GUIDELINES ON PROSTATE CANCER

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Introduction

Please note that this text presents an abridged version of the full text Prostate Cancer (PCa) guidelines and consultation of the more detailed, underlying document, is strongly advised. Prostate cancer is a complex disease, and - aside from disease characteristics - age, comorbidities and individual patient preference will impact treatment choice. All available options need to be discussed in full with the patient.

Epidemiology and risk prevention

Prostate cancer is the most common cancer in males in Europe. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population, and with the potential risk of overtreatment 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 2009 Tumour Node Metastasis (TNM) classification is used for staging.

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
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 prostate-specific antigen [PSA] level)
T2	Tumour confined within the prostate[1]
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[2]
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
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 lymph nodes[3]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis[4]
M - Distant metastasis[5]	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis

M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*

[2] *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.*

[3] *The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.*

[4] *Laterality does not affect the N-classification*

[5] *When more than one site of metastasis is present, the most advanced category should be used.*

EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

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

Diagnostic evaluation
Screening

Guidelines for screening and early detection	LE	GR
An individualized risk-adapted strategy for early detection might be offered to a well-informed man with a good PS and at least 10-15 yrs of life expectancy.	3	B
Early PSA testing should be offered to men at elevated risk for PCa. Risk groups are: • men over 50 yrs of age; • men over 45 yrs of age and a family history of PCa; • African-Americans; • men with a PSA level of > 1 ng/mL at 40 yrs of age; • men with a PSA level of > 2 ng/mL at 60 yrs of age.	2b	A
A risk-adapted strategy might be considered (based on initial PSA level), which may be every 2 yrs for those initially at risk, or postponed up to 8 yrs in those not at risk.	3	C
The age at which early diagnosis of PCa should be stopped is influenced by life expectancy and performance status; men who have < 15-yr life-expectancy are unlikely to benefit based on findings from the PIVOT and the ERSPC trials.	3	A

GR = grade of recommendation; ERSPC = European Randomised Study of Screening for Prostate Cancer; LE = level of evidence; PIVOT = Prostate Cancer Intervention Versus Observation Trial; PS = performance status; PSA = prostate-specific antigen.

Clinical diagnosis

Prostate cancer is usually suspected on the basis of digital rectal examination and/or prostate-specific antigen levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or unexpected discovery from specimens from TURP 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 age and comorbidity into consideration. Procedures that will not affect the treatment decision can usually be avoided.

Synoptic reporting of surgical specimens results in transparent and more complete pathology reporting. The use of a checklist is encouraged (see example).

Example checklist: Reporting of prostatectomy specimens

Histopathological type • Type of carcinoma, e.g. conventional acinar, or ductal
Histological grade • Primary (predominant) grade • Secondary grade • Tertiary grade (if applicable) • Global Gleason score • Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional) • Percentage of prostate involved • Size/volume of dominant tumour nodule
Pathological staging (pTNM) If extraprostatic extension is present: • indicate whether it is focal or extensive • specify sites • Indicate whether there is seminal vesicle invasion If applicable, regional lymph nodes: • location • number of nodes retrieved • number of nodes involved
Surgical margins If carcinoma is present at the margin: • specify sites
Other • Presence of lymphovascular / angio-invasion • Location of dominant tumour • Presence of intraductal carcinoma

Guidelines for the clinical diagnosis of PCa	LE	GR
Transurethral resection of the prostate should not be used as a tool for cancer detection.	2a	A
PCa should be graded according to the ISUP 2005 modified Gleason grading system.	2a	A
Biopsy decision should be based on PSA testing and DRE.	2b	A
Transition zone biopsies are not recommended initially, due to low detection rates.	2b	B
For initial diagnosis, a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies should be performed under US guidance.	2a	B
Transrectal prostate needle biopsies should be taken under antibiotic protection.	1b	A
Local anaesthetic by periprostatic infiltration is recommended for prostate needle biopsies.	1a	A
Prostate core biopsies from different sites should be submitted separately for processing and pathology reporting.	3	A
One set of repeat biopsies is warranted for persistent indications for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at initial biopsy).	2a	B
When clinical suspicion of PCa persists in spite of negative biopsies, MRI-targeted biopsies are recommended.	2b	B

Guidelines for processing prostatectomy specimens	LE	GR
Total embedding is preferred, by conventional (quadrant) or whole-mount sectioning.	3	C
The entire surface should be inked before cutting, to evaluate the surgical margin.	3	A
The apex and base should be examined separately using the cone method with sagittal or radial sectioning.	3	A
Processing and reporting of prostatectomy specimens should follow the 2010 ISUP guidelines.	3	A

Guidelines for staging of PCa

Any risk group staging	LE	GR
Additional imaging is required only if it changes patient management.	4	A*
For local staging, CT and TRUS should not be used.	3	A
For up-front staging, choline PET-scanning should not be used.	2a	A

Low-risk localised PCa	LE	GR
No additional imaging is recommended for staging purposes.		A

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4, bone scan and cross-sectional imaging is required.		A*

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Prostate mpMRI should be used for local staging.	2b	A
CT/MRI and bone-scan should be used in nodal staging and detection of distant metastasis.	2b	A

**Upgraded following panel consensus.*
CT = computed tomography; DRE = digital rectal examination; GR = grade of recommendation; level of evidence; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; TRUS = transrectal ultrasound; PSA = prostate-specific antigen.

Disease management

Deferred treatment

Many men with localised PCa will not benefit from definitive treatment, and 45% of men with PSA-detected PCa would be candidates for deferred management. In men with comorbidity and limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life.

Guidelines overview - Primary treatment of PCa

Primary treatment of prostate cancer			GR
General comments	Patients suitable for several treatment modalities (active surveillance, surgery, radiotherapy) must have these options discussed with them.		A*
	In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable as no single approach has shown clear superiority in terms of functional or oncological results.		A
	EBRT should be offered in all risk groups of non-metastatic PCa.		A
	IMRT is the recommended modality for definitive treatment of PCa by EBRT.		A
	Treatment	**Comment**	
Low risk PCa	**Watchful waiting**	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
		During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression.	B
	Active surveillance	Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 yrs life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A

		Follow-up should be based on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.	A
	Radical prostatectomy	In patients with a life expectancy > 10 yrs, RP should be offered.	A
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B
		LND is not indicated in low-risk PCa.	A
	Radiotherapy	In low-risk PCa the total dose should be 74 to 78 Gy.	A
		In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	A
	Cryotherapy, HIFU	In patients who are unfit for surgery or radiotherapy, cryotherapy or HIFU might be an alternative treatment for PCa. The lack of long-term efficacy compared to standard modality has to be discussed with patients.	C

	Focal treatment	Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A
	Androgen suppression	Unsuitable.	A
Intermediate risk PCa	**Watchful waiting**	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
	Active surveillance	Not an option.	A
	Radical prostatectomy	In patients with a life expectancy > 10 yrs, RP should be offered.	A
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		eLND should be performed if the estimated risk for positive lymph nodes exceeds 5%.	B
		Limited LND should not be performed.	A

		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant EBRT should be discussed as an option because it improves at least biochemical-free survival. (*The highest effect of adjuvant radiotherapy is seen in PCa patients with positive margins.)*	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant EBRT when PSA increases.	A
		Adjuvant HT for pN0 is not recommended.	
		NHT before RP is not recommended.	A
	Radiotherapy	In intermediate- risk PCa the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A
	Androgen suppression monotherapy	No place in asymptomatic patients.	A
High risk PCa	**Watchful waiting**	**High risk localised**: Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	

		High risk locally advanced: In M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSADT > 12 mo and a PSA < 50 ng/mL and non-poorly differentiated tumour.	A
	Active surveillance	Not appropriate.	A
	Radical prostatectomy	NHT before RP is not recommended.	A
		eLND should be performed in high-risk PCa.	A
		Limited LND should not be performed.	A
		High risk localised: In patients with high-risk localised PCa and a life expectancy of > 10 yrs, RP should be offered in a multimodality setting.	B
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (refer to Partin tables/nomograms).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B

		High risk locally advanced: In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	C
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant EBRT should be discussed as an option because it improves at least biochemical-free survival. *(The highest effect of adjuvant radiotherapy is seen in PCa patients with positive margins.)*	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant EBRT irradiation when PSA increases.	A
	Radiotherapy	In patients with **high-risk localised** PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yrs is recommended).	A
		In patients with **locally advanced cN0** PCa, radiotherapy must be given in combination with long-term ADT (2-3 yrs is recommended).	A

	Androgen suppression monotherapy	Reserved for those unwilling or unable to receive any form of local treatment and either symptomatic or asymptomatic with a PSADT < 12 mo and a PSA > 50 ng/mL and a poorly differentiated tumour.	A
N1 patients			
cN1	In patients with cN+ PCa, pelvic EBRT can be given in combination with immediate long-term ADT.		B
pN1 after eLND	Adjuvant ADT is the standard of care for node-positive (pN+) patients.		A
	Adjuvant ADT with additional radiotherapy may have a role.		B
	Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.		B
Metastatic PCa	**Watchful waiting**	In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	B
	Active surveillance	Unsuitable.	A
	Radical prostatectomy	Unsuitable outside clinical trial.	A
	Radiotherapy to the prostate	Unsuitable outside clinical trial.	A

	Androgen suppression	Surgical- or medical castration (LHRH agonist or antagonist).	A
		No recommendation can be made to define the best population for combining castration with upfront Docetaxel.	A
		Castration combined with local treatment / other new hormonal treatments (abiraterone acetate or Enzalutamide) should not be used outside clinical trials.	A
		In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	A
		In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	A

		In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	A
		In M1 patients short term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection.	A
		In M1 patients, administration of anti-androgens as monotherapy should not be considered.	A
		In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	B
		Based on the schedules in use in clinical trials, treatment is stopped when the PSA is < 4 ng/mL after 6 to 7 mo of treatment. Treatment is resumed when the PSA is >10-20 ng/mL.	C

		Combined treatment with LHRH agonists and NSAA is recommended.	A
		Antagonists might be an option.	B
Castrate resistant status	Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.		A
	There is no evidence for treatment of non-metastatic CRPC outside a clinical trial.		A
	Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.		A
	Patients treated with maximal androgen blockade should stop the anti-androgen therapy once PSA progression is documented. *Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.*		A
	No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.		A
	Salvage hormonal treatment using abiraterone acetate is a valid option.		A
	Salvage hormonal treatment using enzalutamide is a valid option.		A
	In patients with mCRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m^2 every 3 weeks has shown a significant survival benefit.		A

	In patients with relapse following salvage docetaxel chemotherapy cabazitaxel, abiraterone acetate and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	A
	In men with mCRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit.	A
	Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	A
	Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	A
	In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must be always initially considered.	A

A Upgraded following panel consensus.*
ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; LHRH = luteinising-hormone-releasing hormone; LND = (extended) lymph node dissection; mCRPC = metastatic castrate-resistant prostate cancer; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSADT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

Guidelines for the treatment of senior adults (> 70 yrs of age)

	GR
Senior adults with localised PCa should systematically undergo health status screening.	A
Health status screening should be performed using the G8 screening tool.	A
Patients with G8 score ≤ 14 should undergo full specialist geriatric evaluation.	A
Senior adults can be classified as follows: 1. Fit or healthy older men, should receive standard treatment; 2. Vulnerable patients (reversible impairment) may be given standard treatment after resolution of geriatric problems; 3. Frail patients (irreversible impairment) should receive adapted treatment; 4. Patients who are too sick with terminal illness should receive only symptomatic palliative treatment.	B

Treatment	**LE**	**GR**
Localised disease		
Fit and vulnerable senior adults (after status optimisation) with life expectancy > 10 yrs and high-risk disease should be offered standard treatment.	2b	A
In frail or 'too-sick' patients, immediate ADT should only be used for symptom palliation.	1b	A
Minimally invasive energy-ablative therapies should not be routine in senior adults. These only have a role in selected fit and vulnerable senior adults with intermediate-risk disease.	3	B

Advanced disease (locally advanced / metastatic disease)		
Evaluation of bone mineral status and prevention of osteoporotic fracture are recommended in patients at high-risk of fractures.	2b	A
New chemotherapeutic and hormonal agents can be used in fit and vulnerable adults.	1b	B

ADT = androgen deprivation therapy; DT = doubling time; G8 = geriatric 8 health status screening tool; GR = grade of recommendation; LE = level of evidence; NHT = neoadjuvant hormonal treatment; IPSS = International Prostatic Symptom Score; PSA = prostate specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate.

Metastatic castrate-resistant PCa

No definitive strategy regarding treatment choice (which drug/drug family first) can be devised.

Figure 1: Potential therapeutic options after PSA-progression following initial hormonal therapy

Guidelines for "non-specific" management of mCRPC	LE	GR
Management of patients with extended symptomatic bone metastases has to be directed at improvement of QoL and mainly pain reduction.	1a	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.	1a	A
Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	1a	A
Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	1b	A
In the management of painful bone metastases, early use of palliative treatments such as radionuclides, EBRT and adequate use of analgesics is recommended.	1a	B
In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must be always initially considered.	1b	A

EBRT = external beam radiotherapy; GR = grade of recommendation; LE = level of evidence; QoL = quality of life.

Follow-up

Follow-up after treatment with curative intent

- After RP, PSA should be undetectable (< 0.1 ng/mL). A PSA of > 0.1 ng/mL after RP is a signal of residual prostate tissue. After an undetectable PSA is obtained following RP, a PSA > 0.2 ng/mL, and rising, is associated with recurrent disease.
- After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is the most reliable sign of recurrence.
- Palpable nodules and increasing serum PSA are often signs of local recurrence.

Guidelines for follow-up after treatment with curative intent	GR
In asymptomatic patients, disease-specific history and serum PSA measurement supplemented by DRE are recommended for routine follow-up. These should be performed at 3, 6 and 12 mo after treatment, then every 6 mo until 3 yrs, and then annually.	B
Imaging to detect local recurrence is only recommended if it affects treatment planning. Biopsy is usually not necessary before second-line therapy, except after EBRT when local salvage treatment is considered.	B
Routine bone scans and other imaging are not recommended in asymptomatic patients if there are no signs of biochemical relapse. In case patients have bone pain or other symptoms of progression, re-staging should be considered irrespective of serum PSA level.	B

Guidelines for follow-up after hormonal treatment	GR
Patients should be evaluated at 3 and 6 mo after the initiation of treatment.	A
As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and side effects.	A
In patients undergoing intermittent androgen deprivation, PSA and testosterone should be monitored at fixed intervals during the treatment pause (one or three mo).	A
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.	A
In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 mo, and as a minimum should include a disease-specific history, DRE and serum PSA determination.	A
In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 mo. As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements. The testosterone level should be checked, especially during the first year.	A
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
When disease progression occurs, or if the patient does not respond to treatment, follow-up should be individualized.	A

In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient has a testosterone level of at least < 50 ng/mL (< 1 mL/L).	B
Routine imaging of stable patients is not recommended.	B

CRPC = castrate-resistant prostate cancer; DRE = digital rectal examination; PSA = prostate-specific antigen.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-80-9), available to all members of the European Association of Urology at their website, http://www.uroweb.org.