EAU-EANM-ESTRO-ESUR-ISUP-SIOG GUIDELINES ON PROSTATE CANCER

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Introduction

Prostate cancer (PCa) is a complex disease, in which disease characteristics, age, co-morbidities and individual patient preference will impact treatment choice. All available management options need to be discussed, in full, with the patient.

Epidemiology and Risk Prevention

Prostate cancer is the second most common cancer in males. It is a major health concern, especially in developed countries due to the greater proportion of elderly men in the general population, and the potential risk of over-treatment following early diagnosis. There are three well-established risk factors for PCa: increasing age, ethnic origin, and genetic predisposition. There is currently no high-level evidence that preventative measures may reduce the risk of PCa.

Classification and Staging Systems

The 2017 Tumour Node Metastasis (TNM) classification is used for staging (Table 1).

Table 1: 2017 TNM classification

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is **not palpable**	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour that is **palpable** and confined within prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends **palpably** through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	

M - Distant Metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*

[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCas after radical prostatectomy (RP) are pathological stage pT2 and the current UICC no longer recognises pT2 substages.

Table 2: EAU risk groups for biochemical recurrence of localised and locally-advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1–2a*	PSA 10–20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade)* cT3–4* or cN+**
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

** Based on digital rectal examination.*

*** Based on CT/bone scan.*

The International Society of Urological Pathology (ISUP) World Health Organization (WHO) 2022 grade groups have been adopted which allow patients to better understand the behaviour of their diagnosed prostate carcinoma, while separating GS 7 adenocarcinoma into two prognostically very distinct categories; grade group 2 for GS 7(3+4) and grade group 3 for GS 7(4+3) (see Table 3).

Table 3: ISUP 2014/WHO 2022 grade

Gleason score	ISUP grade
2–6	1
7(3+4)	2
7(4+3)	3
8(4+4 or 3+5 or 5+3)	4
9–10	5

Clinically significant PCa

The descriptor 'clinically significant' is widely used to identify PCa that may cause morbidity or death in a specific patient from types of PCa that do not. This distinction is particularly important as insignificant PCa that does not cause harm is common. Unless this distinction is made, such cancers are at high risk of being over-treated, with the treatment itself risking harmful side effects to patients. Low-risk PCa is insignificant in almost all men. Some patients with low-volume ISUP 2 cancers may also have insignificant disease dependent upon PSA, magnetic resonance imaging (MRI) findings and percentage of Grade 4 in the histology and as such may also avoid initial treatment. All patients identified as having insignificant PCa need active surveillance (AS) until their life expectancy drops below 10 years. High-risk PCa is significant in almost all men, except when life expectancy is limited.

Early detection

An individualised risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis.

It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

Recommendations for germline testing*	Strength rating
Consider germline testing in men with metastatic PCa.	Weak
Consider germline testing in men with high-risk PCa who have a family member diagnosed with PCa at age < 60 years.	Weak
Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.	Weak
Consider germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Weak

**Genetic counselling is required prior to germline testing.*

Recommendations for screening and early detection	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong

Offer an individualised risk-adapted strategy for early detection to a well-informed man with a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *BRCA2* mutations from 40 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	Weak
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak

In asymptomatic men with a PSA level between 3–10 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • risk-calculator, provided it is correctly calibrated to the population prevalence; • Magnetic resonance imaging of the prostate	Strong
• an additional serum, urine biomarker test	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

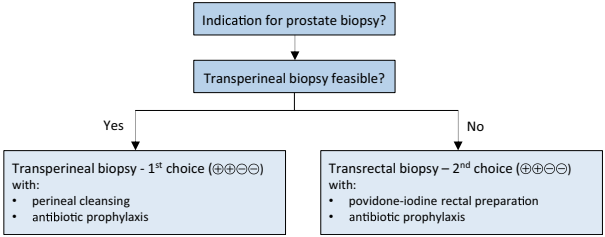
Diagnostic Evaluation

Clinical diagnosis

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores, specimens from transurethral resection of the prostate, or prostatectomy for benign prostatic enlargement. The decision whether to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking the patient's life expectancy into consideration. Diagnostic procedures that will not affect the treatment decision can usually be avoided.

Guidelines for magnetic resonance imaging (MRI) in biopsy decision	Strength rating
Recommendations for all patients	
Do not use MRI as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for MRI acquisition and interpretation and evaluate MRI results in multidisciplinary meetings with pathological feedback.	Strong
Recommendations in biopsy-naïve patients	
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e., PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (e.g., PSA density < 0.15 ng/mL), omit biopsy based on shared decision-making with the patient.	Weak
Recommendations in patients with prior negative biopsy	
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e., PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared decision-making with the patient.	Strong

Figure 1: Prostate biopsy workflow to reduce infectious complications



Recommendations for prostate biopsy	Strength rating*
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong
Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g., fosfomycin trometamol**, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak

Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong

**The above strength ratings are explained here due to the major clinical implications of these recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its Strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy as, although quality of data is low, the clinical benefit is high and practical application simple. A 'Strong' rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.*

***The indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.*

Pathology of prostate biopsies

A biopsy pathology report includes the type of carcinoma and parameters describing its extent (e.g., proportion of positive cores, percentage or mm of carcinoma involvement per core) as well as Gleason score (GS) per biopsy site and global GS. Reporting of a RP specimen includes type of carcinoma, global ISUP grade, pathological stage and surgical margin status.

Guidelines for staging of PCa

Any risk group staging	Strength rating
Use pre-biopsy MRI for local staging information.	Weak

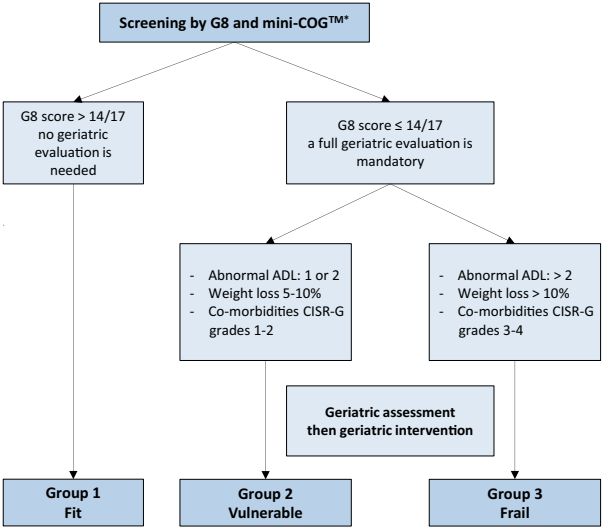
Treatment should not be changed based on PSMA PET/CT findings, in view of current available data.	Strong
Low-risk localised PCa	
Do not use additional imaging for staging purposes.	Strong
Intermediate-risk PCa	
In ISUP grade 3, include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	Weak
High-risk localised PCa/locally-advanced PCa	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong
When using PSMA-PET or whole-body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

Evaluating life expectancy and health status

Recommendations	Strength rating
Use individual life expectancy, health status, and co-morbidity in PCa management.	Strong
Use the Geriatric-8, mini-COG and Clinical Frailty Scale tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak

Offer adapted treatment to patients with irreversible impairment.	Weak
Offer symptom-directed therapy alone to frail patients.	Strong

Figure 2: Decision tree for health status screening (men > 70 years)**



Mini-COG™ = Mini-COG™ cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.
**For Mini-COG™, a cut-off point of < 3/5 indicates a need to refer the patient for full evaluation of potential dementia.*
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Disease Management

Deferred treatment

Many men with localised PCa will not benefit from definitive treatment and 45% of men with PSA-detected PCa may be candidates for deferred management.

In men with co-morbidity and a limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life (QoL).

General guidelines for active treatment of PCa*

Recommendations	Strength rating
No active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all active treatments have side effects.	Strong
Surgical treatment	
Radical prostatectomy (RP) can be safely delayed for at least 3 months from diagnosis in any risk category.	Weak
Inform patients that no surgical approach (open-, laparoscopic- or robotic RP) has clearly shown superiority in terms of functional or oncological results.	Weak

When a lymph node dissection (LND) is deemed necessary based on a nomogram, perform an extended LND template for optimal staging.	Strong
Consider avoiding nerve-sparing surgery when there is a risk of ipsilateral extra-capsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined in a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate, to patients with localised disease (60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks)..	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low-risk or NCCN favourable intermediate-risk disease.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak

Active therapeutic options outside surgery or radiotherapy	
Only offer focal therapy with high-intensity focused ultrasound or cryotherapy within a clinical trial or prospective registry.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

Guidelines for first-line treatment of various disease stages*

Recommendations		Strength rating
Low-risk disease		
Watchful Waiting (WW)	Offer WW to patients with a life expectancy < 10 years.	Strong
Active surveillance (AS)	Manage patients with a life expectancy > 10 years and low-risk disease by AS.	Strong
	Selection of patients	
	Patients with intraductal histology on biopsy should be excluded from AS.	Strong
	Perform magnetic resonance imaging (MRI) before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Weak

	If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
	If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Intermediate-risk disease		
WW	Offer WW to asymptomatic patients with a life expectancy < 10 years.	Strong
AS	Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
	Patients with ISUP grade group 3 disease should be excluded from AS protocols.	Strong

	Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
Radical Prostatectomy (RP)	Offer RP to patients with a life expectancy of > 10 years.	Strong
	Radical prostatectomy can be safely delayed for at least 3 months.	Weak
	Offer nerve-sparing surgery to patients with a low risk of extra-capsular disease on that side.	Strong
Extended pelvic lymph node dissection (ePLND)	Perform an ePLND based on predicted risk of lymph node (LN) invasion (validated nomogram).	Weak
Radio-therapeutic treatment	Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong

	Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Strong
	Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
	Offer high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
Other therapeutic options	Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultra-sound, etc.) or focal ablative therapy within clinical trials or registries.	Strong
	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Weak

High-risk localised disease		
WW	Offer WW to asymptomatic patients with a life expectancy < 10 years.	Strong
RP	Radical prostatectomy can be safely delayed for at least 3 months.	Weak
	Offer RP to selected patients as part of potential multi-modal therapy.	Strong
ePLND	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radio-therapeutic treatment	Offer patients IMRT/VMAT plus IGRT with 76–78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	Do not offer either whole gland or focal therapy.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

Locally-advanced disease		
RP	Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
ePLND	Perform an ePLND.	Strong
Radio-therapeutic treatments	Offer patients with cN0 disease IMRT/VMAT plus IGRT in combination with long-term ADT.	Strong
	Offer patients with cN0 disease and good urinary function, IMRT/VMAT plus IGRT with brachy-therapy boost (either HDR or LDR), in combination with long-term ADT.	Weak
	Offer long-term ADT for at least two years.	Strong
	Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 years of abiraterone to cN0M0 patients with ≥ 2 high-risk factors (cT3-4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong
	Offer IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and 2 years of abiraterone to cN1M0 patients.	Strong
	Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Strong

Therapeutic options outside surgery or radiotherapy	Do not offer whole gland treatment or focal treatment.	Strong
Adjuvant treatment for pN0 and pN1 disease after radical prostatectomy		
pN0 & pN1 disease	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant IMRT/VMAT plus IGRT.	Strong
	In pN1 patients, after an eLND, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak
Non-curative or palliative treatments in a first-line setting		
Persistent PSA after radical prostatectomy		
	Offer a prostate-specific membrane antigen positron-emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak

	Treat men with no evidence of metastatic disease with salvage RT and additional hormonal therapy.	Weak

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

Follow-up during active surveillance

Recommendations for follow-up during active surveillance	Strength rating
Base follow-up during active surveillance (AS) on a strict protocol including digital rectal examination (at least once yearly), prostate-specific antigen (PSA) (at least once every 6 months) and repeated biopsy every 2 to 3 years.	Strong
Perform magnetic resonance imaging (MRI) and repeat biopsy if PSA is rising (PSA-doubling time < 3 years).	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
Base change in treatment on biopsy progression, not on progression on MRI and/or PSA.	Weak
Patients with a PI-RADS 1-2 findings on MRI and a low PSA density (< 0.15) may be excepted from repeat biopsy.	Weak

Follow-up after radical prostatectomy or radiotherapy

- After RP, PSA should be undetectable (< 0.1 ng/mL). Any PSA rise after RP is a relapse. A PSA of > 0.1 ng/mL after RP is a signal of residual prostate tumour tissue.
- After an undetectable PSA is obtained following RP, a PSA > 0.4 ng/mL and rising, best predicts further metastases.
- After RT, an increase in PSA > nadir + 2 ng/mL best predicts further metastases.
- Palpable nodules and increasing serum PSA are often signs of local recurrence.

In case of relapse, the decision for subsequent salvage therapy should NOT be based on the PSA thresholds listed above but on the EAU risk classification and a discussion with the patient.

Recommendations for follow-up after radical prostatectomy or radiotherapy	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

EAU risk categories for biochemical recurrence		
	EAU Low Risk	**EAU High Risk**
After RP	PSA-DT > 1 year AND pathological ISUP grade < 4	PSA-DT < 1 year OR pathological ISUP grade 4–5
After RT	interval to biochemical failure > 18 months AND biopsy ISUP grade < 4	interval to biochemical failure < 18 months OR biopsy ISUP grade 4–5

Guidelines for metastatic disease, second-line and palliative treatments

Recommendations		**Strength rating**
Metastatic disease in a first-line setting		
M1 patients* *All statements are based on metastatic disease defined by bone scintigraphy and CT scan/ MRI.*	Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
	At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong

	Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
	Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
	Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
	Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
	Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease and who are fit for the regimen.	Strong

	Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel.	Strong
	Offer ADT combined with non-curative prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria/M1a disease.	Strong
	Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
	Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
	Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong
Biochemical recurrence after treatment with curative intent		
Biochemical recurrence (BCR) after radical prostatectomy (RP)	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak

	Offer early salvage intensity-modulated radiotherapy (IMRT)/ volumetric arc radiation therapy (VMAT) plus image-guided radiotherapy (IGRT) to men with two consecutive PSA rises.	Strong
	A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
	Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with BCR.	Weak
BCR after RT	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Only offer salvage radical prostatectomy (SRP), brachytherapy, stereotactic body RT, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong

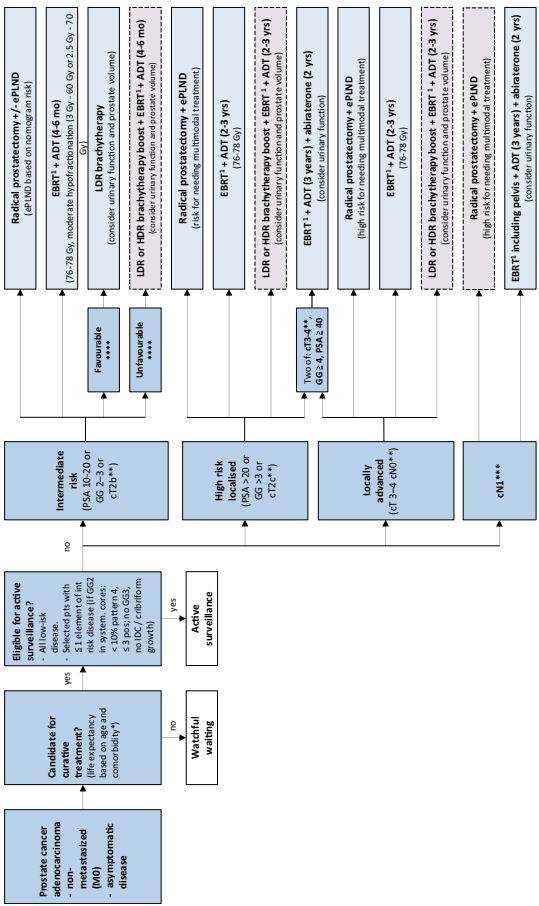
Systemic salvage	Do not offer ADT to M0 patients with a PSA-doubling time (DT) > 12 months.	Strong
Life-prolonging treatments of castration-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents.	Strong
	Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong
Systemic treatments of castrate-resistant disease		
	Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong

	Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
	Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
	Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
	Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
	Avoid sequencing of androgen receptor targeted agents.	Weak
	Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel.	Strong

	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents		
	Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
	Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong
Supportive care of castration-resistant disease		
	Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
	Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as IMRT/VMAT plus IGRT and adequate use of analgesics.	Strong

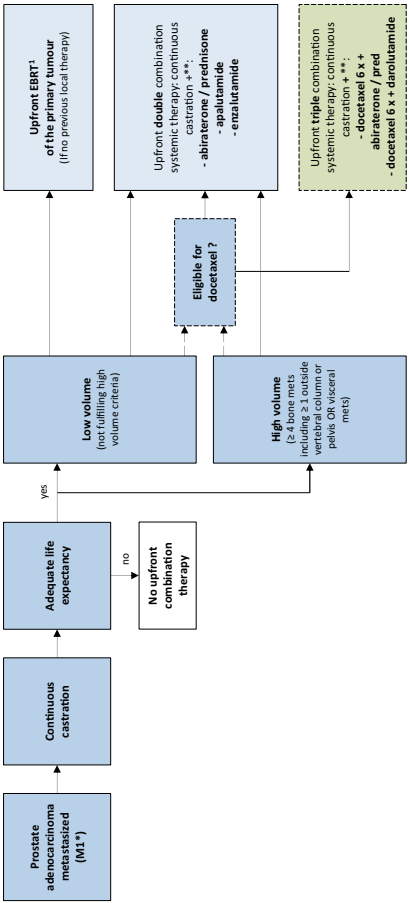
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong
Non-metastatic castrate-resistant disease		
	Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

Figure 3: Treatment non-metastasized (M0) – asymptomatic disease#



** Rule of thumb: Life expectancy 10 years.*
*** Recommendation based on clinical staging using digital rectal examination, not imaging.*
**** Recommendation based on staging using combination of bonescan and CT.*
***** See text, dependent on GG and (biopsy) volume*
[1]EBRT: IMRT/VMAT + IGRT of the prostate
[ ] = weak recommendation
ADT = androgen deprivation therapy; EBRT =external beam radiotherapy; ECE = extracapsular extension; ePLND = extended pelvic lymph node dissection; GG = grade group; HDR = high-dose rate; IDC = intraducal carcinoma; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; LDR = low-dose rate; VMAT = volumetric modulated arc therapy.

Figure 4: Treatment of metastasized (M1*) – disease, M+HSPC#



** Based on staging using combination of bone scan and CT.*
*** Alphabetical order*
[1] EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
[ ] = weak recommendation. Refer to the extended PCa Guidelines for a detailed discussion.
EBRT = external beam radiotherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

[#] Note: Please be aware that the various options in the following flowcharts present a generalised approach only, and cannot take the management of individual patients into account, nor the availability of resources.

Follow-up after treatment with systemic life-prolonging treatments

Recommendations for follow-up during hormonal treatment	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3 to 6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong

When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

Quality of Life

Treating PCa can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of QoL. Prostate cancer care should not be reduced to focusing on the organ in isolation.

Taking QoL into consideration relies on understanding the patient's wishes and preferences so that optimal treatment can be discussed. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa.

Recommendations for quality of life in men undergoing local treatments	**Strength rating**
Advise eligible patients for active surveillance that global quality of life is equivalent for up to 5 years compared to radical prostatectomy or external beam radiotherapy (RT).	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of RT on bowel function with patients.	Strong

Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after 5 years.	Weak

Recommendations for quality of life in men undergoing systemic treatments	**Strength rating**
Offer men on androgen deprivation therapy (ADT), 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise men on ADT to maintain a healthy weight and diet, to stop smoking, reduce alcohol to ≤ 2 units daily and have yearly screening for diabetes and hyper-cholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men with T1-T3 disease specialist nurse-led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	Strong
Offer men starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Offer anti-resorptive therapy to men on long-term ADT with either a BMD T-score of < -2.5 or with an additional clinical risk factor for fracture or annual bone loss is confirmed to exceed 5%.	Strong

This short booklet is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-19-6), available on the EAU website: http://www.uroweb.org/guidelines/.