

SOUTH AFRICAN PROSTATE CANCER GUIDELINES – Draft Version 2017

AUTHORS

1. Anderson D
2. Barnes R
3. Bida Meshack
4. Bigalke M
5. Bongers M
6. Chetty P
7. Coetzee L
8. De Kock M L S
9. De Muelenaere G
10. Demetriou G S
11. Ellmann A
12. Goetsch S
13. Haffejee M
14. Heyns C F
15. Jacobs C
16. Jones L
17. Jordaan A
18. Kotzen J
19. Lazarus J
20. Mackenzie M,
21. Moshokoa E M
22. Mutambirwa S B A
23. Naudé A
24. Porteous P
25. Rapoport B
26. Ruff P
27. Sathekge M
28. Segone A M
29. Urry J
30. Van der Merwe A
31. Vangu M
32. Van Wyk A
33. Wentzel S

1. Department of Radiation Oncology - Groote Schuur Hospital
2. Division of Urology-University of Cape Town (retired)
3. Division of Pathology-Sefako Magatho Health Sciences University
4. Urologist Private Practice-Somerset West, Vergelegen Clinic, Cape Town
5. Urologist Private Practice-Pretoria Urology Hospital
6. Urologist Private Practice-St Augustine Hospital, Durban
7. Urologist Private Practice-Pretoria Urology Hospital
8. Urologist Private Practice-N1 City, Cape Town
9. Oncologist –(retired)
10. Department of Medical Oncology- University of the Witwatersrand
11. Nuclear Medicine Division – Stellenbosch University
12. Pathologist Private Practice-Lancet Laboratories
13. Department of Urology-University of the Witwatersrand
14. Department of Urology-Stellenbosch University
15. Oncologist Private Practice-Gvi Oncology, Panorama Cape Town
16. ICON Clinical Executive
17. Oncologist Private Practice-Westridge Medical Centre,Durban & Pinnacle Point Richards Bay
18. Department of Radiation Oncology-Charlotte Maxeke Academic Hospital & Donald Gordon Medical Center
19. Division of Urology-University of Cape Town
20. Urologist Private Practice-Westhill & Hillcrest Hospitals, Durban
21. Department of Urology-University of Pretoria
22. Department of Urology-Sefako Makgatho Health Sciences University
23. Urologist Private Practice-Panorama Medi Clinic, Cape Town
24. Urologist Private Practice-Olivedale Clinic, Johannesburg
25. Oncologist Private Practice-The Medical Oncology Centre Rosebank, Johannesburg
26. Department of Medical Oncology-University of the Witwatersrand
27. Department of Nuclear Medicine-University of Pretoria
28. Department of Urology-Sefako Makgatho Health Sciences University
29. Department of Urology-Greys Hospital Pietermaritzburg
30. Department of Urology-Stellenbosch University
31. Department of Nuclear Medicine-University of the Witwatersrand

32. Anatomical Pathologist: National Health Laboratory Services and Stellenbosch University

33. Department of Urology-University of the Free State

Commissioned and endorsed by;

South African Urological Association (SAUA)

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Corresponding authors:

Shingai Mutambirwa (sbmutambirwa@hotmail.com)

Bernardo Rapoport (brapoport@rosebankoncology.co.za)

LIST OF ABBREVIATIONS

AS – active surveillance
ASAP – atypical acinar proliferation
5ARI – 5 alpha reductase inhibitors
CAT – computed axial tomography
CLD – clinically localised disease
CRPC – castrate resistant prostate cancer
DRE – digital rectal examination
ERBT – external beam radiation
GS – Gleason score
HRPCa – high risk prostate cancer
IB – interstitial brachytherapy
IRPCa – intermediate risk prostate cancer
LHRH – luteinizing hormone releasing hormone
LND – lymph node dissection
LRPCa – low risk 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
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

ABSTRACT

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 also the second leading cause of cancer mortality after lung cancer.

Emerging data show that 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 PCa.

It is therefore imperative that structured guidelines be available for management of this condition.

Conclusions & Recommendations-

PCa screening, treatment and follow-up should be individualised but encouraged for healthy, motivated males.

PCa is probably the commonest cancer in men in South Africa (SA) and causes a significant amount of morbidity and mortality. 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.

CONFLICT OF INTEREST - All contributing urology authors were paid an unconditional honorarium of R2000 by the SAUA in 2013.

1. INTRODUCTION

The prostate is a gland situated around the urethra at the base of the bladder.

Although its function in production of the enzyme necessary for semen liquefaction has not been proven to be essential for reproduction it is a site for significant urological conditions including cancer.

Prostate cancer (PCa) is probably the commonest cancer in SA males with 1 in 28 men getting PCa in their lifetime and upwards of 20% of these diagnosed cases dying from the disease.^[1,2]

The management of PCa is complex and these guidelines serve as a framework for the treatment of this disease in South Africa with reference to internationally accepted norms.

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

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.

Due to the wide variety of management choices it is essential that the final decision about treatment should be made by a fully informed patient preferably assisted by his partner and/or other family members.

Complete and unbiased information should be given from all relevant experts who may be involved in the patient's diagnosis and treatment.

Patient participation in clinical trials constitutes good clinical practice.

Treating physicians should not allow preconceived opinions or other biases to prevent them from encouraging their patients to participate in clinical trials.

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 given. These can be supplied on request for specific recommendations.

2. PREVENTION

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

Trials of medical therapies using 5-alpha-reductase inhibitors (5ARIs – finasteride and dutasteride) have been shown to reduce prostate cancer risk. ^[7]

However the studies also showed that PCa diagnosed in men on 5ARI treatment was of higher grade than in the placebo group.

Therefore these drugs though effective in the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia cannot currently be recommended for prevention of PCa.

3. DETECTION, DIAGNOSIS AND SCREENING OF PROSTATE CANCER

Digital rectal examination (DRE) and serum prostate specific antigen (PSA) screening of asymptomatic men reduces PCa mortality. ^[29,30,34]

However this is at the cost of increasing over diagnosis and overtreatment and therefore population based screening is not recommended. ^[31,32]

In contrast 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 patients and in those with a positive family history of prostate and/or breast cancer in a first degree relative.

- From the age of 45 years in all other males.
- In addition, patients with a history of lower urinary tract symptoms (LUTS) and/or clinical suspicion of prostate cancer regardless of age group should have their PSA tested. Periodic reassessment will be determined by the initial PSA and DRE result.

3.1. Diagnostic approach to prostate assessment

A focused urological history and clinical examination form the basis of all assessments.

DRE is recommended in all patients. An abnormal DRE is suggested by the presence of nodules, asymmetry, irregularity, and tethering of the overlying mucosa. A normal DRE does not exclude prostate cancer. DRE should include palpation of the rectum and inspection of the faeces on the glove.

3.2. Prostate specific antigen (PSA)

PSA (also known as kallikrein-3) is a glycoprotein enzyme normally found in seminal fluid.

Serum testing of PSA levels is advised as an adjunct to DRE for PCa screening.

In patients undergoing screening who have a normal DRE in the presence of a raised PSA a repeat test after 6 to 8 weeks can be a valid approach to minimize unnecessary biopsies.

PSA level is not reliable screening test for PCa in the presence of active urinary tract infection, recent urinary tract instrumentation and/or urinary retention and a repeat PSA is also recommended after resolution of these conditions before deciding on further work up for PCa.

Routine DRE does not elevate PSA significantly.

3.3. Prostate Cancer Antigen 3 (PCA3)

PCA3 is a urine test utilising a non-coding messenger ribonucleic acid which is up-regulated almost exclusively in PCa.

PCA3 therefore has the advantage over PSA in that it is specific to prostate cancer as opposed to other conditions such as BPH and prostatitis.

PCA3 is tested using the first 10ml of urine passed after prostatic massage.

This test may be of value in stratifying risk categories in patients in whom prostate cancer is suspected.

These include patients who have had one or more negative prostate biopsies who still demonstrate a raised or rising PSA patients or have histology containing atypical acinar proliferation (ASAP) lesions to guide the decision for further biopsies. ^[27]

Patients on active surveillance form another group where PCA3 may assist in decision making.

PCA3 is not currently recommended to be used in place of PSA testing.

PCA3 has been withdrawn from use in SA due to technical issues but this and other molecular and genetic markers may be introduced into PCa management algorithms in the near future.

3.4 Other genetic markers

Advances in genetics to decide on repeat biopsies and risk stratify PCa patients are improving.

Tests such as Polaris and Oncotype Dx may be of use in specific instances.

4. INDICATIONS FOR PROSTATE BIOPSY

Current indications for prostate biopsy include an abnormal DRE and/or a total PSA above the age related norm.

Normal age related total PSA reference ranges are:

- 40 – 50 years 0 - 2.5 ng/mL
- 50 – 60 years 0 - 3.5 ng/mL
- >60 years 0 - 4.0 ng/mL

Free to total PSA ratio and complex PSA can be performed at the clinician's request in men with a total PSA above the age related reference range but less than 10 ng/mL to improve decision making.

Free to total PSA less than 20% indicates a higher risk of the possibility of PCa.

Increased PSA velocity (defined as an increase of greater than 0.75 ng/mL or 25% per year) can also be an indication for a prostate biopsy.

4.1. Biopsy technique

Different biopsy techniques can be employed including perineal and trans-rectal ultrasound (TRUS) guided.

Antibiotic prophylaxis is essential in TRUS guided biopsies.

Written informed consent is required even if biopsy is done without local anaesthesia as an outpatient procedure.

PCa diagnosis can be made without biopsy in carefully selected patients with a clinically malignant prostate on DRE, markedly raised PSA and/or other clinical evidence of advanced disease to limit morbidity and cost.

It is recommended that between six and twelve biopsy cores be taken depending on the size of the prostate and localization of the lesion.

Biopsy cores should include lateral, para-sagittal and suspicious areas.

More biopsies can be taken at the discretion of the urologist.

This may increase the number of diagnosed PCa but runs the risk of over diagnosis of indolent disease with the possibility of overtreatment in some men. ^[28]

4.2. Indications for repeat biopsy

Indications for repeat biopsy are complex and this decision should be based on extensive discussion between the patient and his physician.

These include clinical (e.g. DRE changes) biochemical (e.g. rising PSA) and histological such a previous finding of high grade prostatic intraepithelial neoplasia and/or ASAP.

5. PATHOLOGY OF PCa

The pathologist is an integral part of decision making for a patient with PCa.

Management is directly linked to the report on grading, percentage and numbers of cores as well as ancillary information such as seminal vesicle involvement and peri-neural invasion to mention a few.

The original Gleason grading system has been undergoing changes which are represented by local pathologists in giving the “old” system next to the newer one.

Though this document does not have the capacity to be exhaustive regarding the 2016 WHO Classification (71) a selection of the major relevant changes are given below;

5.1 - In addition to the Gleason score, the Grade Group is added-

5.1.1- Grade group 1: Gleason score 6 or less

5.1.2- Grade group 2: Gleason 3 + 4

5.1.3-Grade group 3: Gleason 4 + 3

5.1.4-Grade group 4: Gleason score 8

5.1.5-Grade group 5: Gleason score of 9 / 10

The 2 groups are captured to reflect the recommendations in the recently published WHO Classification of Tumours of the Urinary System and Male Genital Organs, 4th ed.

Synopsis of the major rationale:

a) To limit the confusion for both treating physicians and patients surrounding the “lowest” Gleason grade being 3+3=6

b) There is a significant prognostic difference in Gleason 3 + 4 (Grade group 2) versus Gleason 4 + 3 (grade group 3). Simply capturing a total Gleason score of 7 will result in a loss of this information.

5.2- Number of cores / Total cores” be changed to Number of POSITIVE cores / Total cores
–

Rationale: To avoid ambiguity.

5.3- “% Cores Positive” be changed to “% Core Tissue Positive”-

Rationale: To avoid ambiguity.

5.4-Consider adding percentage of Gleason pattern 4 for Gleason score of 7-

Rationale: Patients with Gleason score 7 with a small percentage of Gleason pattern 4 may be considered for active surveillance.

6. RISK STRATIFICATION FOR CLINICALLY LOCALISED PCa (RS)

When clinically localised PCa has been diagnosed risk stratification is an important part of planning the most appropriate treatment option for the patient and assessing potential outcomes.

PSA, clinical stage (T) and histological Gleason score (GS) are the mainstay of RS.

Ancillary imaging and laboratory tests may assist in RS.

6.1. Low risk disease (LRPCa)

T1 - T2a and

GS - 2 to 6 and

PSA less than 10 ng/mL

If the life expectancy exceeds ten years treatment options include active surveillance (AS) radical prostatectomy (RP) and radiation therapies (RT) which can be broadly divided into external beam radiotherapy (EBRT) and interstitial brachytherapy (IB).

If life expectancy is less than ten years treatment options include watchful waiting (WW).

6.2. Intermediate risk disease (IRPCa)

T2b – T2c and/or

GS -7 and/or

PSA- 10 – 20 ng/mL

If the life expectancy exceeds ten years treatment options include ERBT, IB RP with pelvic lymph node dissection (LND) or combinations of these.

If the expected survival is less than ten years treatment options include WW

6.3. High risk disease (HRPCa)

T3a or T3b and/or

GS - 8- 10 and/or

PSA \geq 20 ng/ml

This group represents locally advanced but potentially curable disease.

Curative therapeutic options include ERBT and/or IB with long term androgen deprivation therapy (ADT) for 24-36 months, RP with LND. Non curative options include ADT alone.

7. TREATMENT OPTIONS FOR DIAGNOSED PROSTATE CANCER

7.1. CLINICALLY LOCALIZED PROSTATE CANCER (CLD)

CLD present the most curable form of PCa and can occur in all the RS detailed in 5.

CLD is determined using clinical RS and various combinations of other staging investigations (SIs).

The aim of using these SIs is to rule out extra prostatic extension of the PCa and/or skeletal, lymph node and visceral metastases.

7.2. STAGING INVESTIGATIONS FOR CLD

Recommended SIs currently include TRUS, LND, TC-99m methylene diphosphonate (MDP) bone scintigraphy, F18 Choline and Ga68 Prostate specific membrane antigen (Ga68 PMSA), Positron emission Tomography/Computed Tomography (PET/CT), computed axial tomography (CAT) scanning and magnetic resonance imaging (MRI).

As the incidence of local or distant spread is negligible in LRPCa SIs are rarely indicated.

In IRPCa and HRPCa they can be used at the discretion of the treating physician.

MRI guided biopsies can increase diagnostic yield of significant PCa in biopsy naive patients and change the RS of proven cancer particularly LRPCa on AS.

The cost-benefit should therefore be weighed to decide when MRI should be used in biopsy protocols.

Single photon emission tomography (SPECT) may provide better assessment of bone metastases when compared to planar bone scan.

PET/CT is currently not indicated for initial staging of CLD but be of use in select cases of clinically recurrent disease post definitive management.

8. DEFINITIVE MANAGEMENT OPTIONS FOR CLD

A- Deferred treatment

B- Active surveillance - (AS)

C- Watchful waiting - (WW)

D- Radical prostatectomy – (RP)

Retro-pubic

Perineal

Laparoscopic

Robot assisted laparoscopic

All techniques of radical prostatectomy are acceptable with comparable results in efficacy and morbidity.

Salvage radical prostatectomy after radiotherapy has a limited role in a select group of patients.

E- Radiotherapy (RT)

External beam radiotherapy (ERBT)-3dimensional conformal, intensity modulated, proton beam

F- Interstitial brachytherapy (IB)

All techniques of RT are acceptable with comparable results in efficacy and morbidity.

According to risk stratification radiation can be combined with ADT.

G- Cryotherapy

High intensity focused ultrasound (HIFU)

Both these are currently experimental outside clinical trials

H- Androgen deprivation therapy (ADT)

8.1. Active surveillance (AS)

AS is an increasingly recognized management option for men with LRPCa.

Despite encouraging evidence for oncologic efficacy and reduction in morbidity, several barriers contribute to the underuse of this management strategy.

Consistent selection criteria as well as identification and validation of triggers for subsequent intervention are essential.

AS consists of regular monitoring of patients with the intent of curative treatment if disease progression occurs.

Patients should commit to a regular follow-up with DRE and PSA.

Repeat biopsy is indicated every 12 – 24 months or with any indication of disease progression on examination or markers.

AS is an option in men with LRPCa and highly selected IRPCa.

Besides the standard RS stated in 5 other indicators of to guide an AS protocol may include;

- PSA density $< 0,15 - 0,2$
- $\leq 50\%$ of PCa in any biopsy core (8)

8.2. Watchful waiting (WW)

Watchful waiting consists of regular monitoring of the patient with the intention of palliative treatment on disease progression.

Patients should commit to a regular follow-up with DRE and PSA.

These are usually older patients with asymptomatic or minimally symptomatic disease and/or patients with pre-existing co-morbidities which places them at risk of death from other causes in less than ten years.

8.3. RP and RT in metastatic PCa

Outside of a trial these therapies must be used judiciously only in highly select patients.

9. TREATMENT OPTIONS FOR FAILED THERAPY FOR CLD

Failed therapy for CLD can be diagnosed using any combination of pathological staging, symptoms, serial imaging or rising PSA.

9.1. Post RP

In the presence of positive margins, positive lymph nodes or seminal vesicle involvement options include AS, ERBT to prostate bed and pelvic lymph nodes, WW and ADT.

9.2. Rising PSA post definitive management

Options include WW, ADT and targeted radiotherapy to pelvis/prostate bed or metastatic lesions.

9.3. Post RT

Options include WW, ADT and salvage radical prostatectomy in highly selected cases.

10. LOCALLY ADVANCED OR METASTATIC PROSTATE CANCER

The majority of males in South Africa present with locally advanced and/or metastatic disease at presentation.

In addition up to 30% of PCa treated with curative intent progress to this stage. ^[20]

Standard treatment for locally advanced and metastatic PCa is ADT as these cancers are almost uniformly castrate sensitive (SPCa). ^[15]

Unfortunately the vast majority of SPCa eventually stop responding to ADT leading to the development of so called castrate resistance prostate cancer (CRPC) usually with clinical progression of the disease.

The goals of treatment for both SPCa and CRPC are to delay disease progression, improve quality of life and increase survival.

The choice of treatment is dependent on an informed patient decision making, availability of treatment, cost and complications.

Delaying ADT in SPCa until the patient is symptomatic has pros and cons but must be discussed due to the potential toxicity of ADT. ^[34]

Chemotherapy and novel treatments can be considered in high volume SPCa and CRPC.

These indications and other novel therapies are discussed in 10.2.

10.1. Types of ADT

10.1.1. First line

Medical

- Parenteral oestrogens
- Luteinizing hormone releasing hormone agonists or antagonists (LHRH)
- Anti-androgens
- Combinations of above

Surgical

- Bilateral orchiectomy
- Bilateral sub-capsular orchiectomy

10.1.2. Second line

- Ketoconazole
- Withdrawal of anti-androgens
- Corticosteroids

10.2. Systemic treatment of SPCa and CRPC ^[69]

PCa metastasis occurs most frequently to bone.

Bone lesions are predominantly osteoblastic in nature and occur in more than 80% of patients with CRPC (36-37) and a significant number of SPCa who have failed or never had primary treatment.

Bone metastasis can be associated with complications such as severe pain, increased risk of fracture and possible neurologic complications. ^[36]

Use of ADT in all settings of PCa can also lead to osteopenia/osteoporosis and increased fracture risk.

Visceral metastases confer an even poorer prognosis and diagnoses of all metastases require a combination of examination, laboratory and imaging studies discussed in section 6.

10.2.1 Chemotherapy for SPCa

Once prostate cancer progresses it is incurable and further treatments are palliative. ^[37] ADT can be utilized in these patients to reduce tumour burden, control symptoms and prolong overall survival. ^[38]

The median duration of response to ADT is approximately 18–24 months subsequently the majority of patients will progress to CRPC.

CRPC is an aggressive disease that will progress despite testosterone levels of ≤ 50 ng/mL (castrate levels).

CRPC is diagnosed using one or more of the following criteria;

- 1) Continuous rise in serum levels of prostate-specific antigen (PSA)
- 2) Progression of pre-existing disease.
- 3) The appearance of new metastases. ^[42]

To address options to prolong survival in metastatic SPCa patients the Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate

Cancer (CHAARTED) Sweeney et al compared docetaxel chemotherapy plus ADT to ADT alone. ^[39,40]

Stratification was by extent of metastatic disease into high or low volume, high volume defined as visceral metastasis and/or four or more bone metastases.

Both the primary endpoint of overall survival (OS) and secondary endpoint of time to progression (TTP) were met for high volume but not low volume SPCa.

Docetaxel + ADT can therefore be recommended for the high volume SPCa.

10.2.2 Treatments for CRPC aimed at improving overall survival

Docetaxel is the only approved first-line treatment option for patients with CRPC in South Africa.

Approved second-line treatments are cabazitaxel and abiraterone acetate.

Enzalutamide, radium-223 and the PCa vaccine Sipeulucel-T are also proven therapies in CRPC but currently are not registered in South Africa.

10.2.2.1 Docetaxel plus prednisone

Docetaxel and prednisone should be used as first-line treatment for patients with CRPC with OS and TTP benefits particularly with a good performance status. ^[44,45]

10.2.2.2 Cabazitaxel

Cabazitaxel is a potent inhibitor of microtubule depolymerization which unlike docetaxel is resistant to P-glycoprotein an ATP-dependent drug efflux pump that can be expressed by cancer cells. Cabazitaxel demonstrated activity in patients with known docetaxel-resistant CRPC in both preclinical and clinical trials. ^[46]

Cabazitaxel is approved in South Africa for use in patients with metastatic CRPC refractory to docetaxel-based chemotherapy. Patient receiving cabazitaxel should be monitored closely for neutropenic complications ^[47,48]

10.2.2.3 Abiraterone acetate

One of the mechanisms employed by CRPC cells to escape suppression by standard ADT is to utilize adrenal and intra tumour production of androgens. ^[49,50]

CYP17 is an enzyme needed for all androgen production in vivo.

Abiraterone acetate is a highly selective and potent irreversible inhibitor of CYP17.

Abiraterone acetate has a similar mechanism of action to ketoconazole but is approximately ten times more potent than ketoconazole. ^[51]

With proven OS and TTP abiraterone acetate can be used both pre and post chemotherapy but is currently only approved in the post chemo setting in South Africa. ^[52,53,54,55]

10.3 Treatment options for CRPC aimed at symptom control

Effective palliative therapies are crucial to treating metastatic prostate cancer as metastases are a common cause of severe pain.

10.3.1 Chemotherapy

Mitoxantrone plus prednisone

This combination can be used for palliation in patients with CRPC but does not improve survival. ^(41;42;56)

Vinorelbine plus prednisone

This combination offers similar therapeutic gain to mitoxantrone-prednisone combination. ^[70]

10.3.2 Bone-targeted therapy

PCa bone metastases can lead to significant morbidity and mortality often culminating in what are referred to as skeletal-related events (SREs). ^[57]

SREs include radiation or surgery to bone metastases, spinal cord compression and pathological fractures.

In addition both in the SPCa and CRPC scenarios ADT can lead to osteoporosis increasing the risk of pathological fractures. ^[21,23]

Preventing and or delaying the onset of bony metastases complication is the main aim of bone-targeted palliative therapies.

10.3.2.1 Zoledronic acid: The potent bisphosphonate Zoledronic acid is currently the standard of care for prevention of SREs in patients with metastatic CRPC. ^[58,59] Zoledronic acid is recommended for the prevention of SREs in patients with metastatic CRPC and selected SPCa patients on ADT. ^[24,25]

10.3.2.2 Denosumab: Denosumab is a fully-humanised monoclonal antibody, administered subcutaneously that blocks the RANK ligand thereby preventing bone resorption through the activation of osteoclasts. ^[60]

Though proven to be effective this agent is currently not registered in South Africa.

10.3.2.3 Radionuclide therapy: Samarium-153 and Strontium-89 are targeted radioisotopes approved for palliation of bone pain resulting from CRPC but do not improve OS.

These agents rely on selective uptake and prolonged retention at sites of increased osteoblastic activity. ^[61,62]

10.3.2.4 Radium-223: Radium-223 is the newest radioisotope selectively targeting bone metastases with high-energy short-range α -particles.

Radium 223 has proven OS and TTP benefits and is registered overseas in both the pre and post chemotherapy settings of CRPC. ^[67,68]

These agents are registered and available in South Africa.

10.4 Other CRPC agents not registered in South Africa

10.4.1 Enzalutamide is a small molecule, nonsteroidal, AR antagonist that blocks nuclear translocation and coactivator recruitment, prevents DNA binding, induces apoptosis and does not act as an AR agonist when AR is overexpressed. ^[63; 64]

Enzalutamide is registered in the USA post chemotherapy in CRPC and should soon get pre chemotherapy recommendation there.

10.4.2 Sipuluecel T is an autologous dendritic vaccine approved for use in some countries for minimally symptomatic metastatic CRPC. ^[72]

11. SUMMARY OF PROSTATE CANCER TREATMENT OPTIONS

TABLE 1

TNM*	Primary recommended	Optional
T1,T2,N0,M0	Active surveillance (AS) Radical Prostatectomy (RP) Radiotherapy (RT) Watchful waiting (WW)	Neo-adjuvant LHRH agonist or antagonist prior to RT
T3,T4,N0,M0	Androgen deprivation therapy (ADT) plus RT RP	Bicalutamide 150mg monotherapy
N+	ADT	Intermittent ADT Sequential ADT

M+	ADT	Anti-androgen therapy prior to LHRH agonists to prevent flare/SRE Intermittent ADT Sequential ADT Docetaxel
M+ CRPC**	Docetaxel Bisphosphonate	Carbazitaxel Abiraterone acetate Mitoxantrone Vinorelbine Corticosteroids Estramustine and vinblastine Strontium-89 Samarium-153 Radium-223 Denosumab*** Enzalutamide*** Sipuleucal-T***

Abbreviations;

M-metastases (+=yes 0=no)

N-nodes positive (+=yes 0=no)

T-clinical/pathological stage (T1-4)

NOTES

- This table refers to SPCa unless otherwise stated*
- Although surgical and medical castration have been shown to have equivalent efficacy, surgical castration is unacceptable to some men.
- Conversely long term LHRH agonist or antagonist therapy usually is more expensive and requires patient compliance.
- Early ADT has been shown to delay time to progression and may have a survival benefit over delayed ADT in locally advanced PCa.
- Intermittent ADT can be used as there may be a reduction in side-effects as well as cost. Efficacy of intermittent therapy as opposed to continuous ADT remains to be proven, but has shown QOL benefits.
- Timing of chemotherapy is important as chemotherapeutic agents are more effective in patients with good performance status.
- Patient monitoring on ADT includes regular history, examination and appropriate laboratory and radiological investigations. Patients on chemotherapy may require more frequent evaluation

- h. Corticosteroids are recommended for most chemotherapy regimes and must be used with abiraterone acetate.
- i. Can be primary recommended in high burden SPCa*
- j. ADT therapy should be continued regardless of options used for CRPC. **
- k. These will become primary recommendations when/if locally approved.***

11. PREVENTION AND TREATMENT OF COMPLICATIONS RELATED TO PROSTATE CANCER THERAPY

These complications are possibilities for each mode of therapy and will differ depending on patient factors, facilities and the intrinsic nature of the procedure performed. ^[16]

11.1. Erectile dysfunction ^[9]

Epidemiology ^[13]

- Frequently coexists in patients with PCa
- Immediate after RP and may improve with time
- Develops later after RT
- Incidence comparable at 2 years after both RP and RT

Prevention ^[14]

- Nerve sparing surgery
- Early phosphodiesterase-5 (PDE5) inhibitor therapy, vacuum device or intracavernosal prostaglandin after radical prostatectomy
- Bicalutamide as monotherapy or intermittent ADT
- AS

Treatment of erectile dysfunction

- Phospho-diesterase-5 (PDE5) inhibitors ^[10,11]
- Intracavernosal therapy
- Vacuum device ^[12]
- Penile prosthesis

11.2. Urethral stricture/Bladder neck stenosis

Prevention

- Optimal surgical and radiation technique
- AS

Treatment

- Dilatation
- Optical urethrotomy

11.3. 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 cause of incontinence (including medication)

Prevention

- AS
- Nerve sparing surgery
- Controlled exposure to radiation
- Pelvic floor exercise peri-operatively

TABLE 2

MILD (1-2 pads per day)	MODERATE (2-5 pads per day)	SEVERE (>5 pads per day)
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Pelvic floor exercise	Pelvic floor exercise	Artificial sphincter ^[19]
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Bulking agents	Bulking agents	Penile clamp
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Biofeedback	Slings ^[18]	Urethral occlusion devices
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Pharmacological:

α -stimulants

Anticholinergics

β3 Agonists Penile clamp - Intravesical Botulinum toxin

- Peripheral and sacral nerve stimulators

Urethral occlusion devices Urethral occlusion devices

Artificial sphincter ^[19]

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

11.4. 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

11.5. Radiation cystitis

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

11.6. 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

11.7. Gynecomastia

Epidemiology

Can be primary or secondary to any hormonal manipulation but is of special importance when bicalutamide 150 mg monotherapy is used.

Notes on bicalutamide 150 mg monotherapy ^[22]:

Prevention

- Prophylactic mastectomy or single dose (10Gy) radiotherapy or 3 consecutive doses of 250 cG. ^[26]

Treatment

- Subareolar mastectomy

11.8. Hot flushes

Prevention and treatment

- Lifestyle, Diet
- Cyproterone acetate
- Bicalutamide 150mg monotherapy
- Intermittent ADT
- Clonidine
- Low dose oestrogen and or progesterone

11.9. Osteoporosis associated with ADT ^[23]

Prevention and treatment

- Lifestyle/Exercise/Diet
- Bicalutamide monotherapy
- Intermittent ADT
- Calcium supplementation
- Vitamin D
- Bisphosphonates
- Denosumab

11.10. Depression

Prevention and treatment

- Lifestyle/Exercise/Diet
- Regular evaluation/referral to psychiatrist/psychologist
- Anti-depressants

12. TREATMENT OF COMPLICATIONS OF ADVANCED PROSTATE CANCER AND CRPC

12.1. Local complications

A. Infiltration

TABLE 3

ADT naïve

CRPC Palliation

Lower urinary tract symptoms + retention of urine ADT

Transurethral resection prostate

(TURP)

TURP

EBRT

Suprapubic catheter

Urinary diversion

Prostate stents

Ureter ADT

Ureteric bypass eg DJ-stents

Nephrostomy Assess general condition and decide as for ADT naïve or palliation Only if good performance status

Rectum EBRT

ADT

Colostomy EBRT

Colostomy

Colostomy

Pain relief

B. Urethral / Bleeding

Cystoscopy + transurethral resection and fulguration in combination with ADT

Stop

Recurrence

Follow-up

Mild

Severe

Medical

Radiotherapy

Radiotherapy
+ Embolization
(Internal iliac artery)

Oestrogens

Tranexamic acid

Urinary diversion

12.2. Systemic complications

TABLE 4

ADT naïve

CRPC

Lymphatic obstruction/Lymphoedema

ADT

Supportive therapy

Supportive therapy

Hematogenous metastases

1. Skeletal

- ADT
- Bisphosphonates
- EBRT 1st line Bisphosphonates + chemotherapy

2nd line Symptomatic Asymptomatic

Analgesics Follow-up

Corticosteroids

EBRT

Isotopes (Strontium, Samarium)

2. Soft tissue ADT

- EBRT Palliation
- Chemotherapy
- ERBT

3. Bone marrow

- metastases
- Anaemia
- Disseminated Intravascular Coagulation (DIC)
- ADT

Treat medical condition on merit (e.g. blood transfusion)

4. Spinal cord compression Emergency orchidectomy

Corticosteroids

EBRT

Surgical spinal decompression

Corticosteroids

EBRT

Surgical spinal decompression

Supportive measures

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