Egyptian National Guidelines for Prostate cancer

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Abbreviations

ADT (Androgen deprivation therapy)

ART (Adjuvant RT)

AS (Active Surveillance)

AUA (American Urological Association)

BRCA1/2 (Breast Cancer Gene)

BT (Brachytherapy)

CBC & differential (complete blood count & differential)

CT (computed tomography)

CRPC (castrate resistant prostate cancer)

DRE (digital rectal examination)

DT (doubling time)

dMMR (deficient mismatch repair)

EAU (European Association Of Urology)

EBRT (external beam radiotherapy)

ECOG (eastern cooperative oncology group)

ESMO (European Society For Medical Oncology)

HSPC (hormone sensitive prostate cancer)

HRR (homologous recombination repair)

HRD (Homologous recombination deficiency)

H-MSI (high levels of microsatellite instability)

IHD (ischemic heart disease)

IRF (intermediate risk factors)

IMRT (intensity modulated radiation therapy)

IGRT (Image Guided RT)

KFT (Kidney function test)

LFT (liver function test)

LHRH (luteinizing hormone releasing hormone)

LN (lymph node)

MCRPC (metastatic castrate resistant prostate cancer)

MDT (multi disciplinary team)

MHSPC (metastatic hormone sensitive prostate cancer)

MRI (magnetic resonance imaging)

MRI-Bx (MRI guided biopsy)

Mp MRI (multiparametric MRI)

NCCN (National Comprehensive Cancer Network)

NMCRPC (non metastatic castrate resistant prostate cancer)

PARP-inhibitors: poly (ADP-ribose) polymerase Inhibitors

Pca (Prostate Cancer)

PET (positron emission tomography)

PIRADs (Prostate Imaging-Reporting and Data System)

PS (performance status)

PSA (prostatic specific antigen)

PSA DT (PSA doubling time)

PSMA (prostate specific membrane antigen)

PLND (pelvic lymph node dissection)

RP (radical prostatectomy)

RT (radiation therapy)

SBRT (stereotactic body radiotherapy)

S-RT (Salvage RT)

TRUS (transrectal ultrasound)

TRUS-Bx (transrectal guided ultrasound biopsy)

TURP (trans urethral resection of the prostate)

VMAT (Volumetric Modulated Arc Therapy)

Glossary

Localized prostate cancer

Prostate cancer that has not spread beyond the prostate

Locally Advanced prostate cancer

Patients with T3b or T4 disease on their initial evaluation based upon the presence of presumed extra-prostatic extension and/or seminal vesicle involvement, or invasion of adjacent organs and/or regional LN metastases by radiological investigations

Biochemical recurrence

A rise in serum PSA and not accompanied by signs, symptoms, or radiographic evidence of locally recurrent or disseminated disease. (by conventional Imaging and/or PSMA-PET)

A) PSA persistence/recurrence after RP
Failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA >0.1 ng/mL.

B) Biochemical recurrence after EBRT with or without hormonal therapy is defined as a PSA rise by 2 ng/mL or more above the nadir PSA

Metastatic Hormone Sensitive Prostate Cancer (MHSPC)

MHSPC is diagnosed when cancer has spread beyond the prostate to the body and serum testosterone levels are typically >50 ng/dL ,Treatment is often effective with low testosterone levels .

MHSPC High volume criteria (CHAARTED trial)

Presence of visceral metastases

and/or ≥4 bone metastases, including at least one beyond the vertebral bodies and pelvis

MHSPC low volume criteria are defined as those who do not meet the high volume criteria

MHSPC High risk criteria (LATITUDE trial)

At least two of :

a-Gleason score of ≥ 8

b-Bone metastasis of ≥ 3

c-Presence of Visceral metastasis

MHSPC low risk criteria are defined as those who do not meet the high risk criteria

Non metastatic CRPC

Males who are diagnosed with CRPC at a time when the only manifestation of progressive disease is an increase in serum PSA level, without demonstrable radiographic disease progression (on bone scan and conventional CT) or by PSMA-PET involving specific organs, , with PSA DT ≤10 months, and a serum PSA ≥2 ng/mL.

Metastatic CRPC

Metastatic castration-resistant prostate cancer (CRPC) is advanced prostate cancer with evidence of disease progression and spread to other parts of the body despite castrate levels of serum testosterone (<50 ng/dL) after medical or surgical orchiectomy.

Executive Summary

This guidance provides a data-supported approach to the diagnosis, risk stratification, treatment and follow up of patients diagnosed with prostate cancer

Recommendations	Level Of recommendation
1-Screening for prostate cancer	
Early PSA testing (baseline PSA followed by risk-adapted follow-up) can be offered to men >50 years, men >45 years with a positive family history of prostate cancer, and BRCA1/2 carriers >40 years	Conditional
2-Work up for newly diagnosed prostate cancer	
History and physical examination Personal and family history, Physical examination, DRE , Assessment of ECOG performance status should be done	Strong
Assessment of life expectancy is a very essential tool in the plan of management of prostate cancer , Life expectancy should be estimated using: The WHO's Life Tables by country	Strong
Laboratory Studies Base line tumor marker: serum PSA (Total, Free) is the recommended initial laboratory studies for localized prostate cancer	Strong
Radiological Studies TRUS is the initial imaging studies for diagnosis of prostate cancer	
MRI prostate or mpMRI (if available) is to be used in the staging and characterization of prostate cancer	Conditional
Radiologists should utilize PI-RADS V 2.1 in the reporting of multi-parametric MRI (mpMRI) imaging	Strong
Standard MRI techniques should be used for examination of the pelvis and/or abdomen for initial evaluation of intermediate and high / very high risk patients and for planning purposes in radiotherapy protocols	Strong
Bone imaging is indicated in the initial evaluation of intermediate and high / very high risk patients to exclude skeletal metastasis	Strong

PSMA-PET if available to be considered as an alternative to standard imaging of bone and soft tissue in high and very high risk patients .	Conditional
Initial Biopsy Definitive diagnosis of cancer prostate requires 6- 12 core biopsies of the prostate, using a needle under transrectal / transperineal ultrasound guidance.	Strong
For biopsy-naïve patients who have a suspicious lesion on MRI, clinicians can perform targeted biopsies of the suspicious lesion either cognitive or software guided	Conditional
3-Risk stratification and Management of Localized / Locally advanced prostate cancer	
Patients with localized prostate cancer should be classified into very low , low , intermediate (Favourable and unfavourable) , high and very high risk groups	Strong
Risk stratification of clinically localized prostate cancer facilitate care decisions and guide clinicians in the implementation of selected management options..	Strong
Patients with prostate cancer should be managed through a multidisciplinary team (Urologist , Medical Oncologist , Radiation oncologist , Radiologist and Pathologist)	Strong
It is recommended to use one of the following options in the management of very low/low risk groups (according to MDT decision and patient preference): If expected patient survival ≥ 10 years,: • Active surveillance, • RP , • EBRT or • BT mono-therapy.	Strong
In asymptomatic patients with prostate cancer and < 10 years life expectancy , watchful waiting is recommended	Strong

According to MDT decision and patient preference; It is recommended to use one of the following options in the management of favourable intermediate risk groups (Life expectancy ≥ 10 years): • RP and PLND or • EBRT alone or • combined EBRT + BT or • BT monotherapy or • Careful active surveillance	Strong
It is recommended to use one of the following options in the management of favourable intermediate risk prostate cancer (Expected Survival 5-10 Years): • EBRT • BT monotherapy • Watchful waiting	Strong
Brachytherapy monotherapy is a recommended option for patients with very low, low, or favorable intermediate-risk prostate cancer and life expectancy > 10 years with acceptable 10-year recurrence-free survival rate for LDR/HDR brachytherapy	Strong
RP + PLND or EBRT + short course ADT (6 months) are the recommended options for management of unfavourable intermediate risk patients.	Strong
Long term ADT (2- 3 years) combined with EBRT is the recommended primary treatment for high risk or very high risk prostate cancer patients	Strong
RP and PLND is a valid option in very selected cases with high or very high risk prostate cancer based on MDT discussion	Conditional
Locally advanced prostate cancer	
Neoadjuvant ADT (4-6 months) followed by ADT + EBRT , then ADT for 2 years is the recommended treatment option for patients with locally advanced prostate cancer	Strong

RP and PLND can be an option in selected cases of locally advanced prostate cancer according to MDT decision	Conditional
Patients who choose active surveillance program should have regular follow-up with baseline biopsy , serum PSA level , Prostatic MRI and key principles of active surveillance include: PSA every 3months unless there is an earlier clinical indication DRE every 6 months unless there is an earlier clinical indication. Repeat radiological examination +/- Prostatic biopsy if there is a clinical indication	Conditional
Watchful waiting should involve monitoring with a history and physical exam every 12 months (without surveillance biopsies) until symptoms develop.	Strong
Radical prostatectomy RP +/- PLND is the recommended therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, Life expectancy of ≥10 years, and has no serious comorbid conditions that would contraindicate an elective operation	Strong
Extended PLND is recomended when PLND is performed as it provides more complete staging and may cure some patients with microscopic metastases . An extended PLND includes removal of all node-bearing tissue from an area bound by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.	Strong

Robotic surgery could be done (if available) in selected university hospitals after gaining sufficient learning curve	Conditional
Radiotherapy Indications of Post-prostatectomy ART include Adverse pathologic features : Positive margins, Seminal vesicle invasion, Extracapsular extension) or persistent PSA levels (PSA does not fall to undetectable levels).	Strong
Radiotherapy is one of the recommended modalities of radical therapy for localized prostate cancer patients without severe complications, where the results of definitive radiotherapy are comparable to radical prostatectomy for patients with similar recurrence risk.	Strong
Radiotherapy in prostate cancer is recommended to be in the treatment plan through an expert MDT and should be carried out in a well-equipped centres with trained personnel and adopting advanced EBRT techniques that include: IMRT, VMAT , image-guided (IGRT) and SBRT facilities.	Good practice statement
Short-term precise hypo-fractionated radiotherapy can be used as it shortens the treatment course significantly while the treatment results are equivalent to those of conventional high-dose radiotherapy.	Conditional
Addition of a focal boost to the intra-prostatic lesion can be used as it improved disease free survival for patients with localized intermediate- and high-risk prostate cancer without impacting toxicity and quality of life.	Conditional
Prophylactic nodal radiation should be considered in locally advanced prostate cancer and clinically positive nodes , and it should be dose escalated in the presence of positive nodes by imaging procedures.	Strong

Androgen deprivation therapy ADT includes LHRH agonist as Goserline or leuprolide , first generation antiandrogen (Bicalutamide) should be given at least 7 days before LHRH agonist only to avoid flare up phenomenon .	Strong
We recommend against Combined androgen blockade (medical or surgical castration combined with an antiandrogen) as it provides modest to no benefit over castration alone in patients with prostate cancer	Strong
ADT should not be used as monotherapy in clinically localized prostate cancer unless there is a contraindication to definitive local therapy, such as life expectancy less than 5 years and presence of comorbidities. Under those circumstances, ADT may be an acceptable alternative if the disease is high or very high risk	Conditional
Follow Up For patients initially treated with definitive therapy with intent to cure, serum PSA levels should be measured every 3 months for the first 2 years then every 6 months till 5 years and then annually.	Strong
4- <u>Management of biochemical recurrence</u>	
<u>Laboratory Studies</u> Serum PSA (Total, Free) , PSA doubling time (PSA DT) are the recommended laboratory studies for patients with biochemical recurrence	Strong

Radiological Studies Standard MRI techniques for examination of the pelvis and/or abdomen is recommended as part of workup for recurrence or progression	Strong
Bone imaging should be considered for the evaluation of the patient post-prostatectomy when there is failure of PSA to fall to undetectable levels, or when there is undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more subsequent determinations.	Strong
Bone imaging should be considered for the evaluation of patients with an increasing PSA or positive DRE after RT	Strong
In patients with a BCR after local therapy, prostate-specific membrane antigen (PSMA)-PET (if available) to be done in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence.	Conditional
Treatment of biochemical recurrence Salvage RT in addition to Six months ADT (concurrent / Adjuvant) is recommended for patients with BCR following RP and with high-risk features : (Gleason Grade Group 4 to 5, PSADT ≤ 6months, persistently detectable post-operative PSA, seminal vesicle involvement).	Strong
Salvage radiation for a detectable prostate-specific antigen (PSA) after RP is more effective when given at lower levels of PSA.	Strong
Post-prostatectomy SRT is to treat prostate bed ± pelvic LN , where PSA cut-off value for SRT (range: 0.2–0.5 ng/ml) and 0.2 ng/ml is the preferable value	Conditional

Immediate rather than deferred ADT is recommended in men with biochemical recurrence after Radiotherapy is recommended if there are high-risk features for early metastases, including a clinical Gleason score 8 -10, or an interval to biochemical recurrence ≤18 months after definitive radiotherapy	Strong
Salvage RP and PLND can be offered in selected cases with biochemical recurrence after Radiotherapy according to MDT decision	Conditional
5- Management of Metastatic Hormone Sensitive , Non Metastatic Castrate Resistant , Metastatic Castrate Resistant Prostate Cancer	
History and physical examination Including assessment of ECOG Performance status , Presence of peripheral neuropathy , History of seizures or cerebrovascular problems , History of cardiovascular disease and other comorbidities and Risk of fall & fractures	Good practice statement
Laboratory Studies CBC, KFT's and LFT's, Serum Testosterone Level , HbA1c, serum PSA (Total, Free) , PSA DT , serum cholesterol /LDL & HDL & S triglycerides , thyroid functions are the recommended work up for advanced prostate cancer	Good Practice statement
Imaging studies Standard CT techniques should be used for examination of the chest , abdomen and pelvis as an initial evaluation of advanced prostate cancer	Strong
Bone imaging should be considered for the evaluation of patients with advanced prostate cancer	Strong

PSMA-PET if available to be considered as an alternative to standard imaging of bone and soft tissue in patients with advanced cancer prostate .	Conditional
Echocardiogram should be done to assess the cardiac condition as it can guide further management	Strong
Pathological examination Transrectal US Biopsy is recommended in cases with de novo metastatic prostate cancer	Strong
In previously treated PC with previous biopsy , we recommend against re-biopsy from the prostate in metastatic setting	Good practice statement
Biopsy from accessible metastatic lesions to identify patients with small cell/neuroendocrine histomorphologic features can be done in patients with metastatic CRPC	Conditional
Metastatic hormone sensitive prostate cancer	
Patients with low-volume metastatic HSPC should be considered for ADT and local radiotherapy to the prostate if not previously given	Strong
ADT plus docetaxel is the standard of care in treatment of patients with high-volume metastatic HSPC	Strong
ADT plus Apalutamide or Enzalutamide is the standard of care in treatment of patients with high-volume metastatic HSPC who are not candidate for docetaxel	Strong
Radiation therapy to the prostate should NOT be performed in men with high-volume metastatic disease outside the context of a clinical trial unless for palliative intent	Strong

Non Metastatic Castrate Resistant Prostate Cancer	
Castrate levels of testosterone should be documented in patients with signs of progression, If serum testosterone levels are <50 ng/dL, the patient should undergo disease workup with bone and soft tissue imaging	Strong
Apalutamide or enzalutamide should be considered for men with non metastatic CRPC	Strong
Metastatic Castrate Resistant Prostate Cancer	
Abiraterone acetate plus prednisone + ADT is the standard of care in the management of patients with metastatic CRPC previously treated with Docetaxel	Strong
Enzalutamide +ADT is the standard of care in the management of patients with metastatic CRPC previously treated with docetaxel and not candidate for Abiraterone acetate + prednisone	Strong
Docetaxel + ADT is the standard of care in the management of patients with metastatic CRPC not previously treated with Docetaxel	Strong
Patients being treated for CRPC should be closely monitored with radiologic imaging (CT, bone imaging), PSA tests, and clinical exams for evidence of progression.	Strong
Urgent MRI of the spine to detect cord compression is very strongly recommended in men with CRPC with vertebral metastases and neurological symptoms	Strong
6-Special considerations	
Docetaxel should be avoided in patients with ECOG PS≥ 2, IHD, presence of comorbidities, grade III/IV peripheral neuropathy , Absolute neutrophil count < 1000/mm3	Strong
Apalutamide should be avoided in patients with recent cardiovascular disease or hypothyroidism .	Strong

Enzalutamide should be avoided in seizure prone patients or with history of seizures	Strong
Abiraterone should be avoided in patients with uncontrolled diabetes , hepatic impairment , cardiovascular disease	Strong
Therapy should be continued until clinical progression or intolerable toxicity	Strong
Palliative RT is recommended for symptomatic control and prevention of complications from metastatic lesions as bone or brain .	Strong
Bisphosphonate or denosumab is recommended in patients with bone metastases from CRPC at risk for clinically significant skeletal-related events (SREs)	Strong
The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended	Strong
Germline testing for BRCA2 and genes associated with cancer predisposition syndromes can be done in patients with positive family history of cancer .	Conditional
Tumor testing for homologous recombination genes and mismatch repair defects (or microsatellite instability) can be considered in patients with mCRPC	Conditional
Small cell/neuroendocrine carcinoma of the prostate should be considered in patients with disease that no longer responds to ADT and are positive for metastases. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.	Strong
Etoposite / platinum is the standard of care in the management of small cell neuroendocrine tumors of the prostate	Strong
Life style measures is recommended to maintain bone health are recommended for men on ADT: weight-bearing exercise, stop smoking , adequate calcium intake and vitamin D status	Strong

Introduction

Prostate cancer is the fourth most common cancer in Egypt , with estimated number of new cases per year about 5181 (7%) (1)

Organ confined disease , locoregional metastasis , Distant metastasis are presented in 80 % , 15% , 5% of cases with a 5 year overall survival 90-99% , 60-80%, 30-40% respectively (2)

Scope of the Guidelines

These guidelines are developed to improve the quality of care for prostate cancer patients Via providing a uniform standard of care across the country to help in early diagnosis , risk stratification and treatment for prostate cancer , with less aggressive treatment options and improved clinical outcomes. These guidelines cover primary diagnosis, staging, treatment and follow-up of prostate cancer patients.

Target audience

Clinicians who are involved in the care and treatment of patients with prostate cancer, including medical oncologists, radiation oncologists, clinical oncologist, urologists , surgeons, interventional radiologists, radiologists, pathologists, and palliative care specialists.

Methodology

 A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation.

 inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence).
- Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

 All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cut-off point or rank the guidelines (any guideline scoring above 50% on the rigour dimension was retained)

The NCCN , ESMO , AUA , EAU guidelines are the main sources used while formulating the national guidelines for prostate cancer .

Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

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Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

- ***Table 2: Significance of the four levels of evidence***

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

These are made when there is greater uncertainty about the four factors above or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations.

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations

1- Screening for prostate cancer

Early PSA testing (baseline PSA followed by risk-adapted follow-up) can be offered to men >50 years, men >45 years with a positive family history of prostate cancer, and BRCA1/2 carriers >40 years

Conditional recommendation , moderate quality level of evidence (Randomized Study) 3

2- Work up for newly diagnosed prostate cancer

History and physical examination

Personal and family history, Physical examination, DRE , Assessment of ECOG performance status should be done

Strong recommendation, high quality level of evidence (prostate cancer prevention trial) 4

Assessment of life expectancy is a very essential tool in the plan of management of prostate cancer , Life expectancy should be estimated using: The WHO's Life Tables by country

Strong recommendation, moderate quality level of evidence (Global Health Observatory data repository) 5

Laboratory Studies

Base line tumor marker: serum PSA (Total, Free) is the recommended initial laboratory studies for localized prostate cancer

Strong recommendation, high quality level of evidence (Systematic Review , comparative study) 6,7

Radiological Studies

TRUS is the initial imaging studies for diagnosis of prostate cancer,

Strong recommendation, high quality level of evidence (Systematic Review) 6

MRI prostate or mpMRI (if available) is to be used in the staging and characterization of prostate cancer

Conditional recommendation, high quality evidence (prospective study , Meta analysis) 8,9

Radiologists should utilize PI-RADS V 2.1 in the reporting of multi-parametric MRI (mpMRI) imaging

Strong Recommendation, High quality Evidence Level (Systematic Review) 6

Standard MRI techniques should be used for examination of the pelvis and/or abdomen for initial evaluation of intermediate and high / very high risk patients and for planning purposes in radiotherapy protocols

Strong Recommendation , high quality Evidence Level (Diagnostic meta analysis) 9

Bone imaging is indicated in the initial evaluation of intermediate and high / very high risk patients to exclude skeletal metastasis

Strong recommendation, high quality evidence(retrospective analysis) 10

PSMA-PET if available to be considered as an alternative to standard imaging of bone and soft tissue in high and very high risk patients .

Conditional recommendation, high quality evidence(retrospective analysis)11

Initial Biopsy

Definitive diagnosis of cancer prostate requires 6-12 core biopsies of the prostate, using a needle under transrectal / transperineal ultrasound TRUS guidance.

Strong Recommendation; high quality Evidence Level (confirmatory study , prospective Comparative analysis) 12, 13

For biopsy-naïve patients who have a suspicious lesion on MRI, clinicians can perform targeted biopsies of the suspicious lesion either cognitive or software guided

Conditional Recommendation , high quality Evidence Level (prospective multicenter study , Comparative study) 14 , 15

3- Risk stratification and Management of Localized / Locally advanced prostate cancer

Patients with localized prostate cancer should be classified into very low , low , intermediate (Favourable and unfavourable) , high and very high risk groups

Strong Recommendation , high quality Evidence Level (Retrospective analysis) 16

Risk stratification of clinically localized prostate cancer facilitate care decisions and guide clinicians in the implementation of selected management options..

Strong Recommendation , high quality Evidence Level (Systematic Review) 17

Patients with prostate cancer should be managed through a multidisciplinary team (Urologist , medical Oncologist , Radiation oncologist , Radiologist , and Pathologist)

Strong Recommendation , high quality Evidence Level (Retrospective review) , 18

It is Recommended to use one of the following options in the management of very low/low risk groups (according to MDT decision and patient preference):

If expected patient survival ≥ 10 years,:

- Active surveillance or
- RP or
- EBRT or
- BT mono-therapy

Strong Recommendation , high quality Evidence Level (Population based validation) 19

In asymptomatic patients with prostate cancer and limited life expectancy , watchful waiting is recommended

Strong Recommendation, high quality Evidence Level (Systematic review) ,17

According to MDT decision and patient preference; It is recommended to use one of the following options in the management of favourable intermediate risk groups (Life expectancy ≥ 10 years):

- RP and PLND or
- EBRT alone or
- combined EBRT + BT or
- BT monotherapy or
- Careful active surveillance

Strong Recommendation, high quality Evidence Level , (Systematic review , Retrospective analysis) 17, 20

It is recommended to use one of the following options in the management of favourable intermediate risk prostate cancer (Expected Survival 5-10 Years):

- EBRT
- BT monotherapy
- Watchful waiting

Strong Recommendation , high quality Evidence Level (retrospective analysis) 20

Brachytherapy monotherapy is a recommended option for patients with very low, low, or favorable intermediate-risk prostate cancer and life expectancy > 10 years with acceptable 10-year recurrence-free survival rate for LDR/HDR brachytherapy

Strong Recommendation , high quality Evidence , (Literature review), 21

RP + PLND or EBRT + short course ADT (6 months) are the recommended options for management of unfavourable intermediate risk patients.

Strong Recommendation , high quality Evidence Level): (Systematic review , retrospective analysis)17 , 20

Long term ADT (2- 3 years) combined with EBRT is the recommended primary treatment for high risk or very high risk prostate cancer patients

Strong Recommendation , high quality Evidence Level (Randomized trial) 22

RP and PLND is a valid option in very selected cases with high or very high risk prostate cancer based on MDT discussion

Conditional recommendation , high quality level (Retrospective analysis) 23

Locally advanced prostate cancer

Neoadjuvant ADT (4-6 months) followed by ADT + EBRT , then ADT for 2 years is the recommended treatment option for patients with locally advanced prostate cancer

Strong recommendation , high quality level (Randomized trial) 24

RP and PLND can be an option in selected cases of locally advanced prostate cancer according to MDT decision

Conditional recommendation , high quality level (Retrospective analysis) 23

Patients who choose active surveillance program should have regular follow-up with baseline biopsy , serum PSA level , Prostatic MRI and key principles of active surveillance include:

PSA every 3months unless there is an earlier clinical indication

DRE every 6 months unless there is an earlier clinical indication.

Radiological examination +/- Prostatic biopsy if there is a clinical indication

Conditional recommendation, moderate quality evidence (systematic review), 25

Watchful waiting involves monitoring with a history and physical exam every 12 months (without surveillance biopsies) until symptoms develop.

Strong recommendation, high quality evidence (prospective study , cancer epidemiology study) 26, 27

Radical prostatectomy

RP +/- PLND is the recommended therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, Life expectancy of ≥10 years, and has no serious comorbid conditions that would contraindicate an elective operation

Strong recommendation, high quality evidence (retrospective analysis), 28

Extended PLND is recommended when PLND is performed as it provides more complete staging and may cure some patients with microscopic metastases . An extended PLND includes removal of all node-bearing tissue from an area bound by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.

Strong recommendation, high quality evidence (systematic review), 29

Robotic surgery could be done (if available) in selected university hospitals after gaining sufficient learning curve

Conditional recommendation , high quality evidence (retrospective analysis)30

Radiotherapy

Indications of Post-prostatectomy ART include Adverse pathologic features : Positive margins, Seminal vesicle invasion and Extracapsular extension or persistent PSA levels (PSA does not fall to undetectable levels).

Strong recommendation, high quality evidence (randomized clinical trial), 31

Radiotherapy is one of the recommended modalities of radical therapy for localized prostate cancer patients without severe complications where the results of definitive radiotherapy are comparable to radical prostatectomy for patients with similar recurrence risk. Prospective analysis

Strong recommendation, high quality evidence (Prospective analysis), 32

Radiotherapy in prostate cancer is recommended to be in the treatment plan through expert MDT and should be carried out in a well-equipped centres with trained personnel and adopting advanced EBRT techniques that include: IMRT, VMAT , image-guided (IGRT) and SBRT facilities.

Good statement practice

Short-term precise hypo-fractionated radiotherapy can be used as it shortens the treatment course significantly while the treatment results are equivalent to those of conventional high-dose radiotherapy.

Conditional recommendation, high quality evidence (Systematic review, single institution experience), 33, 34

Addition of a focal boost to the intra-prostatic lesion can be used as it improved disease free survival for patients with localized intermediate- and high-risk prostate cancer without impacting toxicity and quality of life.

Conditional recommendation , high quality evidence (randomized trial), 35

Prophylactic nodal radiation should be considered in locally advanced prostate cancer and clinically positive nodes , it should be dose escalated in the presence of positive nodes by imaging procedures.

Strong recommendation, high quality evidence, (Randomized trial) , 36

Androgen deprivation therapy

ADT includes LHRH agonist as Goserline or leuprolide , first generation antiandrogen (Bicalutamide) should be given at least 7 days before LHRH agonist only to avoid flare up phenomenon .

Strong recommendation, high quality evidence (population based cohort study) , 37

We recommend against Combined androgen blockade (medical or surgical castration combined with an antiandrogen) as it provides modest to no benefit over castration alone in patients with prostate cancer

Strong recommendation, high quality evidence (randomized controlled trials) ,38

ADT should not be used as monotherapy in clinically localized prostate cancer unless there is a contraindication to definitive local therapy, such as life expectancy less than 5 years and presence of comorbidities. Under those circumstances, ADT may be an acceptable alternative if the disease is high or very high risk

Conditional recommendation, high quality evidence (overview of randomized trials), 39

Follow Up

For patients initially treated with definitive therapy with intent to cure, PSA testing should be done every 3 months for the first 2 years then every 6 months till 5 years and then annually.

Strong recommendation, moderate quality level of evidence (prostate cancer prevention trial) 4

4- Management of biochemical recurrence

Laboratory Studies

Serum PSA (Total, Free) and PSA doubling time (PSA DT) are the laboratory studies for patients with biochemical recurrence
Strong Recommendation , high quality Evidence (Comparative study), 7

Radiological Studies

Standard MRI techniques for examination of the pelvis and/or abdomen is recommended as part of workup for recurrence or progression

Strong Recommendation , high quality Evidence Level (Diagnostic meta analysis) 9

Bone imaging should be considered for the evaluation of the patient post-prostatectomy when there is failure of PSA to fall to undetectable levels, or when there is undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more subsequent determinations.

Strong recommendation, high quality evidence(retrospective analysis) 10

Bone imaging should be considered for the evaluation of patients with an increasing PSA or positive DRE after RT

Strong recommendation, high quality evidence(retrospective analysis) 10

In patients with a BCR after local therapy, prostate-specific membrane antigen (PSMA)-PET (if available) to be done in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence.

Conditional Recommendation, high quality level (Systematic Review) , 17

Treatment of Biochemical Recurrence

Salvage RT in addition to Six months ADT (concurrent / Adjuvant) is recommended for patients with BCR following RP and with high-risk features :

(Gleason Grade Group 4 to 5, PSADT ≤ 6months, persistently detectable post-operative PSA, seminal vesicle involvement).

Strong Recommendation, high quality level (randomized trial) 40

Salvage radiation for a detectable prostate-specific antigen (PSA) after RP is more effective when given at lower levels of PSA.

Strong Recommendation, high quality level (Systematic Review) , 17

Post-prostatectomy SRT is to treat prostate bed ± pelvic LN , where PSA cut-off value for SRT (range: 0.2–0.5 ng/ml) and 0.2 ng/ml is the preferable value

Conditional recommendation, high quality evidence (retrospective analysis),41

Immediate rather than deferred ADT is recommended in men with biochemical recurrence after Radiotherapy is recommended if there are high-risk features for early metastases, including a clinical Gleason score 8 -10, or an interval to biochemical recurrence ≤18 months after definitive radiotherapy

Strong recommendation , high quality level (Randomized trial) 42

Salvage RP and PLND can be offered in selected cases with biochemical recurrence after Radiotherapy according to MDT decision

Conditional recommendation , high quality level (Retrospective analysis) 23

5- Management of
A)Metastatic Hormone Sensitive ,
B)Non Metastatic Castrate Resistant ,
C)Metastatic Castrate Resistant Prostate Cancer

History and physical examination

Including assessment of ECOG Performance status , Presence of peripheral neuropathy , History of seizures or cerebrovascular problems , History of cardiovascular disease and other comorbidities and Risk of fall & fractures

Good practice statement

Laboratory Studies

CBC, KFT's and LFT's, Serum Testosterone Level , HbA1c, serum PSA (Total, Free) , PSA doubling time (PSA DT) , serum cholesterol /LDL & HDL & S triglycerides are the recommended work up for metastatic prostate cancer

Good practice statement

Imaging studies

Standard CT techniques should be used for examination of the chest , abdomen and pelvis as an initial evaluation of advanced prostate cancer

Strong Recommendation , high quality Evidence (Diagnostic meta analysis) 9

Bone imaging should be considered for the evaluation of patients with advanced prostate cancer

Strong recommendation, high quality evidence(retrospective analysis) 10

PSMA-PET if available to be considered as an alternative to standard imaging of bone and soft tissue in patients with advanced cancer prostate .

Conditional recommendation, high quality evidence(retrospective analysis)11

Echocardiogram should be done to assess the cardiac condition as it can guide further management

Good practice statement

Pathological examination

Transrectal US Biopsy is recommended in cases with de novo metastatic prostate cancer

Strong recommendation, high quality level of evidence (Systematic Review) 6

In previously treated PC with previous biopsy , we recommend against re-biopsy from the prostate in metastatic setting

Good practice statement

Biopsy from accessible metastatic lesions to identify patients with small cell/neuroendocrine histomorphologic features can be done in patients with metastatic CRPC

Conditional recommendation , strong quality level (prospective analysis) 43

A)Metastatic hormone sensitive prostate cancer

Patients with low-volume metastatic HSPC should be considered for ADT and local radiotherapy to the prostate if not previously given

Strong recommendation , high quality level (Randomized clinical trial) 44

ADT plus docetaxel is the standard of care in treatment of patients with high-volume metastatic HSPC

Strong recommendation , high quality Evidence (randomized clinical trial) ,45

ADT plus Apalutamide or Enzalutamide is the standard of care in treatment of patients with high-volume metastatic HSPC who are not candidate for docetaxel

Strong recommendation , high quality Evidence (Randomized clinical trials) 46,47,48

Radiation therapy to the prostate should NOT be performed in men with high-volume metastatic disease outside the context of a clinical trial unless for palliative intent

Good practice statement

B)Non Metastatic Castrate Resistant Prostate Cancer

Castrate levels of testosterone should be documented in patients with signs of progression, If serum testosterone levels are <50 ng/dL, the patient should undergo disease workup with bone and soft tissue imaging

Strong recommendation , high quality level (Literature review), 49

Apalutamide or enzalutamide should be considered for men with non metastatic CRPC

Strong recommendation , high quality level (Randomized clinical trials) 50, 51

C)Metastatic Castrate Resistant Prostate Cancer

Abiraterone acetate plus prednisone + ADT is the standard of care in the management of patients with metastatic CRPC previously treated with Docetaxel

Strong recommendation , high quality level (Randomized clinical trial) 52

Enzalutamide +ADT is the standard of care in the management of patients with metastatic CRPC previously treated with docetaxel and not candidate for Abiraterone acetate + prednisone

Strong recommendation , high quality level (Randomized clinical trials) 53,54

Docetaxel + ADT is the standard of care in the management of patients with metastatic CRPC not previously treated with Docetaxel

Strong recommendation , high quality level (literature review), 55

Patients being treated for CRPC should be closely monitored with radiologic imaging (CT, bone imaging), PSA tests, and clinical exams for evidence of progression.

Strong recommendation, high quality evidence(retrospective analysis) 10

Urgent MRI of the spine to detect cord compression is very strongly recommended in men with CRPC with vertebral metastases and neurological symptoms

Strong recommendation , high quality Evidence (Systematic review) ,56

6 - Special considerations

Docetaxel should be avoided in patients with ECOG PS≥ 2, IHD, presence of comorbidities, grade III/IV peripheral neuropathy , Absolute neutrophil count < 1000/mm3

Strong recommendation , high quality level (randomized clinical trial) 45

Apalutamide should be avoided in patients with recent cardiovascular disease or hypothyroidism .

Strong recommendation , high quality Evidence (randomized clinical trial) 46

Enzalutamide should be avoided in seizure prone patients or with history of seizures

Strong recommendation , high quality Evidence (randomized clinical trial) 47, 48

Abiraterone should be avoided in patients with uncontrolled diabetes , hepatic impairment , cardiovascular disease

Strong recommendation , high quality Evidence (randomized clinical trial) 52

Therapy should be continued until clinical progression or intolerable toxicity

Strong recommendation , high quality Evidence (randomized clinical trials)45, 47, 48, 52

Palliative RT is recommended for symptomatic control and prevention of complications from metastatic lesions as bone or brain .

Strong recommendation , high quality Evidence (Systematic review), 57

Bisphosphonate or denosumab is recommended In patients with bone metastases from CRPC at risk for clinically significant skeletal-related events (SREs)

Strong recommendation , high quality Evidence (Randomized trial),58

The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended

Strong recommendation , high quality level (Randomized trial) 59

Germline testing for BRCA2 and genes associated with cancer predisposition syndromes can be done in patients with positive family history of cancer .

Conditional recommendation , high quality Evidence (comparative study) 60

Tumor testing for homologous recombination genes and mismatch repair defects (or microsatellite instability) can be considered in patients with mCRPC

Conditional recommendation , high quality Evidence (Randomized trial) 61

Small cell/neuroendocrine carcinoma of the prostate should be considered in patients with disease that no longer responds to ADT and are positive for metastases. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.

Strong recommendation , high quality Evidence (Retrospective analysis), 62

Etoposite / platinum is the standard of care in the management of small cell neuroendocrine tumors of the prostate

Strong recommendation , high quality Evidence (retrospective analysis), 63

Life style measures is recommended to maintain bone health are recommended for men on ADT: weight-bearing exercise, stop smoking , adequate calcium intake and vitamin D status

Strong recommendation , high quality Evidence (Retrospective analysis), 64

Clinical indicators for monitoring

For patients newly diagnosed with prostate cancer , Transrectal U/S guided biopsy from prostate , Total/ free PSA , imaging studies should be done

For patients initially treated with definitive therapy with intent to cure, serum PSA levels should be measured.

For patients who are on treatment , Regular PSA levels and radiological assessment upon indication should be done

Research Gaps

Head to Head Comparative study between different novel hormonal treatment in the metastatic setting with overall survival , r PFS and PFS 2 as endpoints together with the safety profile for each

Head to Head comparative study between Triplet and Doublet therapy in metastatic HSPC and nm CRPC in terms of OS , PFS , safety profile

Update of this guideline

This guideline will be updated whenever there is new evidence.

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Annexes

Table 1 : Risk stratification according to clinical /Pathologic features

Risk Group	Clinical/Pathologic Features		
Very low[f]	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[g] • 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	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[g]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[g]
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		

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Table 2 : Definitions of active surveillance and watchful waiting

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Pre-defined schedule	Patient-specific
Assessment/markers used	DRE, PSA, MRI at recruitment, re-biopsy	Not pre-defined, but dependent on development of symptoms of progression
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Eligible patients	Mostly low-risk patients	Can apply to patients with all stages

EAU Recommendations

Table 3 : AJCC TNM staging system for prostate cancer

American Joint Committee on Cancer (AJCC)
TNM Staging System For Prostate Cancer (8th ed., 2017)
***Table 1.* Definitions for T, N, M**
Clinical T (cT)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

Pathological T (pT)

T	Primary Tumor
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological T1 classification.
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Table 4 : : Definition of Histologic Grade Group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Table 5 : Doses and fractionation of EBRT , Brachytherapy and combined

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 Palladium 103 Cesium 131	145 Gy 125 Gy 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 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓		

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