Prostate Cancer Diagnostic and Treatment Guidelines
The Prostate Cancer Foundation of South Africa
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These guidelines are in the process of being reviewed by:
The South Africa Urological Association (SAUA)
The South African Society of Medical Oncology (SASMO)
The South African Society of Clinical and Radiation Oncologists (SASCRO)
Revised guidelines will be published after obtaining the input of these societies

IMPORTANT

Diagnostic and treatment guidelines are intended only as a guide for clinicians and patients. The obligation to be fully informed of the latest available information pertaining to the diagnosis and treatment of prostate cancer lies with the clinician. Diagnostic and treatment guidelines cannot factor in the individual characteristics of each patient, and it is therefore the clinician's responsibility to determine whether the guidelines are relevant for each individual patient that they diagnose and treat.

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INTRODUCTION

The management of prostate cancer (PCa) is complex and these guidelines serve as a framework for the treatment of prostate cancer in South Africa with reference to internationally accepted norms. Dramatic developments in diagnostic and therapeutic modalities have led to significant changes in the treatment of prostate cancer in the past twenty years. Concepts are continually evolving as new evidence becomes available so that guidelines or recommendations should be a continuous process 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 the fully informed patient, assisted by his wife and/or other family members, who should be given access to complete and unbiased information from all the experts who may be involved in his treatment. Patient participation in clinical trials constitutes good clinical practice, and doctors should not allow preconceived opinions or other biases to prevent them from encouraging their patients to participate in clinical trials.

A literature guide is given at the end of these guidelines.

A PREVENTION OF PCA

The use of 5-alpha-reductase inhibitors (5ARIs – finasteride & dutasteride) has been shown to reduce prostate cancer risk in placebo-controlled clinical trials.

Two large randomised studies showed that PCa diagnosed in men on 5ARI treatment was of higher grade than in the placebo group. These drugs are effective in the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH) but can currently not be recommended for prevention of PCa.

B. DETECTION, DIAGNOSIS AND SCREENING OF PROSTATE CANCER

Digital rectal examination (DRE) and serum prostate specific antigen (PSA) screening of asymptomatic men reduces PCa mortality but increases overdiagnosis and overtreatment and is unavailable under the current state health system in RSA. PSA testing 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.

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.

Prostate specific antigen (PSA)

PSA related to cancer screening is not reliable in the presence of active urinary tract infection (UTI), recent urinary tract instrumentation and/or urinary retention. Treat the UTI and repeat the PSA after 6 weeks. Routine DRE does not elevate PSA significantly.

PCA3

PCA3 is a urine test having the advantage over PSA that it is specific to prostate cancer and not other conditions such as BPH and prostatitis. This test may be of value in stratifying risk categories in patients in whom prostate cancer is suspected. It may also be useful in patients who have had one or more negative prostate biopsies and who demonstrate a rising PSA, patients with atypical acinar proliferation (ASAP) lesions and even patients on active surveillance, who may be spared an unnecessary biopsy. This test is done on the first (10ml) post prostate massage urine. PCA3 is not currently recommended to be used in place of PSA testing.

Indications for prostate biopsy

The indications for prostate biopsy include an abnormal DRE and/or a total PSA above the age related norm. At first presentation if DRE is normal and PSA is below 10 a repeat PSA in 6 weeks is advised.

Normal age related total PSA reference range:

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

Free to total PSA ratio (FT) and complex PSA should be performed at the clinician's request in men with a total PSA above the age related reference range but less than 10ng/ml with a negative first prostate biopsy in order to improve decision making in addition to the DRE. If FT is > 20% follow up as opposed to re biopsy is the preferred option.

An increased PSA velocity, (defined as an increase of greater than 0.75ng/ml or 25% per year) is also an indication for a prostate biopsy.

Biopsy technique

Antibiotic prophylaxis is essential and oral quinolones are recommended as the first choice. Written informed consent is required even if biopsy is done without local anaesthesia as an outpatient procedure. Diagnosis can be made without biopsy in elderly patients with a clinically malignant prostate on DRE, markedly raised PSA and/or other clinical evidence of advanced PCa.

Trans-rectal ultrasound (TRUS) images are of limited value in diagnosing prostate cancer. Its most important use is to place needle biopsies accurately. TRUS guided biopsies are optimal, but digital guidance is acceptable if TRUS is not available. Digitally guided biopsies can be used to target palpable nodules. 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 but runs the risk of altering the dynamics of active surveillance (AS) and resulting in overtreatment.

Indications for repeat biopsy

The indications for repeat biopsy are complex and this decision should be based on extensive discussion between the patient and his urologist including the histological finding of high grade prostatic intraepithelial neoplasia [PIN III] and atypical small acinar proliferation (ASAP), rising PSA, DRE changes and possibly use of PCA3.

C. CLINICALLY LOCALIZED PROSTATE CANCER

Various staging investigations including bone scan, CT scanning, TRUS, lymph node dissection (LND) and MRI may be utilized. Since the incidence of skeletal metastases is negligible when PSA is below 10, bone scans are only advised when PSA is > 10 and/or Gleason score is 8 – 10 and/or T Stage is > T_2.
Management options for localized prostate cancer include:

- Radical prostatectomy – (RP)
  - Retropubic
  - Perineal
  - Laparoscopic
  - Robotic assisted laparoscopic

- Radiotherapy (RT)
  - External beam (3 –dimensional conformal or intensity modulated)
  - Interstitial brachytherapy

- Cryotherapy

- High intensity focused ultrasound (HIFU) → Are still experimental outside clinical trials

- Androgen deprivation therapy (ADT)

- Deferred treatment
  - Active surveillance
  - Watchful waiting

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. All techniques of radiotherapy are acceptable with comparable results in efficacy and morbidity. According to risk stratification, radiation can be combined with ADT.

Active surveillance (AS)

Active surveillance is an increasingly recognized management option for men with low-risk prostate cancer. 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. A repeat biopsy is indicated after 12 – 24 months or if there is any sign of disease progression by examination or markers.

AS is an option in men with a tumor matching or approaching the definition of "indolent" or insignificant which would include;

- PSA <10ng/ml
- Gleason score ≤6
- Stage T1-2a
- PSA density <0,15-0.2
- ≤ 50% of PCa in any biopsy core

Watchful waiting (WW)

Watchful waiting consists of regular monitoring of patients with intent of palliative treatment with disease progression. Patients should commit to a regular follow-up with DRE and PSA.
These are usually patients with low risk disease and/or with life expectancy below 10 years and/or an existing co-morbidity profile which places them at risk of death from other causes in less than ten years.

D. RISK STRATIFICATION

Risk stratification is an important part in planning the most appropriate treatment option for the patient and assessing potential outcomes.

Low risk disease

T1 to T2a clinical stage
Gleason score of 2 to 6
PSA less than 10ng/ml

If life expectancy is less than ten years then treatment options include watchful waiting. If the life expectancy exceeds ten years then treatment options include active surveillance, external beam radiotherapy (ERBT), interstitial brachytherapy (IB) and radical prostatectomy (RP).

Intermediate risk disease

T2b – T2c clinical stage and/or
Gleason 7 (3+4) and/or
PSA 10 – 20ng/ml

If the expected survival is less than ten years then treatment options include watchful waiting. If the life expectancy exceeds ten years then treatment options include active surveillance, external beam radiotherapy, interstitial brachytherapy and radical prostatectomy with a lymph node dissection or combinations of the above.

High risk disease

Clinical stage T3a or T3b and/or

Gleason 7 (4+3) to 10 and/or
PSA>= 20

This group represents locally advanced but potentially curable disease. Initial therapeutic options include radiotherapy with ADT, radical prostatectomy with pelvic lymph node dissection, ADT alone or trimodal therapy (brachytherapy plus EBRT plus ADT).

E. FAILED LOCAL THERAPY

1. **Post radical prostatectomy**

   In the presence of positive margins options include, ADT, radiation therapy and WW. Where the histology reveals positive lymph nodes or seminal vesicle involvement then ADT and/or ERBT are the preferred options.

2. **Rising PSA post definitive management**

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

3. **Post radiation therapy**

   Management options for recurrences following radiotherapy or brachytherapy include ADT, watchful waiting and possibly salvage radical prostatectomy in highly selected cases.

F. LOCALLY ADVANCED OR METASTATIC PROSTATE CANCER

The standard treatment for locally advanced PCa is ADT which delays clinical progression and improves quality of life (QOL). At this stage, chemotherapy should be considered only in castrate resistant PCa (CRPC). RP and RT can be considered in selected cases in combination with ADT.

The goals of treatment are delayed disease progression, improved quality of life and possibly increased survival. The choice of treatment is dependent on an informed patient decision and also on the availability of treatment, costs and complications.

The other standard indication for ADT is metastatic PCa. Symptomatic patients with localised prostate cancer unsuitable for curative treatment represent a further indication.

Types of ADT

First line

1. Medical
   - Parenteral oestrogens
   - Luteinizing hormone releasing hormone (LHRH) antagonists

- Luteinizing hormone releasing hormone (LHRH) agonists
- Antiandrogens
- Combinations of above

2. Surgical
   - Bilateral orchidectomy or
   - Seminectomy
   - Combination of above with antiandrogens

Second line

Ketoconazole
Withdrawal of antiandrogens
Corticosteroids

Chemotherapy

First line = Docetaxel
Second line = Mitoxantrone/Prednisone

In CRPC the use of chemotherapy may be indicated. Neuro-endocrine differentiation represents a small subset in which platinum based chemotherapy is indicated.

Treatment options (androgen sensitive disease unless otherwise stated)

TNM	Primary recommended	Optional
T1,T2,N0,M0	See above	Neo-adjuvant LHRH agonist prior to radiotherapy
T3,T4,N0,M0	ADT plus RT or RP	Bicalutamide monotherapy
N+	Continuous ADT	Intermittent / sequential ADT
M+	Continuous ADT	Anti-androgen therapy 14 days prior to LHRH agonists to prevent flare/spinal compression Intermittent / sequential ADT
M+ CRPC	ADT must continue plus chemotherapy (taxanes +/- corticosteroids)	ADT in addition to: Mitoxantrone Corticosteroid Estramustine and vinblastine Platinum based chemotherapy Strontium, samarium Bisphosphonate Denosumab, PCa vaccines, MDV3100,Carbazitaxel, Abiraterone acetate

NOTES

1. Although surgical and medical castration have been shown to have equivalent efficacy, surgical castration is unacceptable to some men. On the other hand long term LHRH therapy usually is more expensive and requires patient compliance.

2. Early ADT has been shown to delay time to progression and may have a survival benefit over delayed ADT in locally advanced PCa.

3. Intermittent therapy could 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 some QOL benefits.

4. Timing of chemotherapy is important as chemotherapeutic agents are more effective in patients with good performance status. Chemotherapy should be considered after failure of 2 lines of ADT. After 3 cycles of chemotherapy re-evaluate for response. If there is a significant reduction of PSA and/or improvement in symptom score, response is implied. There is currently no clear indication for second line chemotherapy. Carbazitaxel is registered for use after failure of docetaxel.

5. Patient monitoring on ADT includes regular history, examination and appropriate laboratory and radiological investigations. Patients on chemotherapy may require more frequent evaluation

G. 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.

1. Erectile dysfunction

Epidemiology
- Frequently coexists in patients with PCa
- Immediate after surgery, tendency to improve
- Develops later after radiation therapy- tendency to worsen with time
- Incidence comparable at 2 years after both surgery and radiation

Prevention
- Nerve sparing surgery
- Early phosphodiesterase-5 (PDE_5) inhibitor therapy, vacuum device or intra-cavernosal prostaglandin after radical prostatectomy
- Bicalutamide as monotherapy or intermittent ADT
- Active surveillance

Treatment of erectile dysfunction
- Phospho-diesterase 5 (PDE_5) inhibitors
- Intracavernosal therapy
- Vacuum device
- Penile prosthesis

2. Stricture/Bladder neck stenosis

Prevention
- Optimal surgical and radiation technique

- Active surveillance

Treatment
- Dilatation
- Optical urethrotomy

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

MILD (1-2 pads per day)	**MODERATE (2-5 pads per day)**	**SEVERE (>5 pads per day)**
Pelvic floor exercise	Pelvic floor exercise	Artificial sphincter
Bulking agents	Bulking agents	Penile clamp
Biofeedback	Slings	Urethral occlusion devices
Pharmacological: α-stimulants Anticholinergics β3 Agonists	Penile clamp	- Intravesical BotulinumToxin - 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 continues to improve
- If no improvement, wait one year

4. Radiation proctitis (and other bowel complications after radiation therapy)

- CO_2 laser therapy
- Formalin instillation
- Prednisone enema
- Hyperbaric oxygen
- Colostomy/Laparotomy
- Generally avoid biopsy of rectal lesion

5. Radiation cystitis

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

6. Urinary retention

- Alpha blockers
- Catheterization
- TUR prostate (recommended to wait at least 6-10 months after real time brachytherapy)
- Urethral stricture management

7. Gynecomastia

Epidemiology

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

Notes on B-150 therapy:

Prevention

- Prophylactic mastectomy or single dose (10Gy) radiotherapy or 3 consecutive doses of 250 cGy; prophylactic EBRT significantly reduces incidence if employed prior to initiation of therapy.

Treatment

- Subareolar mastectomy

8. Hot flushes

Prevention and treatment

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

9. Osteoporosis associated with ADT

Prevention and treatment

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

10 Depression

Prevention and treatment

- Lifestyle/Exercise/Diet
- Evaluate patients regularly/referral to psychiatrist/psychologist
- Anti-depressants

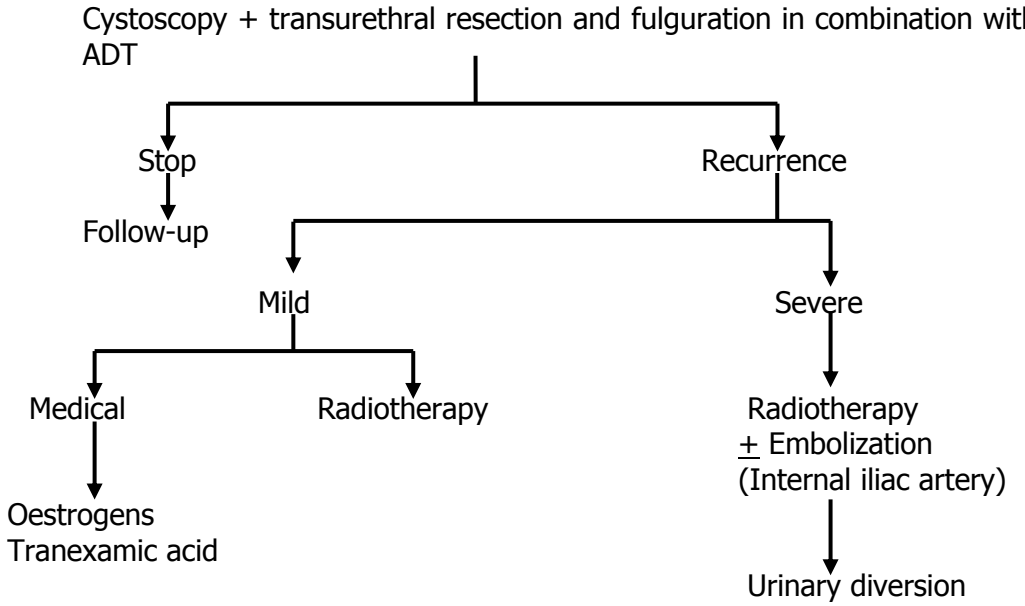
H. TREATMENT OF COMPLICATIONS OF ADVANCED PROSTATE CANCER AND CRPC

I. Local complications

A. Infiltration

	ADT naive	CRPC	Palliation
Peri-prostatic LUTS ± retention	ADT ± Transurethral resection prostate (TURP)	TUR prostate ± EBRT	Suprapubic catheter Urinary diversion Prostate stents
Ureter	ADT Bypass - J-stents Nephrostomy	Assess general condition and decide on palliation	Only if good performance status
Rectum	EBRT and/or ADT and/or Colostomy	EBRT and/or Colostomy	Colostomy for obstruction Pain relief

B. Urethral / Bleeding



II. Systemic Complications

	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 ↓ Analgesics Corticosteroids EBRT Isotopes (Strontium, Samarium) Asymptomatic ↓ Follow-up
2. Soft tissue	ADT EBRT	Palliation ± Chemotherapy ± Radiotherapy
3. Bone marrow metastases ▪ Anaemia ▪ Disseminated Intravascular Coagulation (DIC)	ADT Treat medical condition on merit (e.g. blood transfusion)	Treat medical condition on merit (e.g. blood transfusion)
4. Spinal cord compression	Emergency orchidectomy Corticosteroids EBRT Spinal decompression	Corticosteroids Supportive measures EBRT Spinal decompression

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