AJCC Level of Evidence: I)

ISUP Grade	Gleason Scores	Definition
Grade 1	2–6	Only individual discrete well-formed glands
Grade 2	3+4=7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
Grade 3	4+3=7	Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands
Grade 4	4+4=8	Only poorly formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component of well-formed glands
Grade 5	9–10	Lacking gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

Srigley JR, Delahunt B, Egevad L, Samaratunga H, et al. One is the new six: The International Society of Urological Pathology (ISUP) patient-focused approach to Gleason grading. *Can Urol Assoc J*. 2016 Sep-Oct;10(9-10):339-341.

CLINICAL STAGING AND RISK STRATIFICATION

Tumour (T) staging

Despite the availability of new imaging the AJCC staging manual advises that clinical staging of tumours should be based only on DRE findings and should also not include MRI or biopsy results. This is to ensure that there is a standardised reporting system worldwide, however clinicians should record and report MRI findings in a descriptive manner and using the information to aid decision making.

MRI tumour staging (for descriptive purposes and treatment planning).

T2-weighted imaging remains the most useful method for local staging on MRI. Detection of extra-prostatic extension and seminal vesicle involvement appears to be more accurate at high field strength (3 Tesla). ¹

Primary Tumour ²	
TX	Primary tumour cannot be assessed
TO	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable not visible or visible by imaging
T1a	Incidental tumour in < 5% of TUR tissue
T1b	Incidental tumour in > 5% of TUR tissue
T1c	Needle biopsy prompted by elevated PSA
T2	Tumour confined within the prostate
T2a	Tumour involves one-half of 1 lobe or less
T2b	Tumour involves more than one-half of 1 lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour fixed or invades adjacent structures other than seminal vesicles (eg, bladder, levator muscles, and/or pelvic wall)

Adapted from Posielski NM, Abel EJ, Richards KA. TNM Classification for prostate cancer. Oct 26,2023. Medscape. Available at: <https://emedicine.medscape.com/article/2007051-overview> Accessed on 12 Dec 2023.

Nodal staging

Pelvic lymphadenectomy is the gold standard in nodal staging. However, some lymph nodes may be missed, and the surgical exploration may be associated with complications and morbidity. Imaging has not been able to replace pelvic lymphadenectomy due to the shortfalls in the existing imaging

modalities. Conventional nomograms combining clinical and biopsy findings have been used to estimate the risk of patients harbouring positive LNs however these are based on using systematic biopsy findings.

Clinicians using combined MRI-targeted biopsy and systematic biopsy should use a nomogram such as the 2019 Briganti Nomogram when calculating the risk of lymph node invasion (LNI) in patients diagnosed with magnetic resonance imaging (MRI)-targeted biopsy. A 7% cut off is optimal.

Sentinel node biopsy (SNM) analysis

There currently remains insufficient evidence supporting SNB for nodal staging.

Imaging for Detection of Lymph Node Metastases

CT and MRI

MRI sensitivity, as with CT, in LN staging is less than 40% because the basis for interpretation is based on nodal size. LNs with a short axis >8 mm in the pelvis and >10 mm outside the pelvis are noted as being malignant while smaller nodes may be disregarded. Up to 45% of metastatic lymph nodes are <4 mm. Decreasing the size threshold decreases the specificity of this modality. The sensitivity of these modalities is further compromised in microscopic LN which are low grade and with a PSA < 20 ng/ml.

Choline PET/CT

Due of its low sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases, or to rule out a nodal dissection based on risk factors or nomograms.

Prostate-specific membrane antigen-based PET/CT

PSMA PET/CT imaging is more sensitive for N-staging than MRI, abdominal contrast-enhanced CT or choline PET/CT, largely due to ability to detect metastatic lymph nodes.

Specificity and sensitivity of Ga-68 PSMA PET/CT is 77% and 97%, which is significantly higher than any other modality and this is therefore the preferred imaging modality. However small lymph node metastases under the spatial resolution of PET (~5 mm), may still be missed.

Tc-99m HYNIC PSMA SPECT or SPECT/CT imaging may be used as an alternative in imaging of PCa staging of lymph nodes if PSMA PET/CT is not available. Patient selection is important and may need to be limited to high-risk patients. The sensitivity in detection of smaller lesions may be low because of its low resolution compared to PSMA PET. The sensitivity was further shown to be influenced by the size of the nodes and the PSA level.

Metastases staging

Imaging for detection of bone and visceral metastases

Bone metastases (M1b) are common and may account for up to 80% of deaths from this disease.

MDP bone scintigraphy (BS) is still the most widely used imaging modality for evaluating bone metastases. This modality has the advantage of whole-body imaging, low cost, easy availability and accessibility. BS is also highly sensitive and can detect small changes, of 5-10%, in bone turnover. It is unfortunately limited by the inability to characterize some of the osteoblastic changes accurately, resulting in the poor specificity and making these studies less than ideal.

A BS is indicated in patients who present with high-risk features and symptoms of having bone metastases, and generally not recommended in patients with a new diagnosis of low-risk PCa with PSA <10 ng/ml, Gleason score <8 and no bone pain. In some guidelines even this cut-off risk is refined to a PSA <20 ng/ml, stage T4 and Gleason <8. The diagnostic accuracy of BS is improved by 3-dimensional SPECT imaging which increases detection of spinal and lumbosacral lesions by approximately 20%-50%. Multimodality imaging with fusion of SPECT and CT data as well as hybrid SPECT/CT imaging, through the combination of functional and morphological data, has reduced some of the limitations of BS.

The role of the BS, in light of its limitations, may be considered in cases where bone pain palliation with radionuclide therapy such as Samarium-153 ethylenediamine tetra methylene phosphonic acid (153Sm EDTMP) or Strontium-89(89Sr), is considered and the avidity of the bone metastases needs to be confirmed in preparation.

Sodium Fluoride (Na[18F]) PET/CT is an alternative to MDP BS. Compared with BS, it provides greater spatial resolution, better image quality, better sensitivity and better specificity. It can more accurately detect occult bone metastases at lower prostate specific antigen (PSA) levels than can BS with MDP. Despite its excellent advantages in investigating bone metastases, it is less cost effective and reported to offer no real added value over SPECT bone scintigraphy regarding outcomes and treatment decision making. Based on existing evidence, NaF has not been able to show an advantage over MDP BS with regard to changing patient management. Bone scans may detect fewer metastases, but still manage to detect metastasis in patients in whom more metastases might be seen on the NaF PET/CT but has not been statistically superior compared with BS. Solitary metastasis is detected in only a few patients by NaF PET-CT.

Choline PET/CT has been reported to detect skeletal metastases in addition to the added information it offers on soft tissue involvement compared to bone scintigraphy. Choline PET/CT is more specific than BS which tend to yield false-negative results for bone marrow metastases and osteolytic bone metastases.

A positive bone scan reflects only reactive bone formation, whereas a positive choline PET/CT reflects the presence of tumour cells. Choline PET/CT has a higher detection rate than FDG PET/CT as cancers with a low or intermediate Gleason score have limited glucose uptake. FDG PET/CT is also less accurate and may yield false-positive results since both the tumours and other bone diseases take up glucose.

Radiographic imaging with CT and MRI is more sensitive than bone scan and targeted conventional radiography (e.g. plain abdominal X-ray) in detecting bone metastases in high-risk patients.

Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography, abdominopelvic CT and Choline PET/CT. However, the routine use of WB-MRI at staging is not supported due to its low availability, scarce expertise and the absence of strong validation data on its role in staging.

In a meta-analysis by Shen et al, the pooled sensitivities of Choline PET/CT, MRI, and BS in the diagnosis of bone metastases in patients with PCa were 0.91 [95 % confidence interval (CI): 0.83–0.96], 0.97 (95 % CI: 0.91–0.99), 0.79 (95 % CI: 0.73–0.83), respectively. The pooled specificities for

detection of bone metastases using choline PET/CT, MRI, and BS, were 0.99 (95%CI: 0.93–1.00), 0.95 (95%CI: 0.90–0.97), and 0.82 (95 % CI: 0.78–0.85), respectively.

PCa-targeted PET for staging is preferred when using prostate-specific membrane antigen (PSMA)-targeted PET/CT imaging only and considered necessary in a minority of patients based on risk and symptoms for the other PET radiopharmaceuticals. PSMA PET/CT imaging is able to identify additional lesions in primary staging in intermediate and high-risk disease patients compared to conventional imaging. It has been shown that in high grade tumours and at higher stages of the disease there is increased cell membrane PSMA expression which further increase with eventual progression to advanced PCa and castrate resistance.

Rowe et al compared PSMA PET/CT using the second generation PSMA based radiotracer, [18F]F-DCFPyL, with conventional imaging. The results showed a clear advantage for PSMA PET/CT in the detection of metastatic disease where 139 (138 definite, 1 equivocal) metastatic sites were detected compared with only 45 lesions on conventional imaging (30 definite, 15 equivocal).

PSMA PET/CT outperformed Choline PET/CT in the imaging of metastatic disease, showing liver and skeletal metastases better due to having a higher target-to-background ratio.

PSMA PET/CT has also demonstrated higher diagnostic accuracy compared to the conventional bone scan in the evaluation of skeletal metastases.

PSMA SPECT/CT has also been shown to perform better than bone scan, demonstrating a higher sensitivity and specificity. Additionally, this scan is able to evaluate soft tissue involvement and may be used in metastatic staging in areas without easy access to PET/CT imaging.

PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning. Hofman M et al. Lancet 2020

In South Africa, the relative cost and reliability of PSMA PET/CT or MRI justify their use as the preferred imaging tests for the detection of bone and visceral metastases. It is also worth noting that due to PSMA expression in other visceral malignancies such as lung, renal and hepatocellular cancer, correlation may be needed should there be suspicion of concomitant malignancy.

M staging Reporting

Distant Metastases ³	
Mx	Regional nodes not assessed
M0	No Metastases
M1	No distant
M1a	Non-regional lymph nodes (outside true pelvis)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Risk Stratification of localised prostate cancer

Risk stratification of localised prostate cancer can be done using the EAU or the NCCN risk stratification guidelines.

EAU Risk Stratification for biochemical recurrence of localised and locally advanced prostate cancer (based on systemic biopsy)

Risk Group	ISUP Grade	PSA Level	Tumour stage	LOCALISED DISEASE
Low	1	<10 ng/mL	cT1–T2a*	
Intermediate Favourable	2	<10 ng/mL	cT1–2b*	
	1	10-20 ng/mL	cT1-2b*	
	1	<10 ng/mL	cT2b*	
Intermediate Unfavourable	2	10-20 ng/mL	cT1–2b*	
	3	<20 ng/mL	cT1–2b*	
High	4/5	any	any	
	any	> 20 ng/mL	any	
	any	any	cT2c*	
	any	any	cT3-4* and/or cN+**	LOCALLY ADVANCED DISEASE

* Based on digital rectal examination. ** Based on CT/bone scan.

Adapted from table 4.3 EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2025.
ISBN 978-94-92671-29-5. EAU Guidelines Office, Arnhem, The Netherlands.
Available at: <http://uroweb.org/guidelines/compilations-of-all-guidelines/>

NCCN Risk Stratification for Clinically Localised Disease

Risk Group	Clinical/Pathologic Features		
Very low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core^a • PSA density <0.15 ng/mL/g		
Low ^f	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate ^f	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▶ cT2b–cT2c ▶ Grade Group 2 or 3 ▶ PSA 10–20 ng/mL	Favourable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)^a
		Unfavourable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)^a
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) can be considered as a single positive core.

References for Clinical Staging

1. Van der Poel H, et al. Imaging and T Category for PCa in the 8th Edition of the Union for International Cancer Control TNM Classification. *Eur Urol Oncol* (2019).

2. Posielski NM, Abel EJ, Richards KA. *TNM Classification for prostate cancer*. Oct 26,2023. Medscape. Available at: <https://emedicine.medscape.com/article/2007051-overview> Accessed on 12 Dec 2023.
3. American Joint Committee on Cancer (AJCC) 8th Edition (2016) (198)

TREATMENTS FOR LOCALISED PROSTATE CANCER

Before initiating treatments for localised disease an evaluation of life expectancy, health status, frailty and co-morbidity should be conducted.

For localised disease a life expectancy of 10 years is mostly commonly used as a cut-off for patients to be able to benefit from active treatments. Life expectancy should be assessed using a validated screening tool to assess both cognitive and physical status. Examples are the Geriatric 8 (G8) screening tool which determines whether patients are fit or frail and the mini mental state examination (MMSE) which is effective as a screening tool for cognitive impairment.

Several other nomograms are available as an objective tool to determine life expectancy. The basic premise is that local treatment should only be offered to those who would survive long enough to benefit from therapy. The following nomogram may be used:

<https://cancernomograms.com/nomograms/18>

Shared decision making is essential. Patients should be fully informed of all treatment options available to them even if these are not provided by the specialist that they are consulting. Patients should be fully informed of the advantages and disadvantages of all the treatment options and their potential impact on quality of life in order to make an informed decision.

Treatment options for localised prostate cancer

- ❖ Watchful waiting
- ❖ Active surveillance
- ❖ Radical prostatectomy - with/without radical lymph node dissection
- ❖ Radiotherapy:
 - External beam radiotherapy (EBRT)
 - Brachytherapy (BT)
 - EBRT and BT

Deferred treatment options

All active treatments carry a risk of significant side effects that may affect quality of life. Deferring treatments in patients who are unlikely to survive for 10 years due to co-morbidities or in patients who have low risk disease that is unlikely to progress is recommended.

Active surveillance (AS)

Active surveillance aims to avoid unnecessary treatment and spare men from the side effects of these. Disease progression is closely monitored with the objective of intervening timeously if there is progression to ensure that active treatments are still potentially curative.

Patient selection for active surveillance

- ❖ Low risk disease
- ❖ Favourable intermediate risk disease with no adverse risk features

Factors that may exclude men as candidates for AS include:

- extensive disease on MRI
 - high PSA density
- Pathology features found on the biopsy including:
- predominant ductal carcinoma (including pure intraductal carcinoma)
 - cribriform histology
 - sarcomatoid carcinoma
 - small cell carcinoma
 - extra capsular extension
 - lymph node vesicle invasion in needle biopsy
 - perinural invasion
 - high risk disease

The NICE protocol is recommended for monitoring patients on active surveillance

Timing	Test
At enrolment in active surveillance	Multiparametric MRI if not previously performed ^a
Throughout active surveillance	Monitor PSA kinetics ^b
Year 1 of active surveillance	Every 3–4 months: measure PSA ^c Every 6–12 months: perform DRE ^d At 12 months: rebiopsy ^a
Years 2–4 of active surveillance	Every 3–6 months: measure PSA ^c Every 6–12 months: perform DRE ^d
Year 5 and every year thereafter until active surveillance ends	Every 6 months: measure PSA ^c Every 12 months: perform DRE ^d

^aIf there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy.

^bMay include PSA doubling time and velocity.

^cMay be carried out in primary care if there are agreed shared-care protocols and recall systems.

^dShould be performed by a healthcare professional with expertise and confidence in performing DRE.

Watchful Waiting

This option is reserved for men who present with asymptomatic localised disease in whom curative treatment options are not suitable. Men with a life expectancy of < 10 years because of age or co-morbidities are considered suitable candidates. Unlike active surveillance, patients are not actively monitored but rather watched for localised or systemic disease progression and treated palliatively when the need arises.

RADICAL PROSTATECTOMY

The goal of a radical prostatectomy is to remove all cancer whilst preserving pelvic organ function as far as possible. The entire prostate and the seminal vesicles are removed.

A prostatectomy can be performed by open-, laparoscopic- or robot-assisted (RALP) approaches. The first robotic assisted laparoscopic prostatectomy (RALP) was performed in South Africa in 2013 and this has become the preferred minimally invasive surgery. It provides the minimally invasive advantages of laparoscopic surgery with improved surgeon ergonomics and greater technical ease of suture reconstruction of the vesicourethral anastomosis.

Although functional and oncological outcomes appear to be similar for all techniques, RALP has the advantage of reduced hospital stay, and blood transfusion rates compared to open surgery.

Prostatectomies performed by high volume surgeons at high volume centres have the best outcomes.

Pre-operative preparation

Appropriate education should be provided to ensure that patients can provide informed consent for the procedure. Patients with existing erectile dysfunction and or incontinence should be advised that these will adversely affect post-surgery outcomes.

Pre-operative pelvic floor exercises

Post operative incontinence is one of the most frustrating side effects experienced by men post-surgery. Pre-and post-operative pelvic floor exercises have been shown to provide significant improvement in incontinence rates at 3 months post-operatively. Patients can be referred to physiotherapists who have undergone specialised training in pelvic floor dysfunctions for a supervised program. A listing of these physiotherapists can be found on the PCa Foundation's website.

Prophylactic antibiotics

Prophylactic antibiotics should be used in accordance with local and institutional guidelines.

Neoadjuvant androgen deprivation therapy

There is insufficient evidence to show that Neoadjuvant ADT improves PSA relapse-free survival or cancer specific survival, so this is not currently considered standard clinical practice.

Timing of radical prostatectomy

Treatment can be deferred for up to 3 months with no apparent impact on oncological outcomes.

Robotic anterior versus Retzius-sparing dissection (RS-RA)

There is insufficient data to recommend one technique over another. There is data showing that Retzius-sparing dissection may increase the risk of positive surgical margins albeit with improved early continence outcomes. Patients should be counselled accordingly.

Pelvic lymph node dissection (PLND)

There is a lack of evidence to show that performing PLND during RP improves oncological outcomes and overall survival. Patients should be advised of this and there should be shared decision making given the complications that can occur as a result of PLND.

The individual risk of patients harbouring positive LNs can be estimated based on validated nomograms.

For patients who have had a systemic biopsy use Brigantin Partin and MSKCC nomograms.

For patients who have had an MRI targeted biopsy use 2019 Briganti Nomogra and 7% as a cut-off which will result in missing only 1.5% of patients, but at the cost of finding no lymph node involvement in 70% of patients.

Extended pelvic lymph node dissection ePLND provides the most accurate information for staging and prognosis but at the expense of exposing patients to higher morbidity rates than a limited PLND. 20% of men will experience some complication after ePLND.

There is some data that suggests not performing PLND in intermediate-risk patients whose staging PSMA /PET is negative particularly as there is no survival benefit.

Although EAU guidelines still recommend performing PLND in high-risk patients with negative PSMA PET, the potential morbidity should be discussed with patients and there should be shared decision making.

Management of the dorsal venous complex

Given the small differences in outcomes, the surgeon's choice to ligate prior to transection or not, or whether to use sutures or a stapler can be based on their preference.

Nerve-sparing surgery

Preservation of the neurovascular bundles (NVB) with parasympathetic nerve branches of the pelvic plexus helps to prevent erectile function, although pre-surgical erectile function is also a key factor. However, nerve sparing procedures have been shown to improve continence so should be conducted even if erectile function is not a factor for the patient.

All pre-operative risk factors for side-specific EPE such as PSA, PSA density, clinical stage, ISUP grade, and PI-RADS score, EPE and capsule contact length on MRI, should guide decision making and the priority should be to obtain cancer cure.

Removal of seminal vesicles

It is standard practice to remove the seminal vesicles when performing a prostatectomy, however in some patients the tips of the seminal vesicles can be challenging to dissect free. In addition, the cavernous nerves run past the SV tips which poses a risk of ED. In these cases, and where there is a low risk of cancer having spread to the seminal vesicles the tips may be spared.

Techniques of vesico-urethral anastomosis

There are a variety of approaches, methods and techniques for performing the vesico-urethral anastomosis. As there is a lack of high-certainty evidence to show the superiority of any particular technique, the chosen method is at the surgeon's discretion.

Bladder neck management

Preservation of the bladder neck leaves the internal lissosphincter intact and has been shown to improve continence rates post-surgery. Bladder neck preservation should be performed routinely when the cancer is distant from the base but not in the presence of a large median lobe or a previous TURP.

Urethral length preservation

Every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post RALP. Patients with a an MUL of < 12 mm are likely to have delayed continence recovery. Preservation of as much urethral length as possible during RALP will maximise the chance of early return to continence. Although measurement of membranous urethral length is not currently standard practise it is quick and easy for a radiologist to perform and would add no extra cost to an MRI. Urologists can advise patients that this may be one of many factors that could affect continence recovery times post-surgery.

Cystography prior to catheter removal

Although it is not standard practise, cystography may be used prior to catheter removal to check for a substantial anastomotic leak.

Urinary catheter

A urinary catheter is routinely placed during RALP to enable bladder rest and drainage of urine while the vesicourethral anastomosis heals. Although some data shows improved favourable short-term functional outcomes if the catheter is removed early (2 – 3 days post operatively vs 1 week), no long-term differences were found.

Use of a pelvic drain

Traditionally a pelvic drain has been used for potential drainage of urine leaking from the vesicourethral anastomosis and for blood, or lymphatic fluid when a PLND has been performed. Provided the anastomosis is found to be watertight intra-operatively, it is reasonable not to use a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

Pathological (p) staging

One of the advantages of surgery is that pathological staging can take place using all tissue removed during the prostatectomy. This provides the most accurate assessment of the extent of disease and allows for better prediction of outcomes. Staging includes evaluation of tumour burden, status of surgical margins, extracapsular disease, and seminal vesicle and pelvic lymph node involvement.

The Pathological TNM staging system is shown below

Pathological tumour staging (pT)

pT2	Organ confined
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of the bladder neck**
pT3b	Seminal vesicle invasion
pT4	Tumour is fixed or invades adjacent structures other than the seminal vesicles (eg. bladder, rectum)

Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease). It is an independent risk factor for biochemical recurrence.

Pathological lymph node staging (pN)

pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional nodes(s)

Adjuvant treatment for patients at risk for relapse after pN0 and pN1 disease after radical prostatectomy who have an undetectable PSA

(Based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis)

Risk factors for disease progression in patients who undergone a prostatectomy include patients with:

- ISUP grade > 2 in combination with extra capsular extension and particularly those with SV invasion (pT3b)
- and/or positive surgical margins
- tumour volume within the lymph nodes

- capsular perforation of the nodal metastases
- Lymph node density > 20%

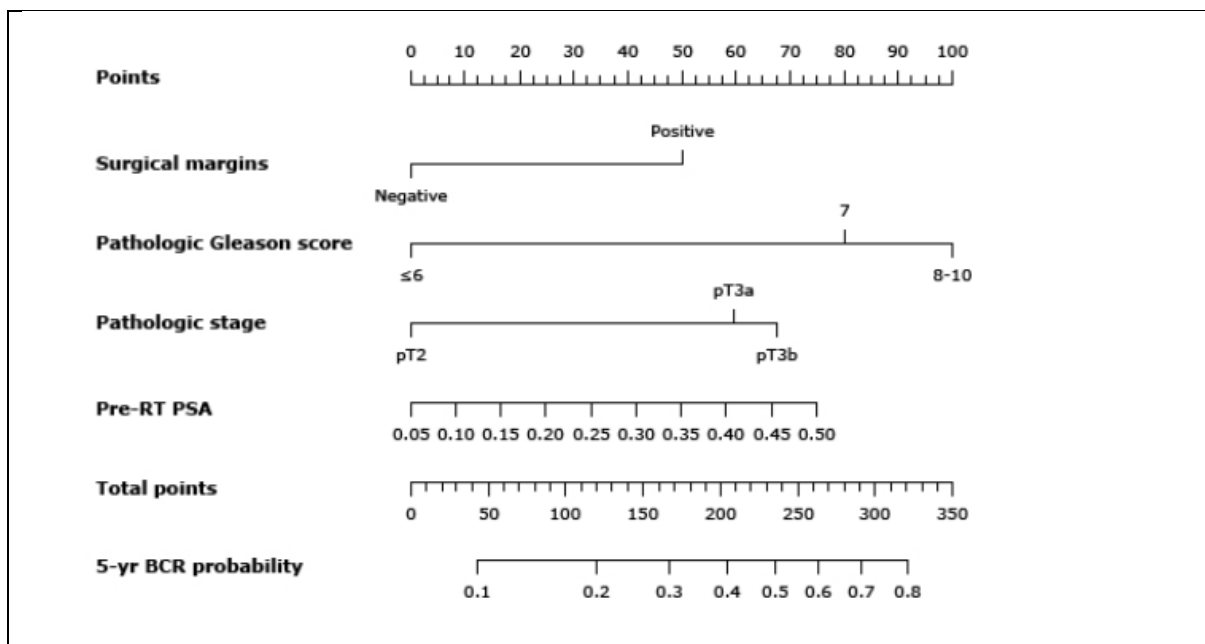
EAU Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) to pN0 patients	Strong
In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT)	Strong
In pN1 patients, after an extended lymph node dissection, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT 3. Offer observation (expectant management) to a patient after eLND and < 2 nodes and a PSA < 0.1 ng/mL	Weak

Persistent PSA after radical prostatectomy (RP) and treatment failure

The half-life of serum PSA is approximately 2–3 days while that of free PSA is considerably shorter, 110 mins. The timing of follow up PSA as many feel that a repeat PSA 30 days after surgery may be too soon.

Pathological assessment is important in identifying patients with a high risk of biochemical recurrence and in whom adjuvant radiotherapy should be considered. These include T3 disease, positive resection margins, GS >8 on post RP. Randomised studies are underway to determine if adjuvant vs. salvage radiotherapy is appropriate in patient with high-risk pathological features.

Nomograms may assist to guide decision making for adjuvant therapy



Briganti A, Karnes RJ, Joniau S, et al. Prediction of Outcome Following Early Salvage Radiotherapy Among Patients with Biochemical Recurrence After Radical Prostatectomy. Eur Urol 2013 Dec 12. DOI: 10.1016/j.eururo.2013.11.045

Several molecular pathological tests are available internationally but not in South Africa, to identify these high-risk groups. These include Decipher®, Oncotype Dx® and Polaris®. These tests are now being utilized earlier to determine the best possible local treatment strategy.

Ongoing monitoring post RP is required as 20-40% of patients may develop biochemical failure. In the absence of high-risk features, PSA should be checked 3-4 months post RT. A detectable PSA post-RP is usually defined as a PSA of > 0.1 ng/ml. This may be caused by persistent local disease, pre-existing metastases, or residual benign prostate tissue. Although not all patients with a persistent PSA experience recurrence it is prognostic of an increased risk of metastasis and death.

The most widely accepted criterion for patients who have undergone radical prostatectomy is that of the American Urological Association (AUA). According to AUA guidelines, a biochemical recurrence is defined as a serum PSA ≥ 0.2 ng/mL, which is confirmed by a second determination with a PSA ≥ 0.2 ng/mL. Persistent increase in PSA post RP may be an indicator for salvage radiotherapy. It should be offered promptly before PSA levels exceed 0.5 ng/ml in order to ensure a higher biochemical recurrence free survival (BRFS), as well as freedom from distant metastases.

The total dose of radiotherapy to the tumour bed is approximately 64-66 Gy in conventionally fractionated radiotherapy. Higher doses have not been found to be of any benefit. Studies are exploring the use of hypofractionated protocols for local prostate bed radiotherapy and results appear favourable thus far.

Adjuvant androgen deprivation therapy

Based on the results of RTOG 9601, short term ADT together with RT may be considered in patients with a PSA 0.6 ng/ml post RT. A total of 6 months ADT is appropriate, starting 2 months before radiotherapy. The ASTRO/AUA guidelines recommend adjuvant RT be considered in any case where the PSA exceeds 0.2 ng/ml prior to salvage therapy.

Pelvic nodal radio therapy (PLN RT)

The decision on whether the PLN RT should be included is debatable. It should be considered where other high risk pathological factors exist including a pre-RT PSA > 0.6ng/mL. Imaging may assist with decision making.

Imaging in patients with persistently elevated PSA after RP

Traditional bone scan and MRI has a low detection rate in men with a PSA below 2 ng/mL and Ga68 PSMA PET CT imaging is therefore recommended. Studies that looked at the role of adjuvant/salvage radiotherapy post RP did not embrace radioactive tracer studies that are not easily available. Most centres in Europe do not have access to PSMA PET imaging and therefore may not incorporate these modalities into the workup of biochemical failure post RP. Nevertheless, studies are ongoing. The EMPIRE-1 study has indicated that PSMA directed therapies are beneficial in this group. A short PSA doubling time is indicative of an increased risk of metastatic disease.

(https://www.mskcc.org/nomograms/prostate/psadoubling_time)

Positive PSMA PET/CT rates	Post-RP PSA ranges
33%	0 – 0.19
46%	0.2 – 0.49
57%	0.5 – 0.99
82%	1 – 1.99
97%	> 2 ng/mL

Radiotherapy (RT) for treating localised prostate cancer

RT is an option for all risks groups of PCa. The options are:

- External Beam Radiation Therapy (EBRT)
- Brachytherapy (BT): high dose rate (HDR) or low dose rate (LDR) BT
- Combination of EBRT and BT

External beam radiation therapy (EBRT)

May be offered as

- Conventionally fractionated (1.8Gy-2Gy per fraction)
- Dose escalated conventional RT
- Moderately hypofractionated RT (3.4-3.4Gy per fraction)
- Ultrahypofractionated RT (>5Gy per fraction)

Brachytherapy (BT)

- LDR: utilises I-125, Pd-103 and is reserved for low and favourable intermediate risk disease
- HDR: Ir 192 delivered through transperineal catheters. Generally reserved for high-risk disease where it is combined with EBRT.

American Brachytherapy Society criteria for permanent brachytherapy of the prostate

From: Int J Radiat Oncol Biol Phys 1999; 44:790.

Contraindications/Clinical exclusion criteria

Life expectancy <5 years

Large or poorly healed TURP* defect

Unacceptable operative risks

Distant metastases

Relative contraindications for brachytherapy

These patients are not ideal candidates for brachytherapy but have nevertheless been successfully implanted. Beginners should not implant these patients.

Patients at increased risk of developing complications.

Large median lobes

Previous pelvic irradiation

High AUA symptom score

History of multiple pelvic surgeries

Severe diabetes with healing problems

Technical difficulties that may result in inadequate dose coverage

Previous TURP

Gland size >60 cc at time of implantation

Prominent median lobe

Positive seminal vesicles

*TURP: transurethral resection of the prostate

** AUA: American Urological Association

NCCN guidelines recommendations for prostate radiotherapy

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if RT is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	Regional N1	Low Volume M1 ^a
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
	2.2 Gy x 35 fx + micro-boost to MRI-dominant lesion to up to 95 Gy (fractions up to 2.7 Gy)		✓	✓	✓		
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓
Brachytherapy Monotherapy							
LDR							
Iodine 125	145 Gy		✓				
Palladium 103	125 Gy	✓	✓				
Cesium 131	115 Gy						
HDR							
Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
EBRT and Brachytherapy (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR							
Iodine 125	110–115 Gy			✓	✓		
Palladium 103	90–100 Gy						
Cesium 131	85 Gy						
HDR							
Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓		

Elective pelvic nodal radiotherapy

This should be determined by the risk of pelvic nodal disease. Somewhat controversial given the lack of survival benefit. Dose fractionation schedules from been hypofractionated to allow for simultaneously delivery with moderate hypofractionation schedules (44Gy in 20 fractions).

Androgen deprivation therapy (ADT) and radiotherapy (RT) for localised disease

ADT is recommended as adjuvant therapy for unfavourable intermediate risk, high and very high-risk disease. The duration of ADT is determined by risk group.

Unfavourable intermediate risk: 6 months

High-risk: 24 months.

The Canadian PCS IV has confirmed that there is no benefit with extended adjuvant ADT in high-risk PCa (18 months vs 36 months).

Adjuvant systemic therapy

Adjuvant abiraterone or enzalutamide offers a metastases free survival advantage when combined with radiotherapy only for high-risk disease. There is no overall survival advantage. However, trials are ongoing.

Options other than surgery or radiotherapy for the primary treatment of localised prostate cancer

There is insufficient evidence to support the treatment of localised disease with anything other than a radical prostatectomy or radiotherapy.

Immediate ADT monotherapy has only been shown to benefit patients with a PSA-DT < 12 months, and either a PSA > 50 ng/mL or a poorly differentiated tumour. ADT monotherapy other than in the above situation is not considered standard of care.

Experimental Whole Gland Treatments

Cryotherapy

This treatment involves the use of freezing techniques to cause cell death using 17-gauge cryo-needles under TRUS guidance. There is insufficient high-level data to show effective curative oncological outcomes, and the treatment is therefore regarded as experimental.

High-intensity focused ultrasound (HIFU) for whole-gland treatment

This treatment uses focused ultrasound waves to heat malignant tissue by destroy tissue above 65°C. The treatment is predominantly delivered from the rectal cavity which makes it difficult to reach the anterior part in large prostates. There is insufficient high-level data to show effective curative oncological outcomes and the treatment is therefore regarded as experimental.

Focal therapies

More men are being diagnosed with early stage PCa with smaller tumours often only on one side of the prostate. The objective of focal therapy is to ablate only the region of the prostate containing the tumour thereby limiting damage to the neurovascular bundles, sphincter and urethra. This can be achieved using modalities such as cryotherapy, HIFU, photodynamic therapy (PDT, irreversible electroporation (IRE), and focal radiotherapy. Although these treatments have shown favourable functional outcomes with minimal side effects, there is insufficient long-term data to make recommendations.

AS per EAU guidelines, focal therapy using HIFU or cryotherapy should be performed within the context of a prospective registry. All other ablative modalities should only be offered in well-designed prospective trial setting.

THE PREVENTION AND MANAGEMENT OF TREATMENT COMPLICATIONS FOR LOCALISED PROSTATE CANCER

In men with localised disease, research has shown improved quality of life (QOL) outcomes when there is psychosocial support by a multidisciplinary rehabilitation team that includes a nurse and physiotherapist. This should include planning of patients' needs related to lifestyle changes such as toilet habits, sexual function and psychological problems.

Clinicians are encouraged to form multidisciplinary teams of healthcare professionals to support patients and to help them manage treatment side effects.

Exercise

Exercise programs during radio therapy combined with ADT result in consistent benefits for cardiovascular fitness and muscle function with a reduction in urinary symptoms. In men undergoing active surveillance, 12 weeks of high-intensity interval training may improve cardiovascular fitness and suppress PSA progression. This data illustrates the importance of a holistic approach and demonstrates the contribution of improvements in overall health to improved treatment outcomes.

The following complications are possibilities for each mode of therapy and will differ depending on patient factors, facilities and the intrinsic nature of the procedure performed.

Sexual Function

Approximately 81-93% of patients report that PCa treatments negatively affect their sex lives, with 20-58% of men reporting cessation of sexual activity with a partner. All patients and their partners should be counselled that all active prostate cancer treatments may result in short term as well as long term erectile dysfunction (ED). Most patients do not return to pre-treatment erectile function after treatment. However, pre-existing ED is associated with higher rates of post-treatment ED after radical prostatectomy, regardless of the surgical technique used, and after radiotherapy, regardless of the radiotherapy used.

All patients undergoing a radical prostatectomy should be advised that they will have anejaculation after the procedure as well as changes in orgasmic function, a potential loss of penile length and other possible side effects such as climacturia.

Erectile dysfunction (ED)

Epidemiology

- ED frequently coexists in patients with PCa so pretreatment assessment with a validated questionnaire such as the IIEF5 may be useful to measure post treatment deterioration in erectile function
- ED often occurs immediately after radical prostatectomy and may improve with time depending on pre-surgery erectile function and nerve-sparing vs non-nerve sparing surgery
- ED develops later after radiotherapy
- The incidence of ED is comparable at 2 years after both RP and RT

Prevention

- Nerve sparing surgery
- Vessel sparing radiation has been described as a technique designed to preserve sexual function
- Early supervised penile rehabilitation provides the best outcomes for men who wish to recover erectile function
- Active surveillance

Lifestyle modification should be recommended to patients to optimise their overall health and sexual health. This includes not smoking, engaging in physical activity, weight loss when required, increasing consumption of healthy plant-based foods and reducing consumption of red and processed meat.

Management of erectile dysfunction

Given the significant sexual difficulties throughout survivorship, a biopsychosocial sexual health assessment is critical for men who wish to remain sexually active. Clinicians should offer screening and assessment of sexual dysfunction prior to treatment and regularly throughout follow-up visits, or referral of patients to a sexologist.

- Early penile rehabilitation by a multidisciplinary team provides the best outcomes for men who wish to recover erectile function. This may include a combination of pharmacological and non-pharmacological strategies aimed at preserving penile length, erectile function and the quality of the corpora cavernosa
- Firstline treatment usually includes the prescription of phospho-diesterase-5 inhibitors (PDE5Is), however these may not fully restore erectile function
- A Vacuum device can be used with or without PDE5I's. Vacuum devices are also used as a means of oxygenating the penile tissue. This is done without a constricting band. Patients achieve an erection with a larger ring and hold the erection for 3 minutes. This can be done six times during the day
- If there is no response, or an inadequate response to the above treatments, intracavernosal injection therapy should be commenced
- When all the above treatments fail a penile prosthesis is the remaining option for men who wish to achieve an erection
- Non-penetrative sexual activity (Outercourse) can be taught by a pelvic floor physiotherapist or sexologist. Erections are not necessary for orgasmic build up and ejaculation/climax. This sensation of orgasm and climax is important for neuro-muscular fire up/excitation and memory recall. This also helps with the rehabilitation of erections
- When penetration is not desired, outercourse can be used as an alternate form of sexual intimacy
- Psychosocial therapy: Counselling on the use of erectile aids is supported by evidence. Couples also benefit when they are encouraged to communicate, expand sexual repertoire to non-penetrative sexual activity, and support each other during the recovery process.

Reference: Wittmann et al. Guidelines for sexual health care for prostate cancer patients: Recommendations of an internal panel. *Journal of Sexual medicine*, 2022;19:1655-169

Incontinence

Epidemiology

Can occur after both surgery and radiation therapy or be independent of PCa treatment. Incidence, pathogenesis and treatment are different. Always exclude local or systemic causes of incontinence (including medication)

Prevention

- Active surveillance
- Nerve sparing surgery
- Controlled exposure to radiation

- Referral to a physio therapist for pelvic floor exercises pre and post prostatectomy

Management of incontinence

Treatment recommendations for mild, moderate and severe incontinence

MILD (1-2 pads per day)	MODERATE (2-5 pads per day)	SEVERE (>5 pads per day)
Pelvic floor exercises	Pelvic floor exercises	Artificial sphincter
Bulking agents	Bulking agents	Penile clamp
Biofeedback	Slings	Urethral occlusion devices
Pharmacological: - α -stimulants - anticholinergics - β 3 Agonists	Penile clamp	- Intravesical Botulinum toxin - Peripheral and sacral nerve stimulators
Urethral occlusion devices	Urethral occlusion devices	Artificial sphincter

NOTES for invasive management of incontinence:

- Wait at least two years if patient has some improvement
- If no improvement within one year, earlier intervention is indicated

Radiation proctitis (and other bowel complications after radiation therapy)

- CO2 laser therapy
- Formalin instillation
- Prednisone enema
- Hyperbaric oxygen
- Colostomy
- Generally, avoid biopsy of rectal lesion

Radiation cystitis

- Clorpactin, silver nitrate, formalin instillation
- Prednisone instillation
- Hyperbaric oxygen
- Urinary diversion

Urinary retention

- Alpha blockers
- Catheterization
- Post RT Transurethral resection of the prostate (recommended to wait at least 6-10 months post therapy to minimize incontinence complications)
- Urethral stricture management

TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

There is insufficient high-level evidence to recommend an optimal treatment solution. The following guidelines from the EAU apply, however all recommendations are based on conventional imaging with isotope bone scan and CT/MRI abdomen/pelvis.

EAU guidelines for the treatment of locally advanced prostate cancer

Recommendations	Strength rating
<i>Radical prostatectomy (RP)</i>	
Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
<i>Extended pelvic lymph node dissection (ePLND)</i>	
Perform an ePLND.	Strong
<i>Radiotherapeutic treatments</i>	

Offer patients with cN0 disease intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guide radiation therapy in combination with long-term androgen deprivation therapy (ADT)	Strong
Offer patients with cN0 disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT	Weak
Offer long-term ADT for at least 2 years	Strong
Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 years of abiraterone to cN0M0 patients with > 2 high-risk factors (cT3-4, Gleason > 8 or PSA > 40 ng/mL)	Strong
Offer IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and 2 years of abiraterone to cN1M0 patients.	Strong
Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT	Strong
<i>Therapeutic options outside surgery or radiotherapy</i>	
Do not offer whole gland treatment or focal treatment	Strong

BIOCHEMICAL RECURRENCE (BCR) AFTER LOCALISED TREATMENTS

About one third of patients will experience a rise in PSA levels without evidence of metastases within 10 years of curative treatment for localised PCA.

Definition of biochemical recurrence after Radiotherapy

Biochemical recurrence (BCR) after radiotherapy, irrespective of whether short term androgen deprivation therapy has been administered is defined as:

Any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir. (RTOG-ASTRO Phoenix Consensus Conference definition)

Definition of biochemical recurrence after a radical prostatectomy

Definitions of biochemical recurrence after a radical prostatectomy vary. Traditionally if PSA is consecutively higher than 0.2 ng/ml twice and keeps increasing, it is defined as BCR, however a PSA > 0.4 ng/mL (BCR) and rising is the threshold that best predicts further metastases.

Because not all patients with BCR will have the same outcomes it is recommended that other factors are used for planning of treatments. In view of this the EAU recommends stratifying patients into high and low risk to predict distant metastases, prostate-cancer-specific mortality and overall mortality.

Risk stratification of patients with biochemical recurrence

	EAU Low Risk	EAU High Risk
After radical prostatectomy	PSA-Doubling Time > 1 year AND pathological ISUP grade < 4	PSA-Doubling Time < 1 year OR pathological ISUP grade 4–5
After Radiotherapy	Interval to biochemical failure > 18 months AND biopsy ISUP grade < 4	interval to biochemical failure < 18 months OR biopsy ISUP grade 4–5

Imaging to assist treatment planning in patients with biochemical recurrence

After radical prostatectomy

Use PSMA PET/CT if the PSA is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.

If PSMA PET/CT is not available, and the PSA level is > 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.

After Radiotherapy

Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.

A less preferred options is to perform prostate magnetic resonance imaging (MRI) to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.

Treatments for biochemical only recurrence

Early intervention radiation treatment appears to improve survival rates. Studies have shown that after a radical prostatectomy more than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level, resulting in an 80% chance of being progression-free after 5 years.

Treatments for biochemical recurrence after a radical prostatectomy

Adapted from EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients

Note that the evidence level for this is weak and clinician discretion is advised
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises
Do not delay salvage radiotherapy (SRT) based on a negative (PET/CT) scan, if otherwise indicated.
Do not wait for a specific PSA threshold before starting salvage radiotherapy if that is the treatment choice (at least 64 Gy) should be given as soon as possible.

Treatments for biochemical recurrence after radiation therapy
Offer monitoring, including prostate-specific antigen (PSA), to EAU defined low-risk BCR patients Note that the evidence level for this is weak and clinician discretion is advised
Only offer salvage radical prostatectomy (RP), brachytherapy, stereotactic body radiotherapy, to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.

Androgen deprivation therapy for biochemical recurrence/non metastatic hormone sensitive prostate cancer nmhPCA

This group of patients have an increasing PSA level with no symptomatic or clinical evidence of cancer after active treatments for localized disease. There is no standard recommendation for the commencement of ADT in these patients. The decision should be made based on PSA doubling time, the impact of the side effects of ADT, comorbidities, life expectancy and patient and physician anxiety.

Options include initiating ADT early or close observation of the patient until cancer progression occurs and then initiation of ADT. NCCN guidelines are recommended as per the table below:

Treatment Management	Factors influencing the decision
Initiate early ADT	Elevated PSA and/or shorter PSA doubling time
	Long life expectancy
Observation only	Prolonged PSA doubling time
	Older patients
	comorbidities

	tolerance of side effects and increased risk for cardiometabolic disease
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Actuarial studies have shown that the median time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years. The decision to start ADT should therefore be based on EAU biochemical risk stratification, the patient's life expectancy, fitness for treatment. Any potential benefit of early initiation of androgen deprivation therapy must be weighed against the impact of the side effects of ADT on quality of life (QOL) and the increase in the risks for cardiometabolic diseases.

There is no consensus on when to start ADT in men with high risk BCR or on what treatment regime to use. Options include:

- continuous ADT monotherapy
- ADT combined with a 1st generation non-steroidal antiandrogen such as bicalutamide
- monotherapy with bicalutamide which has not been proven to have less of a survival benefit than ADT monotherapy and has been shown to have less sexual side effects and better physical capacity.

New recommendation for men with high risk BCR

Recently, results of the Embark trial have shown that enzalutamide as monotherapy or in combination with an LHRH agonist provides significantly improved metastasis-free survival as compared with an LHRH agonist alone, with no worsening in the time to decline in FACT-P total scores. The use of enzalutamide monotherapy or a combination of ADT and an LHRH agonist are therefore recommended as the preferred option to ADT monotherapy for patients with high risk BCR.

Patients who received enzalutamide monotherapy had fewer hot flashes, but gynecomastia, nipple pain, and breast tenderness were more common. Clinicians should therefore consider prophylactic treatment for gynecomastia if they use enzalutamide monotherapy.

OLIGOMETASTATIC PROSTATE CANCER AND METASTASIS-DIRECTED THERAPY

Definition

There is general agreement that this is a transitional disease state between localized and polymetastatic disease. However, there is no agreed-on definition for oligometastatic PCa. There should be a limited number of macroscopic lesions $\leq 3 - 5$ but this is not defined by a specific imaging technique.

Imaging

Traditional imaging is unreliable as it tends to underestimate the disease extent. PSMA PET-CT appears to be the most useful imaging technique overall due to its ability to detect lesions even with low PSA levels.

Treatment

The purpose of diagnosing patients as having oligometastatic disease is to identify patients who may benefit from metastases directed therapy (MDT) with the aim of delaying systematic therapy to avoid ADT side effects and their negative impact on quality of life.

There is sufficient data from the STOMP and ORIOLE trials to show that MDT using SBRT delays the need for ADT as opposed to surveillance only. In the UK the NHI has now approved SBRT for up to 3 metachronous oligometastatic lesions.

In view of this, the recommendation is that patients should be defined as having oligometastatic disease, if they have up to 3 lesions identified by PSMA PET-CT and that the recommended treatment is SBRT. A shared decision with the patient should be made about whether to delay ADT.

METASTATIC HORMONE SENSITIVE PROSTATE CANCER m(HSPC)

Introduction

The majority of males in South Africa present with locally advanced and/or metastatic disease at presentation.^{1,2} Data used for recommendations is based on the definition of M1 disease as determined by radiographic imaging and bone scintigraphy due to the lack of data from studies utilising newer more accurate imaging.³

Disease classification

Metastatic disease that occurs after radical local treatment of the primary tumour is classified as metachronous metastatic prostate cancer.³

Metastatic disease that is first diagnosed in the advanced stage is classified as de novo or synchronous prostate cancer.³

Patients with metachronous metastatic disease generally have a better prognosis than patients with synchronous disease.³

Metastatic PCa is classified as high or low volume and/or high and low risk based on the CHAARTED and LATITUDE studies.³

	High	Low
CHAARTED (volume)	> 4 Bone metastases including > 1 outside the vertebral column or pelvis AND/OR Visceral metastasis (lymph nodes are not classified as visceral metastases)	Not high
LATITUDE (risk)	> 2 high-risk features of: • > 3 Bone metastasis • Visceral metastasis • > ISUP grade 4	Not high

Prognostic groups based on PSA levels³

Based on a large SWOG 9346 cohort, the PSA level after 7 months of ADT was used to create 3 prognostic groups:

PSA after 7 months after start of ADT	Median survival on ADT monotherapy
< 0.2 ng/mL	75 months
0.2 ≤ 4 ng/mL	44 months
> 4 ng/mL	13 months

Treatments for hormone sensitive metastatic prostate cancer (mHSPC)

Primary androgen deprivation therapy (ADT) has been the standard of care for over 50 years.³

However the advent of the androgen receptor pathway inhibitors (ARPIs) and the introduction of chemotherapy earlier in the treatment pathway for high volume disease has improved patient survival and outcomes considerably, and ADT as monotherapy is now no longer considered standard of care.³

First line Treatment

Surgical castration with a bilateral orchiectomy or chemical castration with the use of a LHRH agonist or LHRH antagonist all achieve similar oncological outcomes.³

For men who present with metastases at the time of diagnosis (synchronous disease) ADT monotherapy is no longer considered standard of care, and wherever possible ADT should be combined with a new androgen receptor pathway inhibitor (ARPI) on initiation of ADT (doublet therapy).³

The addition of docetaxel to ADT plus an ARPI (triplet therapy), improves overall survival in patients with synchronous high-volume disease. This option should be based on fitness for chemotherapy, patient preference, side effects, availability of docetaxel and logistics.³

Recommended androgen deprivation therapy options

Patient profile	Preferred Treatment Option
Recommended for men who require a rapid reduction of testosterone for complications such as spinal cord compression and/or urinary retention ³ Recommended for men who are unable to access a urology or oncology department or an appropriate healthcare professional at the required intervals for injectable ADT drugs	Bilateral orchiectomy ³
Recommended for men with pre-existing cardiovascular disease or cardiovascular risk factors ³	LHRH antagonists ³
Recommended for all other men ³	LHRH agonists ³ Combine with bicalutamide for 2-4 weeks to prevent testosterone flare when necessary

Early versus deferred androgen deprivation therapy

Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease, as data indicates that early intervention probably extends time to death for any cause and time to death from prostate cancer (Pca).³

Deferring treatment for patients with metastatic prostate cancer should only be considered in men who are asymptomatic and who express a strong desire to avoid treatment-related side effects.³ Men should be counselled about the the increased risks of developing symptoms and of dying from cancer by deferring treatment.³ However, this data is based on conventional imaging, and newer imaging technologies may identify patients with oligometastatic disease who could benefit from metastases directed therapy in order to delay ADT. Patients who wish to delay the initiation of ADT must be willing to commit to regular follow ups.³

Before commencing with ADT patients should undergo the following:

- a comprehensive history and physical examination that includes falls risk and height measurement should be performed prior to initiating ADT⁴
- a full baseline cardiometabolic health risk assessment and monitoring for cardiovascular complications whilst receiving ADT⁴
- An evaluation of bone mineral density with a DEXA scan⁴
- Clinicians should obtain baseline calcium and 25-hydroxyvitamin D levels at the start of ADT⁴

Non-steroidal anti-androgen monotherapy with bicalutamide

Bicalutamide is an oral non-steroidal anti-androgen. For patients with M1 disease it has been shown to be less effective in terms of overall survival, clinical progression, and treatment failure than ADT monotherapy and is therefore not recommended as standard of care.³

Combined androgen blockade with bicalutamide

This treatment offers a small survival advantage (< 5%) over ADT monotherapy with increased side effects. It is inferior to the newer combination therapies with ARPIs and should therefore only be used if an ARPI is unavailable.³

Intermittent versus continuous androgen deprivation therapy

This option should only be considered for men who are the best PSA responders and for whom survival is considered secondary to quality of life. Results from the SWOG 9346 trial did not show that intermittent ADT was inferior to continuous ADT in terms of overall survival, but continuous ADT in combination with an ARPI has become the standard of care.³

Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT if there are signs of disease progression.⁵

Combination therapy with an androgen receptor pathway inhibitor (ARPI) - New standard of care

Combination of ADT together with either abiraterone acetate plus prednisone, enzalutamide or apalutamide improves overall survival, time to radiographic progression, time to pain, and time to chemotherapy.³ For optimal treatment outcomes this doublet therapy should be implemented on initiation of ADT in men who are fit enough and is now regarded as standard of care for the treatment of m(HSPC).³

Combination therapy with docetaxel for de novo high-volume m(HSPC)

For de novo metastatic high-volume hormone sensitive prostate cancer, the use of ADT combined with docetaxel upfront improves survival. However, the overall survival benefit is further improved by adding an ARPI to ADT and docetaxel (triple therapy).³

Combining docetaxel alone with ADT should only be considered if no ARPI is available or all available ARPIs are contraindicated. Usage of docetaxel should be reserved for men who are fit enough for chemotherapy.³

Treatment of the primary tumour in newly diagnosed m(HSPC)

In men with newly diagnosed m(HSPC) the addition of radiotherapy to the primary tumour increases overall survival in low volume disease only.³ It is therefore recommended in this situation and not for unselected patient groups.³

References:

1 Benedict MOA, Steinberg WJ, Claasen F, et al. The profile of Black South African men diagnosed with prostate cancer in the Free State, South Africa. S Afr Fam Pract (2004). 2023 Jan 10;65(1).

2 Le Roux HA, Urry RJ, Sartorius B et al. Prostate Cancer at a regional hospital in South Africa: we are only seeing the tip of the iceberg. South African Journal of surgery. 01 Dec 2015, 53(3 and 4):57-62

3 EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6. Available at: <https://uroweb.org/guidelines/prostate-cancer/summary-of-changes/2023>

4 Kokorovic A, So AI, Serag H, et al. Canadian Urological Association Guideline on androgen deprivation therapy: Adverse events and management strategies. Can Urol Assoc J 2021;15(6):E307-22. <http://dx.doi.org/10.5489/cuaj.7355>.

5 NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 4.2023 — September 7, 2023.

CASTRATE RESISTANT PROSTATE CANCER (CRPC)

Men treated on androgen deprivation therapy eventually show signs of disease progression. LHRH agents should be continued when adding additional treatments as all studies to date have been done on this basis.

Definition

Castration Resistance is defined as testosterone < 50 ng/dL or 1.7 nmol/L plus either:

Biochemical progression:

Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

Or

Radiological progression:

either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours).

Treatment of non-metastatic castrate resistant PCa

Regular PSA testing in men on ADT has resulted in the earlier detection of biochemical recurrence.

Approximately one third of these men will develop bone metastases within two years as detected by

conventional imaging. If there are no visible signs of metastases on imaging, baseline PSA level, PSA velocity and PSA-DT can be used as predictors of time to first bone metastasis, bone metastasis-free survival and OS.

With the increasing availability of more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more of these men will be diagnosed earlier with early mCRPC.

Imaging recommendations by PSA level for men with castrate testosterone levels

For asymptomatic men	Imaging
When PSA reaches 2 ng/mL	PSMA PET/CT or Bone and CT scan or whole-body MRI with DWIBS if PSMA PET/CT is not available (NCCN)
When PSA reaches 5 ng/mL	Repeat PSMA PET/CT or Bone and CT scan or whole-body MRI with DWIBS if PSMA PET/CT is not available (NCCN)
Test PSA every 3 months After every doubling of the PSA	Repeat PSMA PET/CT or Bone and CT scan or whole-body MRI with DWIBS if PSMA PET/CT is not available (NCCN)
For symptomatic men	PSMA PET/CT or whole-body MRI with DWIBS

Recommended treatment options based on conventional imaging

Patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) can be treated with apalutamide, darolutamide or enzalutamide. These agents have been shown to prolong time to metastases and overall survival.

With the increasing availability of more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more of these men will be diagnosed earlier with early mCRPC.

Treatment of metastatic castrate resistant prostate cancer (mCRPC)

Patients with mCRPC are best treated by a multidisciplinary team.

Genetic Testing

When available patients with mCRPC should be offered somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.

Factors to be considered for treatment planning

The following factors must be considered when planning further treatment:

- previous treatment for mHSPC and for non-mHSPC
- previous treatment for nmCRPC and mCRPC
- quality of response and how soon patients progressed on previous treatment
- known cross resistance between ARPIs (ARPIs)
- co-medication and known drug interactions

- known genetic alterations and microsatellite instability–high (MSI-H)/mismatch repair–deficient (dMMR) status
- known histological variants and DNA repair deficiency (to consider platinum or targeted therapy like PARPi)
- local approval status of drugs and reimbursement situation
- available clinical trials
- The patient and his co-morbidities

First-line treatment of metastatic castrate resistant prostate cancer (mCRPC)

First-line treatment for mCRPC will be influenced by which treatments were used when metastatic cancer was first discovered and the results of genetic testing.

Androgen receptor pathway inhibitors (ARPIs)

Abiraterone (with prednisone) or enzalutamide can be used in this setting if they have not been used previously including for patients who have had one or two lines of chemotherapy. Enzalutamide has been shown to provide significant improvement over bicalutamide in progression free survival.

Treatment of patients with somatic or germline HRR gene mutations

Poly (ADP-ribose) polymerase inhibitors (PARPi) block the enzyme poly ADP-ribose polymerase (PARP). The primary mechanism of action of PARP inhibitors is via induction of synthetic lethality in cells with underlying deficiencies in homologous recombination repair (HRR). These drugs have demonstrated a benefit in radiologic progression-free survival (rPFS) and in improving overall survival.

Niraparib in combination with abiraterone acetate

In men with a deleterious or suspected deleterious BRCA-positive mCRPC a combination tablet of a PARP inhibitor (niraparib) and abiraterone acetate is available. It must be prescribed together with prednisone. In the Magnitude study the combination drug showed improvements in radiographic progression-free survival (rPFS), symptomatic progression (TSP) and time to initiation of cytotoxic chemotherapy. There was also an improvement in overall survival (OS).

Olaparib

Olaparib is approved as monotherapy in patients with somatic or germline HRR gene mutations with mCRPC who have progressed following prior treatment with enzalutamide or abiraterone and/or a taxane-based chemotherapy. olaparib was associated with longer progression-free survival and better measures of response and patient reported end points than either enzalutamide or abiraterone.

Chemotherapy with Docetaxel

If patients have been treated with abiraterone or enzalutamide they can be offered chemotherapy. Docetaxel is the recommended standard first-line chemotherapy agent. The dosage is 75 mg/m², 3-weekly doses combined with prednisone 5 mg twice a day. It has improved survival over mitoxantrone plus prednisone. Age alone should not exclude patients from chemotherapy. The dose can be adjusted to docetaxel 50 mg/m² every two weeks in men who may not tolerate the standard dose. Patients must be carefully monitored.

Oestrogens

The use of oestrogens is not recommended in any of the major international guidelines. However, they can be used if other standard of care options are not available or cannot be tolerated. Parenteral and transdermal oestrogens avoid first-pass hepatic metabolism and therefore the

cardiovascular complications of oral oestrogens. They do not appear to cause osteoporosis. Nipple hypersensitivity and gynecomastia are problematic side effects associated with oestrogens and clinicians should treat prophylactically.

Second-line treatment for metastatic castrate resistant prostate cancer (mCRPC) and sequencing of treatments

Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It is therefore recommended in patients who have previously been treated with docetaxel or in patients treated with abiraterone or enzalutamide who show disease progression within 12 months.

Sequencing of treatment options

Chemotherapy

In view of the toxic side effects of chemotherapy with docetaxel and subsequent cabazitaxel, it is recommended that these should be applied early enough in the treatment pathway when the patient is still fit enough for chemotherapy.

Sequencing of androgen receptor pathway inhibitors (ARPIs)

Sequencing of ARPI's is not recommended especially in patients who had a short response (< 12 months), to the first ARPI for mCRPC because of cross resistance. Chemotherapy and a PARP inhibitor should be considered as next options.

Docetaxel rechallenge

There is limited data to suggest retrying docetaxel if it was used for mHSPC. It seems to be less active than the use of an ARPI at progression.

ARPI before or after docetaxel

There is level 1 evidence for both sequences, so choice of first treatment should be based on shared decision making with the patient and treatment availability.

ARPI → docetaxel → cabazitaxel or docetaxel → ARPI → cabazitaxel

Both third-line treatment sequences are supported by level 1 evidence so the treatment sequence should be based on shared decision making with the patient and treatment availability.

Radium-223

This is the only bone-specific drug that is associated with a survival benefit. Its usage is also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QOL. For safety reasons it should only be used after docetaxel and treatment with at least one ARPI.

Due to an increased risk of fractures the European Medicines Agency recommends that radium-223 should only be used as monotherapy or in combination with an LHRH analogue for the treatment of patients with metastatic castration-resistant PCa (mCRPC), symptomatic bone metastases and no known visceral metastases, who are in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. The use of Radium-223 is not recommended in patients with a low number of osteoblastic bone metastases.

Platinum chemotherapy

Patients with mCRPC and alterations in DDR genes or who progress after PARP inhibitors are more sensitive to platinum chemotherapy than unselected patients. Platinum can be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Trials are ongoing. Platinum-based chemotherapy has been shown to confer palliative benefit, objective responses, and longer progression-free survival in phase II studies of metastatic castration-resistant prostate cancer (mCRPC), although improved overall survival (OS) has not been demonstrated.

Lutetium (Lu-177-PSMA)

Treatment with ¹⁷⁷Lu-PSMA has emerged as a promising systemic modality, which involves the delivery of targeted radiation therapy in the form of β -particles to sites of tumour tissue. Patients are selected (amongst other criteria) based on the prior PSMA-based SPECT/PET/CT imaging (^{99m}Tc-, ⁶⁸Ga- or ¹⁸F-PSMA), which should demonstrate sufficient receptor expression in order to consider PSMA-based targeted radionuclide therapy.

Lutetium is indicated for PSMA-positive M1 CRPC that has been treated with ARPIs and taxane-based chemotherapy. It has proven efficacy in improving overall survival and progression free survival.

The full procedure for utilizing lutetium as a treatment option for men with mCRPCA is outlined in the South African guidelines for receptor radioligand therapy (RLT) with Lu-177-PSMA in PCa which is available on Prostate Cancer Foundation's Website.

Monitoring of Treatment for castrate resistant prostate cancer (CRPC)

Baseline medical and clinical examination that should be performed

Blood Tests	Testing interval
PSA*	Perform a baseline test
total testosterone level	Retest every 2 to 3 months
full blood count	
renal function	
baseline liver function tests	
alkaline phosphatase	
total testosterone level	
Imaging Tests*	Perform a baseline test
bone scan	

CT of chest, abdomen and pelvis	Retest every 6 months even in the absence of signs and symptoms
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**PSA Testing*

Do not use PSA alone to monitor disease progression as visceral metastases may develop in men without causing a rising PSA.

**The use of choline or PSMA PET/CT scans for monitoring disease progression in CRPC is unclear.*

The decision to stop or change treatment

The ECOG Performance Status Scale can be used to assess a patient's ability to tolerate treatments. Patients with a score of 0-1 are likely to tolerate treatment.

Patients with a score of ≥ 2 are less likely to benefit.

At least two of the following three criteria below should be present when deciding to stop or change treatment:

- PSA progression
- radiographic progression
- clinical deterioration

It is important to establish whether a patient is still benefitting clinically from a treatment in order to make a decision regarding changing treatment or treatment cessation.

It is recommended that treatment be started or changed immediately in men with symptomatic progressing metastatic disease.

Symptomatic management in metastatic castrate resistant prostate cancer (mCRPC) and palliative care

Men who have progressed to this advanced stage of disease face a number of challenges and are best treated by a multidisciplinary team. Palliative care should form a key component of the treatment management.

Bone metastases

Most men with mCRPC will have painful bone metastases which cause significant morbidity and mortality often culminating in skeletal-related events (SREs). Preventing and or delaying the onset of bony metastases complications is the main aim of bone-targeted palliative therapies.

A single fraction of External beam radiation is highly effective.

If this option is not available a single infusion of a third-generation bisphosphonate can be used.

SREs include vertebral collapse or deformity, spinal cord compression and pathological fractures.

Spinal cord compression is an emergency and patients should be educated about the symptoms to enable them to seek treatment timeously. High-dose corticosteroids must be administered and a MRI performed as soon as possible. Referral to a neurosurgeon or orthopaedic surgeon is required. EBRT should be administered post-surgery.

Treatments to prevent skeletal-related events (SREs)

Zoledronic acid: The potent bisphosphonate zoledronic acid is currently the standard of care for prevention of SREs in patients with metastatic CRPC. Zoledronic acid is recommended for the prevention of SREs in patients with metastatic CRPC and selected patients on ADT.

Denosumab is a fully humanised monoclonal antibody, administered subcutaneously that blocks the RANK ligand thereby preventing bone resorption through the activation of osteoclasts. It has been proven to be more effective than Zoledronic acid in delaying or preventing SREs.

These drugs have potentially serious side effects that require appropriate precautions. Patients must undergo a dental examination before starting therapy as the risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection. Serum calcium must be monitored, and patients should be given calcium and vitamin D supplementation.

Palliative Care

Clinicians need to address end of life issues with patients and their families with advanced prostate cancer. Communication and counselling are the foundation upon which support and care is provided to patients. To assist with this, support from a multidisciplinary palliative care team is recommended.

The Association of palliative care (APCC) provides both clinical and psychosocial palliative care guidelines. These are available at: <https://apcc.org.za/Resources/clinical-guidelines/>

A listing of palliative care centres is also available on the APCC website at: <https://apcc.org.za/find-a-palliative-care-centre/>

MANAGING THE SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY (ADT)

Androgen deprivation causes castrate levels of testosterone which results in changes to physical, psychosocial and sexual function resulting in major impact on quality of life. The use of a multidisciplinary team of healthcare professionals is recommended to help men and their families to better manage the physical and psychological effects of ADT.

Cardiometabolic Health

This refers to the impact of ADT on cardiovascular disease (CVD), body composition, and metabolic parameters (including lipid profiles, insulin resistance, and glucose homeostasis).

Cardiometabolic domains affected by androgen deprivation therapy

Domain	Effect of androgen deprivation therapy
Cardiovascular complications	Increases the risk of cardiac complications, particularly in men with pre-existing cardiovascular disease
Thromboembolic and cerebrovascular events:	Increased risk for: • venous thromboembolism • stroke
Body composition	Increased risk for: • weight gain and fat accumulation • decrease in lean body mass • decrease in muscle mass
Metabolic parameters	Increased risk of: • insulin resistance • glucose intolerance

	• changes in lipid profile • type 2 diabetes • worsened glycaemic control in men with existing diabetes • metabolic syndrome
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Adapted from: Kokorovic A, So AI, Serag H, et al. Canadian Urological Association Guideline on androgen deprivation therapy: Adverse events and management strategies. Can Urol Assoc J 2021;15(6):E307-22. <http://dx.doi.org/10.5489/cuaj.7355>

Management of Cardiometabolic Risks caused by androgen deprivation therapy (ADT)

Advise the patient's general practitioner or primary care clinic when initiating ADT that there may be adverse effects. Counsel the patient on appropriate lifestyle changes and refer to other healthcare professionals where appropriate.

Baseline investigations including:

- fasting plasma glucose oral glucose tolerance test, or Hgb A1c
- full lipid profile: triglycerides, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and total cholesterol

Perform a full baseline cardiometabolic risk assessment or refer to a biokineticist/ pharmacy clinic or primary healthcare clinic. Measurements should include:

- blood pressure
- weight
- waist circumference
- body mass index (BMI)

Repeat the above tests at 6-to-12-month intervals depending on the initial risk categorisation.

Refer patients to a biokineticist for a supervised exercise program where possible or provide information on an appropriate exercise program for men on ADT.

In patients with a history of myocardial infarction (MI) or stroke, referral to a cardiologist for assessment and medical optimization prior to initiating ADT should be done.

Hot flushes

This is a common symptom of ADT that can affect QOL in men. It is characterised by an intense feeling of warmth across the face, throat and chest area which may be accompanied by profuse sweating, nausea, anxiety and palpitations. Some men have only occasional flushes and others experience them frequently. They can cause sleep disturbance which contributes to fatigue.

Managing hot flushes

Medications that can be used to treat hot flushes are shown below with efficacy rates and potential side effects:

Medications	Example of Medication	Effectiveness	Most common side effects
Hormonal	medroxyprogesterone	70% - 80%	bloating, blood clots

	estradiol patches	70% - 80%	gynecomastia
Antiandrogens	cypoterone-acetate	70% - 80%	fatigue, weakness
Antidepressants	venlafaxine	50% - 60%	anorexia, dry mouth, insomnia, nausea
Anti-seizure	gabapentin	50% - 60%	dizziness, fatigue somnolence

Lifestyle changes are an important way for men to manage hot flushes and patients should be advised to avoid potential triggers. These include:

- Wearing lighter cotton clothing and using lighter bedding
- Use fans and air conditioners or ensure that the room has good ventilation
- Avoiding hot spicy foods that cause sweating
- Reduce or eliminate alcohol as it reduces heat tolerance

Acupuncture is an option for men who are unwilling to use medication, however there are no randomized clinical trials to support efficacy.

Cognitive function and mental health

Use of ADT may cause changes in cognition and can lead to depression and the development of dementia. In studies, self-reported cognitive changes of ADT included difficulties with concentration, information processing, verbal fluency, visual information processing, visuospatial function, memory, and executive function, as well as neuro-fatigue and apathy.

ADT may cause depression and worsening of depressive symptoms in patients with pre-existing depression.

Patients on ADT may be at increased risk for developing dementia and/or Alzheimer's disease.

Managing Cognitive changes

Clinicians should monitor patients throughout ADT for cognitive changes and depression. Dementia has potential legal implications in terms of the legal capacity that a person requires to manage their affairs and to make important decisions, including providing informed consent for medical treatment. Many patients on ADT are elderly and already at risk for dementia.

A simple baseline test such as the mini mental state examination (MMSE) is extremely useful to evaluate cognitive decline and for referral to a psychiatrist should further evaluation be required.

Changes in body composition

Maintaining a healthy body composition is a challenge for many men when they commence with ADT. Caloric intake may need to be adjusted due to the decrease in the basal metabolic rate caused by the loss of muscle mass from ADT induced hypogonadism.

Vitamin D and calcium supplementation may be required to help with bone health. For vitamin D deficiency a dose of at least 800 IU/day colecalciferol can be recommended.

Referral to a dietician to assist with dietary changes is recommended for men who require assistance with maintaining a healthy body composition.

Physical changes

The impact of the physical changes caused by ADT should not be underestimated. They can have a major impact on a man's self-esteem and sense of masculinity. Changes may include:

- a reduction in penis size (one study has shown a decrease on average from 10,76 to 8.05 cm)
- testicular atrophy
- gynecomastia and mastodynia
- an increase in body fat and a decrease in muscle mass

Sexual Function

ADT has a major impact on sexual function. Within a few months of starting ADT, either with LHRH agonist or surgical castration, 90% of men will experience a loss of libido. Many men will also experience erectile dysfunction which can have a major impact on a man's self-esteem and affect their relationship with their partner.

Other changes in sexual function that may occur include:

- fewer or no nocturnal and awakening erections
- a reduction in the volume of the ejaculate
- decreased sensitivity to sexual stimulation
- difficulty achieving an orgasm

Managing the sexual side effects of androgen deprivation therapy

Sexual dysfunction should be anticipated and men who want to continue being sexually active should be referred to a sexologist for multimodal treatment.

Intermittent ADT may improve libido and erectile function and should be considered in appropriately selected patients. Rather than simply providing the patient with a list of potential side effects, clinicians should discuss the anticipated effect of the potential changes. When possible, partners should be included in the treatment discussion.

Intermittent ADT may improve libido and erectile function and should be considered in appropriately selected patients.

1. Managing low libido

Some data support has showed a positive effect of bupropion on sexual desire and can be considered as a treatment option. Professional sexual therapy can invoke awareness of sexual fantasies, relying on their potential to trigger sexual desire and arousal. Counselling can also recruit past sexual fantasies and explore expanding erogenous zones. Cognitive reframing of sexual experiences and mindfulness techniques may also be helpful for men on ADT.

2. Managing erectile dysfunction

Men who have good erectile function before starting ADT may benefit from penile rehabilitation using established medical treatments several times a week to ensure that erectile tissue is oxygenated. Oral medications (PDE5 inhibitors) are usually the first

treatment of choice but if they are ineffective, vacuum pump devices, constriction bands, intravenous injectables and penile implants are options.

3. Managing orgasmic dysfunction

Successful treatment of a patient with orgasmic difficulties requires experimentation and open-mindedness regarding the use of sexual aids, such as vibrators, masturbatory aids or penetrative aids to induce orgasm. Referral to a sexual therapist can also aid in experimentation with other sources of stimulation (i.e., new breast sensitivity, perineal or perianal stimulation). Men should also be instructed that prolonged stimulation will be required to achieve orgasm with a flaccid penis, and that the use of a lubricant can help protect the skin from potential irritation.

Reference: Androgen Deprivation Therapy for PCa: Recommendations to Improve Patient and Partner quality of life. Elliot et al. J Sex Med 2010; 7:2996-3010

Fatigue and anaemia

Extreme tiredness is a common complaint of men on ADT and the cause can be multifactorial. The anxiety of dealing with a diagnosis of advanced PCa, pain and coping with other treatment side effects can contribute. Patients may not be able to perform at levels that they were previously able to. Anaemia is a common side effect of ADT and is usually normocytic and normochromic. Haemoglobin levels do not normally decrease to clinically relevant levels. Managing fatigue and anaemia

Exercise has been shown to be the most successful treatment for fatigue and referral to a biokineticist is recommended.

Symptomatic anaemia should be investigated by checking for common secondary underlying causes such as vitamin B12 folate or iron deficiencies. In extreme cases blood transfusion and erythropoietin can be considered.

Bone health and osteoporosis associated with androgen deprivation therapy

ADT negatively affects bone health by causing decreased bone mineral density (BMD), osteoporosis, and increasing the risk for clinical fractures. Many PCa patients are already at risk for osteoporosis due to their age. BMD loss occurs at a maximum rate during the first year of therapy but continues to decline with prolonged use. Men receiving ADT have a 23% increased risk of fracture.

Managing changes to bone health

Baseline assessment

- A comprehensive history and physical examination to include falls risk and height measurement should be performed prior to initiating ADT
- screen men when initiating long-term ADT for osteoporosis using BMD testing with dual energy x-ray absorptiometry (DEXA)
- DEXA should be repeated every 2–3 years in men at low risk for fractures receiving ADT
- In men with osteopenia or those at moderate or high risk for fractures DEXA should be repeated every 1–2 years until treatment cessation
- obtain baseline calcium and 25-hydroxyvitamin D levels at the start of ADT

Diet, alcohol and supplements

Patients who smoke should be referred for treatment to facilitate smoking cessation.

Patients should be advised to limit alcohol intake

Calcium and vitamin D supplementation (800–2000 IU PO daily) should be initiated at the start of ADT

Pharmacological Interventions

In men with osteoporosis and those with history of fragility fractures in the hip or spine, those with a history of multiple fragility fractures, or those with a moderate or high 10-year fracture risk should be treated with a bisphosphonate or denosumab at doses recommended for the general population.

Gynecomastia

Gynecomastia can be primary or secondary to any hormonal manipulation but is of special importance when bicalutamide 150 mg monotherapy is used. Prevention of gynecomastia can be achieved by prophylactic mastectomy or single dose (10Gy) radiotherapy or 3 consecutive doses of 250 cG.

Treatment

Subareolar mastectomy

Exercise guidelines for men on androgen deprivation therapy

Exercise plays a key role in mitigating many of the the side effects of ADT including:

- Reduction of cardiometabolic risks
- Helping to maintain bone health
- Helping maintain mental health
- Helping and improvements in sexual function.

Wherever possible patients should be referred to a biokineticist for an appropriate exercise program. If this is not possible, they should be referred to a reliable source that provides guidance on exercise for men on ADT.

Exercise assists in the improvement of several of the side effects of ADT including:

- Health-related physical fitness components:
 - Assisting with maintenance/increase of aerobic capacity^{1a, 2}
 - Improving/maintaining body composition²
 - Assisting in maintenance/improvement of lean muscle mass and strength^{1a, 2}
 - Improving physical function and maintaining flexibility^{1a, 2}
- Skill related physical fitness components:
 - Improving/maintaining agility²
 - Improving coordination and ability to perform activities of daily living (ADL)^{2, 3}
 - Improving proprioception (stationary and in motion) and decreasing risk of falling/fracture^{1b, 3}

- Assisting in maintenance/improvement of lean muscle power (rate of work)²
- Improving reaction time and speed of motion/movement²
- Reducing fatigue^{1a}
- Additional benefits may include:
 - Reducing bone loss^{1b}
 - Improved sexual function^{1b}
 - Reduced rates of depression and anxiety^{1b}
 - Enhanced feelings of well-being⁴

Although there is currently no proven agreement on the exact frequency and intensity of exercise which should be prescribed, for men on ADT, exercise has been proven to assist as an adjunct treatment for these patients, especially within the initial 6-9 months of treatment initiation^{3, 5, 6, 7}. It is recommended that a Biokineticist initially be consulted to assist in risk profiling, baseline analysis and exercise prescription/supervision on the initiation of ADT.

An exercise regime should include a combination of aerobic exercise, resistance training, weight bearing exercise and flexibility training.^{1c}

Exercise Guidelines to assist biokineticists with managing men on androgen deprivation therapy are available on the healthcare professional's section on the The Prostate Cancer Foundation's website at <https://prostate-ca.co.za/>

SUMMARY OF PROSTATE CANCER TREATMENT OPTIONS BY STAGE

Treatment options by disease stage		
Localised Prostate cancer	Low Risk disease	Active surveillance Watchful waiting Low dose brachytherapy Radical prostatectomy External beam radiation
	Intermediate Risk disease	Active surveillance Watchful waiting Radical prostatectomy External beam radiation + neoadjuvant androgen deprivation therapy Low dose Brachytherapy + External beam radiation + neoadjuvant androgen deprivation therapy
	High Risk disease	Watchful waiting Radical prostatectomy + extended pelvic lymph node dissection External beam radiation + neoadjuvant androgen deprivation therapy Low dose Brachytherapy + External beam radiation + neoadjuvant androgen deprivation therapy
Locally advanced Prostate cancer		Watchful waiting Radical prostatectomy + extended pelvic lymph node dissection Low dose or high dose brachytherapy boost + External beam radiation + neoadjuvant androgen deprivation therapy
Non-metastatic castrate resistant prostate cancer		For BCR after radical prostatectomy: In EAU defined low-risk patients offer monitoring Offer Early salvage external beam radiation to men with 2 consecutive PSA rises For biochemical recurrence after radiation therapy: In EAU defined low-risk patients offer monitoring Only offer salvage radical prostatectomy, brachytherapy or stereotactic body radiotherapy, to highly selected patients with biopsy-proven local

		recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres. Androgen deprivation therapy In high-risk patients weigh up benefits of ADT vs SE's ADT + enzalutamide or enzalutamide monotherapy is superior to ADT alone
Non-metastatic Castrate resistant prostate cancer		For patients at high risk of developing metastasis (PSA-DT < 10 months) ADT + apalutamide ADT + darolutamide ADT + enzalutamide
Metastatic Prostate cancer	Hormone sensitive	Doublet therapy with: - ADT + abiraterone/prednisone - ADT + enzalutamide - ADT + apalutamide - Triplet therapy for high volume disease ADT + ARPI + docetaxel Add radiotherapy for low volume disease ADT alone for frail patients who cannot tolerate the above Treatments Bone health agent
	Castration- resistant (first line) & Depending on previous treatments	ADT is continued and the following may be added: ARPI's: Abiraterone/ Enzalutamide/apalutamide Cabazitaxel if docetaxel has been used Radium 223Ra for patients unfit for above treatments & bone-only metastases
	Castration- resistant (second line) & Depending on previous treatments	ADT is continued and the following may be added: ARPI's: Abiraterone/ Enzalutamide/apalutamide (Sequencing of ARPI's is not recommended especially in patients who had a short response (< 12 months), to the first ARPI for mCRPC because of cross resistance (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations PSMA can be used in pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA