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 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.

The International Society of Urological Pathology (ISUP) World Health Organization (WHO) 2014 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 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. This distinction is particularly important to prevent overtreatment, as the majority of low-risk PCa do not require treatment and so can avoid unnecessary harmful side effects. In addition, 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.

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 counseling 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 and 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
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

Recommendations for prostate biopsy	Strength rating*
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong

At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc and 10 to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive.	Strong
Where MRI has shown a suspicious lesion magnetic resonance (MR)-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine in men 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
Use a single oral dose of either cefuroxime or cephalexin or cephazolin as antibiotic prophylaxis for transperineal biopsy. Patients with severe penicillin allergy may be given sulphamethoxazole.	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.

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

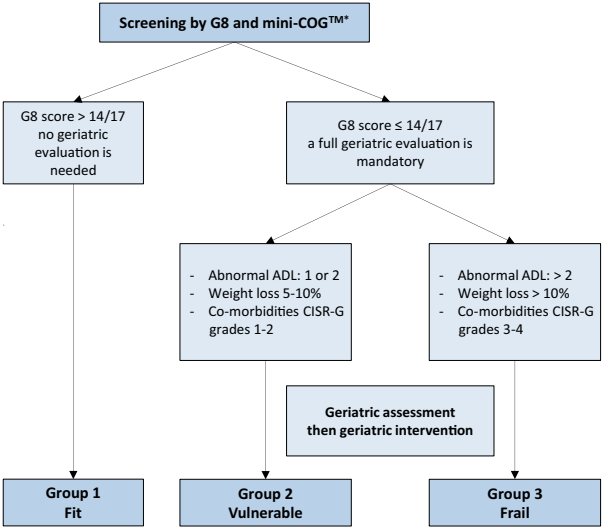
Any risk group staging	**Strength rating**
Use pre-biopsy MRI for staging information.	Weak
Low-risk localised PCa	
Do not use additional imaging for staging purposes.	Strong
Intermediate-risk PCa	
In ISUP grade 3, include at least a cross-sectional abdominopelvic imaging and bone-scan for metastatic 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 1: 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
Inform patients that based on robust current data with up to 12 years of follow-up, 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).	Strong
Inform patients that all active treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.	Strong

Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular 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.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 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- or intermediate-risk disease (ISUP grade 2 and ≤ 33% of biopsy cores involved).	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10-20 ng/mL.	Weak

Offer LDR or HDR brachytherapy boost combined with IMRT /VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Only offer cryotherapy and high-intensity-focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

Guidelines for first-line treatment of various disease stages

Recommendations		**Strength rating**
Low-risk disease		
Active surveillance (AS)	*Selection of patients*	
	Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
	Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong
	Perform an 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
	Follow-up strategy	
	Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
	In case of PSA progression or change in DRE or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
Active treatment	Offer surgery or radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND.	Strong

Radiotherapy	Offer low-dose rate (LDR) brachytherapy to patients with low risk PCa and good urinary function.	Strong
	Use intensity-modulated radiation therapy (IMRT)/ volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
Other options	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Strong
	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

Intermediate-risk disease		
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 must 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
RP	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong

ePLND	Perform an ePLND in intermediate-risk disease based on predicted risk of lymph node invasion (validated nomogram).	Strong
Radiotherapy	Offer LDR brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
	For IMRT/VMAT plus IGRT use 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 ADT (4–6 months).	Strong
	Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
	Offer HDR brachytherapy boost combined with IMRT/VMAT and IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
	In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76-78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	Weak

Other therapeutic options	Only offer whole-gland ablative therapy (such as cryotherapy, HIFU, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak
High-risk localised disease		
RP	Offer RP to selected patients with high-risk localised PCa as part of a 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
Radiotherapy	In patients with high-risk localised disease, use IMRT/VMAT plus IGRT with 76-78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR) in combination with long-term ADT (2 to 3 years).	Weak

Other options	Do not offer either whole gland or focal therapy to patients with high-risk localised disease.	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 selected patients with locally-advanced PCa as part of multi-modal therapy.	Strong
ePLND	Perform an ePLND prior to RP in locally-advanced PCa.	Strong
Radiotherapy	Offer patients with locally-advanced disease IMRT/VMAT plus IGRT in combination with long-term ADT.	Strong
	Offer patients with locally advanced disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT.	Weak
	Offer long-term ADT for at least 2 years.	Weak

	Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or ≥ 2 high-risk factors (cT3-4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong
Other options	Do not offer whole gland treatment or focal treatment to patients with locally-advanced disease.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-DT < 12 months, and either a PSA > 50 ng/mL, a poorly differentiated tumour or troublesome local disease-related symptoms.	Strong
	Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Weak
Adjuvant treatment after radical prostatectomy		
Do not prescribe adjuvant ADT in pN0 patients.		Strong
Only offer adjuvant IMRT/VMAT plus IGRT to high-risk patients (pN0) with at least two out of three high-risk features (ISUP grade group 4–5, pT3, positive margins).		Strong

Discuss three management options with patients with pN1 disease after an ePLND, 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		
Localised disease		
Watchful waiting (WW)	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
Localised-advanced disease		
WW	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA-DT > 12 months, a PSA < 50 ng/mL and well-differentiated tumour, who are unwilling or unable to receive any form of local treatment.	Weak
Persistent PSA after RP		
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography (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 radiotherapy and additional hormonal therapy.		Weak

Follow-up after treatment with curative intent

- 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.

EAU Low-Risk BCR:

- Following RP: PSA-doubling-time > 1 year AND pathological ISUP grade < 4.
- Following RT: interval to biochemical failure > 18 months AND biopsy ISUP grade < 4.

EAU High-Risk BCR:

- Following RP: PSA-DT < 1 year OR pathological ISUP grade 4–5.
- Following RT: interval to biochemical failure < 18 months OR biopsy ISUP grade 4–5.

Recommendations for follow-up	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

Guidelines for metastatic disease, second-line and palliative treatments

Recommendations	Strength rating
Metastatic disease in a first-line setting	
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 luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy before starting ADT, especially to patients with an impending clinical complications like spinal cord compression or bladder outlet obstruction.	Weak
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 antagonists 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 chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate RT (using the doses and template from the STAMPEDE study) 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 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

Recommendations for imaging in biochemical recurrence	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	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 MRI 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

Recommendations for second-line therapy after treatment with curative intent		Strength rating
Biochemical recurrence after treatment with curative intent		
Biochemical recurrence (BCR) after radical prostatectomy (RP)	Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
	Offer early salvage IMRT/VMAT plus IGRT to men with two consecutive PSA rises.	Strong
	A negative 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 biochemical recurrence.	Weak
Biochemical recurrence after RT	Offer monitoring, including PSA, to EAU low-Risk BCR patients.	Weak
	Only offer salvage RP, brachy-therapy, 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 under-taken in experienced centres.	Strong

Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > 12 months.	Strong
Life-prolonging treatments of castrate-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 the 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 naïve, 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 castrate-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

Follow-up after treatment with 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 '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 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 on ADT is confirmed to exceed 5%.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-16-5), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.