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

(Limited text update April 2024)

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh, E. Briers, Expert Patient Advocate (European Prostate Cancer Coalition/Europa UOMO), D. Eberli, G. De Meerleer, M. De Santis, S. Gillessen, A.M. Henry, G.J.L.H. van Leenders, J.Oldenburg, I.M. van Oort, D.E. Oprea-Lager, G. Ploussard, M Roberts, O. Rouvière, I.G. Schoots, J. Stranne, T. Wiegel
Guidelines Associates: T. Van den Broeck, O. Brunckhorst, A. Farolfi, G. Gandaglia, N. Grivas, M. Lardas, M. Liew, E. Linares Espinós, P-P.M. Willemse
Guidelines Office: J. Darraugh, N. Schouten, E.J. Smith

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 of 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 (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 do not. This distinction is particularly important as insignificant PCa that does not cause harm is so 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 grade group 2 cancers may also have insignificant disease dependent upon PSA, magnetic resonance imaging (MRI) findings and percentage of grade group 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 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 (DRE) 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

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.

Recommendations for individual 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 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 *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 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 up to eight years in those not at risk.	Strong
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

Recommendations for germline testing*	Strength rating
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 a family history of multiple cancers on the same side of the family.	Strong
Offer germline testing to patients with *breast cancer gene* (BRCA) mutations on somatic testing	Strong

Recommendations for screening and individual early detection	Strength rating
In asymptomatic men with a prostate-specific antigen (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: • 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

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.

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 Prostate Imaging Reporting & Data System (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, ultrasound (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 exam (DRE) and/or Prostate-specific antigen (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

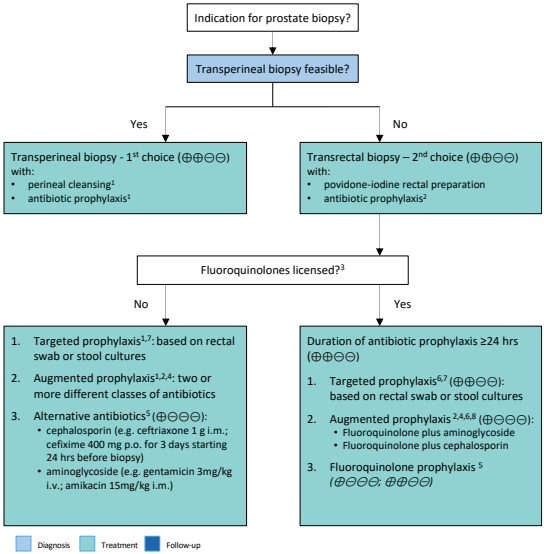
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (PSA density < 0.20 ng/mL/cc, negative DRE findings, no family history), omit biopsy and offer PSA monitoring; otherwise consider systematic biopsy.	Weak
When MRI is indeterminate (PI-RADS = 3), and clinical suspicion of PCa 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 12 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.	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

** Note on strength ratings:*
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.*

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-transperineal 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. Only one RCT comparing targeted and augmented prophylaxis.

6. Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.
7. Various schemes: fluoroquinolone plus aminoglycoside (3 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).

GRADE Working Group grades of evidence. 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: local guidance in relation to the use of fosfomycin trometamol for prostate biopsy needs to be checked.*

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, include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	Weak

Perform A prostate-specific membrane antigen positron emission tomography (PSMA-PET)/Computed Tomography (CT) if available to increase accuracy.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening using PSMA-PET/CT if available and at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

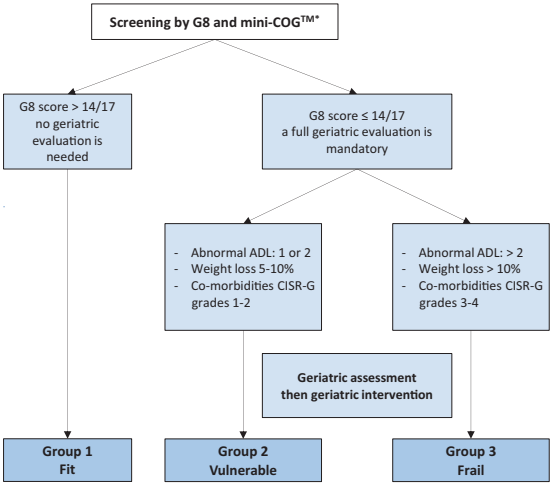
Disease Management

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 2019:116; 116.*

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 > ten 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 the treatment of prostate cancer*	Strength rating
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
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

Inform patients that all local treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic RP) has clearly shown superiority in terms of functional or oncological results.	Weak
Consider avoiding nerve-sparing surgery when there is a risk of ipsilateral extra-capsular extension (based on cT stage, ISUP grade group, magnetic resonance imaging, or with this information combined in a nomogram).	Weak
In patients undergoing a lymph node dissection you should perform an extended PLND.	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 four weeks or 70 Gy/28 fractions in six weeks).	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function or National Comprehensive Cancer Network (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	
Offer focal therapy with HIFU 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.*

Recommendations for active surveillance (AS) strategy	**Strength rating**
Base the strategy of AS on a strict protocol including digital rectal examination (at least once yearly), Prostate-specific antigen (PSA) (at least once every six months) and repeated biopsy every two to three years.	Strong
Patients with a low risk PCa, a stable magnetic resonance imaging (MRI) (PRECISE 3) and a stable, low PSA density (< 0.15) may be excused from repeat biopsy.	Weak
Perform MRI and repeat biopsy if PSA is rising (PSA-doubling time < three years).	Strong
Base change in treatment on biopsy progression, not on progression on MRI and/or PSA.	Weak

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 core involvement > 50%/core of ISUP grade group 2 disease.	Weak

Recommendations for the management of low-risk disease*	**Strength rating**
Watchful Waiting	
Manage patients with a life expectancy < ten years by watchful waiting.	Strong
Active surveillance (AS)	
Manage patients with a life expectancy > ten years and low-risk disease by AS.	Strong
Selection of patients	
Patients with cribriform or 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.	Strong
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

Strategy of surveillance	
Repeat biopsies should be performed at least once every three years for ten years.	Weak
In case of prostate-specific antigen progression or change in digital-rectal examination or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*
PI-RADS = Prostate Imaging Reporting & Data System

Recommendations for the treatment of intermediate-risk disease*	Strength rating
Watchful Waiting (WW)	
Offer WW in asymptomatic patients with life expectancy < ten years (based on co-morbidities and age).	Strong
Active surveillance (AS)	
Offer AS to selected patients with ISUP grade group 2 disease (e.g. < 10% pattern 4, Prostate-specific antigen (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 > ten 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) (4-6 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 (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 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.*

NCCN = National Comprehensive Cancer Network

Recommendations for radical and palliative treatment of high-risk localised disease*	Strength rating
Watchful Waiting	
Offer WW to asymptomatic patients with life expectancy < ten years.	Strong
Radical prostatectomy (RP)	
Offer RP to selected patients as part of potential multi-modal therapy.	Weak
Extended pelvic lymph node dissection (ePLND)	
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 (see Section 6.2.4.1).	Strong
Radiotherapeutic treatment	
Offer patients intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy 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 those 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 radical- and palliative treatment 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 (ePLND)	
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 rate 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
Therapeutic options outside surgery or radiotherapy	
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 eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	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 PSMA PET/CT 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 radiotherapy and additional hormonal therapy.	Weak

Recommendations for imaging in patients with biochemical recurrence	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions (EAU BCR risk groups).	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

Guidelines 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 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 prostate-specific antigen (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 to M0 patients with a PSA-doubling time > 12 months.	Strong
Offer enzalutamide with or without androgen deprivation therapy to M0 patients with a BCR and PSA-doubling time ≤ 9 months after radical treatment	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 prostate-specific antigen (PSA) measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

Recommendations for the first-line treatment of hormone-sensitive metastatic disease*	Strength rating
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 LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction.	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 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

**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 naiive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
Offer patients previously untreated for metastatic castrate-resistant PCa (mCRPC) and harbouring an HRR or BRCA mutation abiraterone in combination with olaparib if the patient is fit for both agents.	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.	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.	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 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
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within twelve months of treatment with abiraterone or enzalutamide.	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

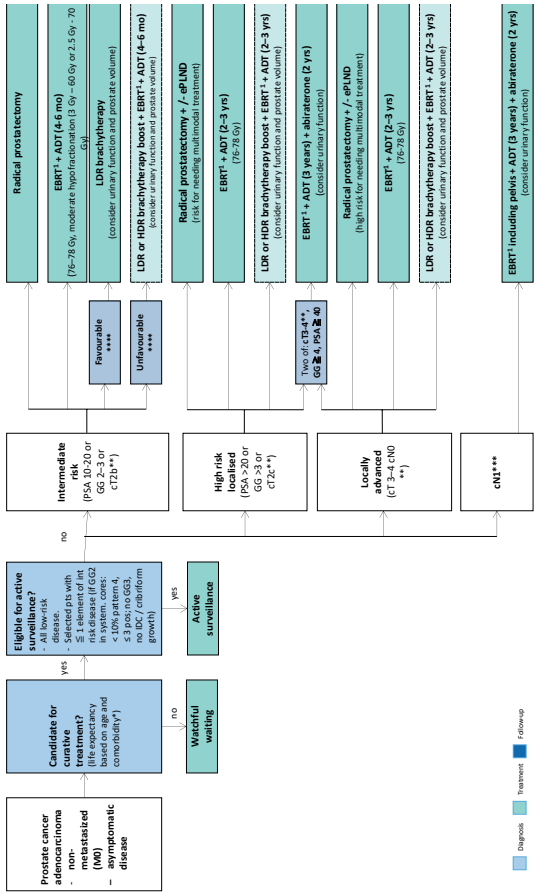
Recommendation for non-metastatic castrate-resistant prostate cancer (CRPC)	**Strength rating**
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < ten months) to prolong time to metastases and overall survival.	Strong

Supportive care of castrate-resistant disease

These recommendations are in addition to appropriate systemic therapy.

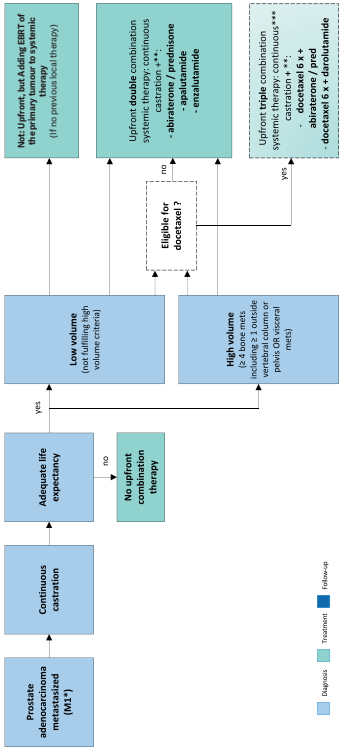
Recommendations for supportive care of castrate-resistant prostate cancer (CRPC)	Strength rating
Offer bone protective agents to patients with metastatic CRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as 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 followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	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.*
1EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
= weak recommendation.
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

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 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 3-6 months.	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 for offer bone protection to avoid fractures	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 androgen deprivation therapy (ADT), 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 'quality of life (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 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 annual bone loss on ADT is confirmed to exceed 5%.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-23-3), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.