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.

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 Gleason score (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) (Table 2).

Table 2: International Society of Urological Pathology 2014 grade group system

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 (4+5 or 5+4 or 5+5)	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 rarely do. This distinction is particularly important as insignificant PCa 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 prostate-specific antigen (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 ten years. High-risk PCa is significant in almost all men, except when life expectancy is limited.

Table 3: EAU risk groups for biochemical recurrence of localised and locally-advanced prostate cancer based on systematic biopsy

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

ISUP = International Society of Urological Pathology;
PSA = prostate-specific antigen.
** Based on digital rectal examination.*
*** Based on CT/bone scan.*

Recommendations for classification and staging systems	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Clinical stage should be based on digital rectal examination only; additional staging information based on imaging should be reported separately.	Strong
Use the International Society of Urological Pathology (ISUP) 2019 system for grading of PCa.	Strong

Diagnostic Evaluation

The diagnostic pathway for PCa aims for timely detection of significant PCa, while leaving insignificant PCa undetected, balancing diagnostic accuracy with the burden on an individual and healthcare provider. Patient-specific factors such as lower urinary tract symptoms (LUTS), family history, age, and comorbidity should always be considered.

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.

The recommendations for individual early detection, germline testing and screening and individual early detection are detailed below.

Recommendations	Strength rating
Individual early detection	
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 fifteen 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 *breast cancer gene 2 (BRCA2)* mutations from 40 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two 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 eight years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of less than fifteen years are unlikely to benefit.	Strong

Germline testing*	
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
Offer germline testing in men with a family history of high-risk germline mutations or multiple cancers on the same side of the family.	Strong
Offer germline testing to patients with *BRCA* mutations on somatic testing.	Strong
Screening and individual early detection	
In asymptomatic men with a PSA level between 3 and 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 and 20 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • magnetic resonance imaging of the prostate;	Strong
• risk-calculator, provided it is correctly calibrated to the population prevalence; • an additional serum, urine biomarker test.	Weak

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

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 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.

Recommendations for MRI imaging in biopsy indication and strategy	Strength rating
Do not use magnetic resonance imaging (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
Where MRI has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak
Perform MRI before prostate biopsy in men with suspected organ confined disease.	Strong
In men with suspicion of locally advanced disease on digital rectal examination (DRE) and/or PSA > 50 ng/mL, or those not for curative treatments, consider limited biopsy without MRI.	Weak
When MRI is positive (i.e., PI-RADS ≥ 4), combine targeted biopsy with perilesional sampling.	Weak

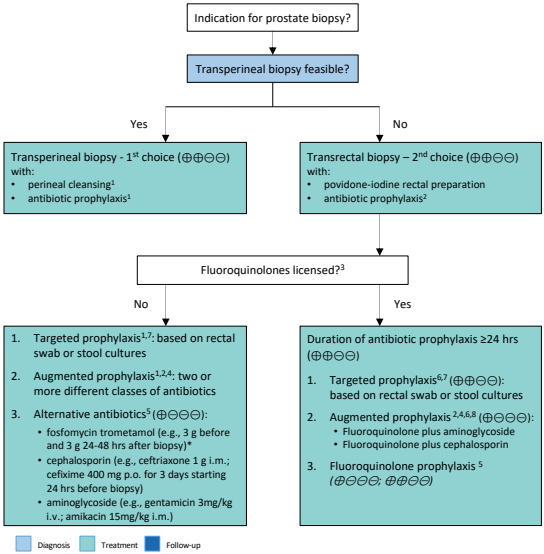
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (PSA density < 0.20 ng/mL/cc, negative DRE findings, no family history), omit biopsy and offer PSA monitoring; otherwise consider systematic biopsy.	Weak
When MRI is indeterminate (PI-RADS = 3), and clinical suspicion of PCa is very low (PSA density < 0.10 ng/mL/cc, negative DRE findings, no family history), omit biopsy and offer PSA monitoring; otherwise consider targeted biopsy with perilesional sampling.	Weak
If MRI is not available, use a risk calculator and systematic biopsies if indicated.	Strong
When performing systematic biopsy only, at least twelve cores are recommended.	Strong

Recommendations for performing prostate biopsy	**Strength rating***
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications and better antibiotic stewardship.	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

Use either target prophylaxis based on rectal swab or stool culture; or augmented prophylaxis (two or more different classes of antibiotics); 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.*

Figure 1: Prostate biopsy workflow to reduce infectious complications*



Suggested workflow on how to reduce post biopsy infections.

1. *Two systematic reviews including non-RCTs and two RCTs describe comparable rates of post-biopsy infection in patients with and without antibiotic prophylaxis.*
2. *Be informed about local antimicrobial resistance.*
3. *Banned by European Commission due to side effects.*
4. *Contradicts principles of Antimicrobial Stewardship.*
5. *Fosfomycin trometamol (4 RCTs), cephalosporins (2 RCTs), aminoglycosides (2 RCTs).*
6. *Only one RCT comparing targeted and augmented prophylaxis.*

7. *Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.*
8. *Various schemes: fluoroquinolone plus aminoglycoside (4 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).*

High certainty: (⊕⊕⊕⊕) very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: (⊕⊕⊕⊖) 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 certainty: (⊕⊕⊖⊖) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Figure adapted from Pilatz et al., with permission from Elsevier.
** Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in some countries 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.*

Recommendations for staging of prostate cancer	**Strength rating**
Any risk group staging	
Use pre-biopsy magnetic resonance imaging (MRI) for local staging information.	Weak
Low-risk localised disease	
Do not use additional imaging for staging purposes.	Strong

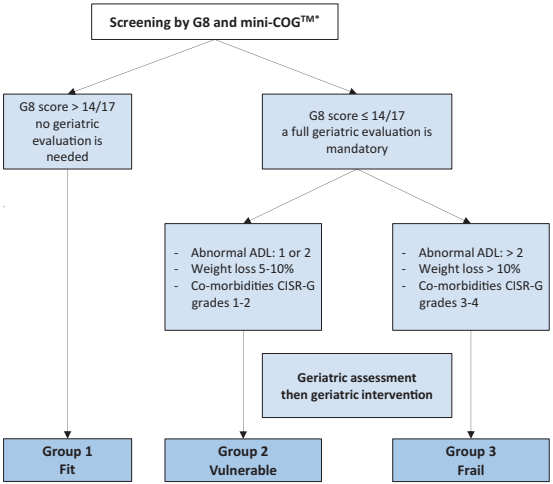
Intermediate-risk disease	
For patients with International Society of Urological Pathology (ISUP) grade group 3 disease perform prostate-specific antigen-positron emission tomography/computed tomography (PSMA-PET/CT) if available to increase accuracy or at least cross-sectional abdominopelvic imaging and a bone-scan.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening using PSMA-PET/CT if available or at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

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).

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



Mini-COGTM = Mini-COGTM cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.
** For Mini-COGTM, a cut-off point of ≤ 3/5 indicates a need to refer the patient for full evaluation of potential dementia.*
***Reproduced with permission of Elsevier, from Boyle H.J., et al., Eur J Cancer 2019.*

Recommendations for evaluating health status and life expectancy	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 or watchful waiting to patients with irreversible impairment.	Weak
Offer palliative symptom-directed therapy alone to frail patients.	Strong

Recommendations for active surveillance strategy	Strength rating
Offer active surveillance (AS) as standard of care for low-risk disease.	Strong
Exclude patients with cribriform or intraductal histology on biopsy from AS.	Strong
Perform magnetic resonance imaging (MRI) before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
Take targeted and perilesional biopsy cores (of any PI-RADS ≥ 3 lesion) if a confirmatory or repeat biopsy is performed.	Strong

Perform per-protocol confirmatory prostate biopsies if MRI is not available.	Weak
Do not perform confirmatory biopsies if a patient has had upfront MRI and targeted biopsies.	Weak
Base the strategy of AS on a strict follow-up protocol including PSA (at least once every six months), digital rectal examination (DRE) (at least once yearly), and repeated biopsy (every 2-3 years for 10 years).	Strong
Exclude patients with a low-risk PCa, a stable MRI (PRECISE 3) and a stable low PSA density (< 0.15) from repeat biopsy when MRI is repeated before repeat biopsy. In addition, serial DRE may be omitted if MRI is stable.	Weak
Perform MRI and repeat biopsy if PSA is rising (PSA-doubling time < 3 years).	Strong
Base change in treatment on biopsy progression, not on progression on MRI, PSA, and/or DRE.	Weak

Management by disease stages

Recommendations for the management of low-risk disease	Strength rating
Manage patients with a life expectancy < 10 years by watchful waiting.	Strong
Manage patients with a life expectancy > 10 years and low-risk disease by active surveillance .	Strong

Recommendations for the management of intermediate-risk disease*	Strength rating
Expectant management	
Offer watchful waiting in asymptomatic patients with life expectancy < 10 years (based on co-morbidities and age).	Strong
Offer active surveillance (AS) to selected patients with ISUP grade group 2 disease (e.g., < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low extent of tumour in biopsies (≤ 3 positive cores with Gleason score 3+4 and ≤ 50% cancer involvement/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 grade group 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 three months.	Weak
Offer nerve-sparing surgery to patients with a low risk of extra-capsular disease on that side.	Strong
Radiotherapeutic 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) (four to six months).	Strong
Offer focal boosting to MRI-defined dominant intra-prostatic tumour when using conventionally fractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that Organ at Risk constraints are not exceeded.	Weak

Offer ultra-hypofractionated IMRT/IGRT or SBRT, using either 36.25 Gy (40 Gy to prostate) in 5 fx or 42.7 Gy in 7 fx delivered alternate days.	Weak
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 (four to six 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 (four to six months).	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, 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

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

Recommendations for the management of high-risk localised disease*	Strength rating
Expectant management	
Offer watchful waiting to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Offer RP to selected patients as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (PLND)	
In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatment	
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 long-term androgen deprivation therapy (ADT) (two to three years).	Strong
Offer focal boosting to MRI-defined dominant intra-prostatic tumour when using normo-fractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that Organ at Risk constraints are not exceeded.	Weak

Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (two to three years).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy.	Strong
Only offer ADT monotherapy to patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

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

Recommendations for management of locally-advanced disease*	**Strength rating**
Radical prostatectomy (RP)	
Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
Extended pelvic lymph node dissection (PLND)	
In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Radiotherapeutic treatments	
Offer patients with cN0 disease intensity-modulated radiation therapy (IMRT)/ volumetric modulated arc therapy (VMAT) plus image-guide radiation therapy in combination with long-term androgen deprivation therapy (ADT).	Strong

Offer patients with cN0 disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose or low-dose rate), 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 two 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 two years of abiraterone to cN1M0 patients.	Strong
Other therapeutic options	
Do not offer whole gland treatment or focal treatment.	Strong

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

Recommendations for adjuvant treatment for pN0 and pN1 disease after radical prostatectomy*	**Strength rating**
Do not prescribe adjuvant androgen deprivation therapy (ADT) to pN0 patients.	Strong
In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT).	Strong

In pN1 patients, after an extended lymph node dissection, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT. 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT. 3. Offer observation (expectant management) to a patient after ePLND and ≤ 2 nodes and a undetectable PSA.	Weak

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

Recommendations for the management of persistent PSA after radical prostatectomy	**Strength rating**
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) scan to men with a persistent and rising prostate-specific antigen (PSA) if the results will influence subsequent treatment decisions.	Weak
Treat men with persistent PSA and no evidence of distant metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

Recommendations for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence (BCR) after radical prostatectomy	
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive prostate-specific antigen (PSA) rises.	Strong
A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
Offer monitoring, including PSA to EAU low-risk BCR patients.	Weak
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
Recommendations for BCR after radiotherapy	
Offer monitoring, including PSA to EAU low-risk BCR patients.	Weak
Only offer salvage radical prostatectomy (RP), brachytherapy, stereotactic body radiotherapy, 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

Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy (ADT) to M0 patients with a PSA-doubling time > 12 months.	Strong
Offer enzalutamide with or without ADT to M0 patients with a high-risk BCR, defined as a PSA doubling time of ≤ 9 months and a PSA level of ≥ 2ng/mL above nadir after radiation therapy or ≥ 1 ng/mL after radical prostatectomy with or without post-operative radiation therapy	Strong
Recommendations for follow-up after radical prostatectomy or radiotherapy	
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and serum PSA measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

Systemic treatments for prostate cancer

Recommendations for the first-line treatment of hormone-sensitive metastatic disease*	**Strength rating**
First-line treatment	
Discuss all patients with hormone-sensitive metastatic disease in a multidisciplinary team.	Strong

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
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting luteinising hormone-releasing hormone (LHRH) agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Offer LHRH antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction at the start of ADT.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications 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 who are fit for the regimen.	Strong
Offer ADT combined with darolutamide to patients with M1 disease who are fit for the regimen.	Weak

Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with 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.	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 a well-designed prospective cohort study.	Strong
Supportive care	
Assess osteoporosis risk factors and perform a dexa scan when commencing long-term ADT, to mitigate osseous complications.	Strong
Offer bone protection to avoid fractures in patients receiving combination treatment.	Strong
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates and monitor serum calcium.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy/volumetric arc radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong

In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery potentially followed by radiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

**All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.*

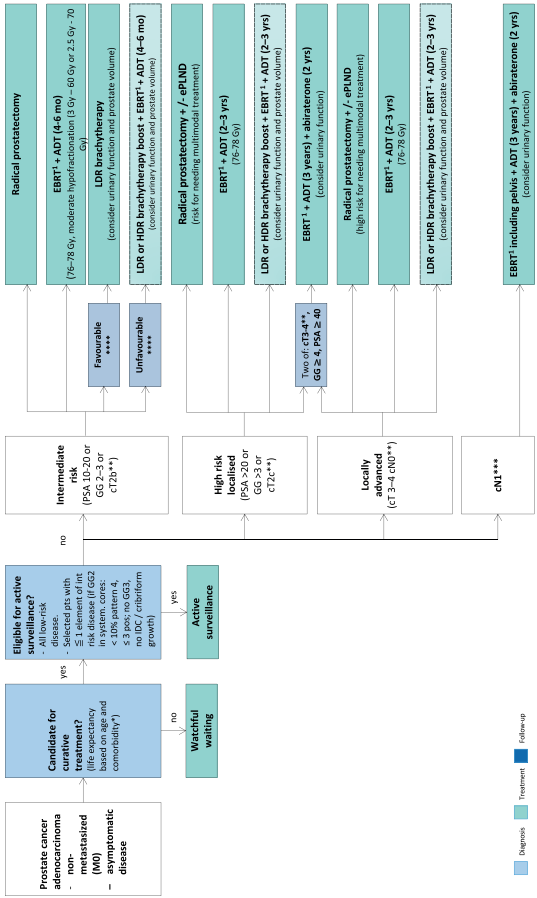
Recommendations for life-prolonging treatments of castrate-resistant disease	**Strength rating**
Ensure that testosterone levels are confirmed to be < 50 ng/dL before diagnosing castrate-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary 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

Recommendations for systemic treatments of castrate-resistant disease	Strength rating
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, ^{177}lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T, and for patients with DNA homologous recombination repair [HRR] alterations olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, talazoparib/enzalutamide).	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naïve docetaxel with 75 mg/m^2 every three weeks.	Strong
Offer patients previously untreated for mCRPC and harbouring an *HRR* or *BRCA* mutation abiraterone in combination with olaparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer patients previously untreated for mCRPC and harbouring a *BRCA* mutation abiraterone in combination with niraparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong

Offer patients previously untreated for mCRPC and harbouring an *HRR*-mutation enzalutamide in combination with talazoparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	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 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
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and who have progressed within twelve months of treatment with abiraterone or enzalutamide for mCRPC.	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

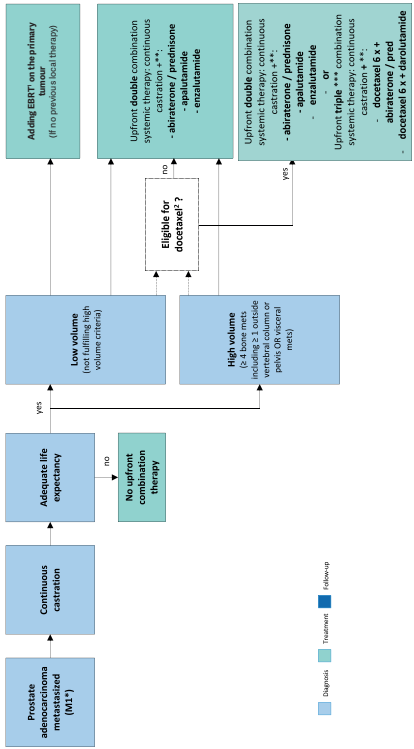
Recommendation for non-metastatic castrate-resistant disease	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

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 bone scan and CT.*
***** See text, dependent on GG and (biopsy) volume.*
1EBRT: 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.*
*** *Not for low volume, metachronous disease.*
EBRT[1]: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
2 Triple therapy was better than ADT plus docetaxel but randomised data comparing it to ADT plus ARTA is missing.
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

Recommendations for follow-up after treatment with curative intent	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and a prostate-specific antigen measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

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 on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
In patients receiving combination treatment offer bone protection to avoid fractures.	Strong
In patients with stage M0 disease, schedule follow-up at least every six 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 three to six months including imaging at regular intervals.	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
In patients on long-term ADT, as a minimum requirement, include a medical history including assessment of ADT-induced complications, 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 should be 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 patients eligible for active surveillance that global quality of life is equivalent for up to five 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 five years.	Weak

Recommendations for quality of life in men undergoing systemic treatments	**Strength rating**
Offer men on androgen deprivation therapy (ADT), twelve 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 hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men after any radical treatment 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.	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 when annual bone loss on ADT is confirmed to exceed 5%.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-29-5), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.