GUIDELINES ON PROSTATE CANCER

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Introduction

Prostate cancer (PCa) is the most common cancer in elderly males in Europe. It is a big health concern, especially in developed countries with their greater proportion of older men in the general population.

There are three well-established risk factors for PCa: increasing age, ethnic origin, and genetic predisposition.

There is currently no evidence to suggest that dietary interventions would reduce the risk of PCa.

Screening

Early prostate specific antigen (PSA) testing could be used to detect the cohorts of men at risk and in need of further follow-up. An individualized risk-adapted strategy for early detection might be offered to a well-informed man with a least 10-15 years of individual life expectancy.

Systemic population-based screening is not advised since it is associated with harms such as overdiagnosis and overtreatment.

Staging system

The 2009 Tumour Node Metastasis (TNM) classification is used for staging (Table 1).

Table 1: Tumour Node Metastasis (TNM) classification of cancer of the prostate

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent 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 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 bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphinter, 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

M - Distant Metastasis[4]	
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 prostatic capsule, is not classified as T3, but as T2.*

[3] *The regional lymph nodes are the nodes of the true pelvis, which are essentially the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.*

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

Gleason grading system

Prostate Cancer grading is based on the 2005 International Society of Urological Pathology (ISUP) modified Gleason grading system.

Diagnosis and staging

Prostate cancer is usually suspected on the basis of digital rectal examination (DRE) and PSA levels. Definitive diagnosis depends on the histopathological verification of adenocarcinoma in prostate biopsy cores or operative specimens. 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 more

transparent and more complete pathology reporting. The use of a checklist is encouraged (see example).

Checklist for processing and pathology reporting of radical prostatectomy (RP) specimens

Histological type Type of carcinoma, e.g. conventional acinar, ductal, etc.
Histological grade Primary (predominant) grade Secondary grade Tertiary grade (if applicable) Total/global Gleason score Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional) Percentage of prostatic gland involved Tumour size of dominant nodule (if identified), greatest dimension in millimetres
Pathological staging (pTNM) If extraprostatic extension is present: indicate whether it is focal or extensive specify site(s) Indicate whether there is seminal vesicle invasion If applicable, regional lymph nodes: location number of lymph nodes retrieved number of lymph nodes involved
Surgical margins If carcinoma is present at the margin: specify sites and extra- or intraprostatic involvement

Other
If identified, presence of angio-invasion and/or intraductal carcinoma
Location (site, zone) of dominant tumour (optional)
Perineural invasion (optional):
if present, specify extra- or intraprostatic location

Guidelines for the Diagnosis and Staging of PCa

Recommendations for the Diagnosis of PCa	LE	GR
Prostate cancer should be graded according to the ISUP 2005 modified Gleason grading system.	2a	A
The decision to biopsy should be based on PSA testing and DRE.	2b	A
For initial diagnosis, a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies should be performed under ultrasound imaging 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 prostatic sites should be submitted separately for processing and pathology reporting.	3	A
Processing and reporting of prostatectomy specimens by pathology should follow the guidelines provided by the ISUP.	3	A
When available, mMRI of the prostate can be used to trigger a (targeted) repeat prostate biopsy.	2b	B

One set of repeat biopsies is warranted in cases with persistent indication for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy).	2a	B
Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	3	C

DRE = digital rectal examination; ISUP = International Society of Urological Pathology; mMRI = multiparametric magnetic resonance imaging; PSA = prostate-specific antigen.

Recommendations for the Staging of PCa	**LE**	**GR**
Imaging is not indicated for staging in low-risk tumours.	3	A
For local staging (T-staging) of PCa most relevant information will be provided by the number and sites of positive prostate biopsies, the tumour grade, and the level of serum PSA.	2	A
For local staging, CT and TRUS should not be used.	3	A
Prostate mMRI should be used in local staging only if its results change patient management.	2b	A
Prostate mMRI is not recommended for staging purposes in patients with low-risk prostate cancer.	2b	B
Lymph node status (clinical N-staging) need only be assessed when potentially curative treatment is planned.	3	B

Lymph node imaging (using CT or MRI) is recommended in asymptomatic patients only in case of PSA level > 10 ng/mL or Gleason score ≥ 8 or clinical stage ≥ T3 (i.e. intermediate-/high-risk situations).	2b	A
Bone scan is recommended in asymptomatic patients only in case of PSA level > 10 ng/mL or Gleason score ≥ 8 or clinical stage ≥ T3 (i.e. intermediate-/high-risk situations).	2b	A
Bone scan is indicated in patients with symptoms evocative of bone metastases.	3	A

CT = computed tomography; mMRI = multiparametric magnetic resonance imaging; TRUS = transrectal ultrasound.

Treatment of Prostate Cancer

An overview of the treatment options for patients with PCa, subdivided by stage at diagnosis, is presented below.

Active surveillance and watchful waiting

Active surveillance is also known as 'active monitoring'. As opposed to watchful waiting, active surveillance aims at the proper timing of curative treatment rather than the delayed application of palliative treatment options.

Recommendations for Active Surveillance and Watchful Waiting	LE	GR
Active surveillance		
Active surveillance is an option in patients with the lowest risk of cancer progression: over 10 years of life-expectancy, cT1-2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 (at least 10 cores), ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy)	2a	A
Follow-up should be based on DRE, PSA and repeated biopsies	2a	A
The optimal timing for follow-up is still unclear (yearly or every two years)	2a	A
Patients with biopsy progressions should be recommended to undergo active treatment	2a	A
Watchful waiting		
Watchful waiting may be offered to all patients not willing to accept the side-effects of active treatment, particularly patients with a short life-expectancy	1b	A
When on watchful waiting, the decision to start any non-curative treatment should be based on symptoms and disease progression.	1a	B

DRE = digital rectal examination.

Experimental therapeutic options for clinically localized PCa

Recommendations	GR
In patients who are unfit for surgery or radiotherapy, cryotherapy can be an alternative treatment for PCa.	C
If HIFU is offered, the lack of long-term comparative outcome data (> 10 y) should be discussed with the patient.	C
Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A

HIFU = high-intensity focused ultrasound.

Guidelines for the Primary Treatment of PCa			
Stage	**Treatment**	**Comment**	**GR**
T1a	Watchful waiting	In patients with < 10-year life expectancy standard treatment for Gleason score ≤ 6 and 7 adenocarcinomas.	B
	Active surveillance	In patients with > 10-year life expectancy, re-staging with TRUS and biopsy is recommended.	B
	Radical prostatectomy	Optional in younger patients with a long life-expectancy, especially for Gleason score ≥ 7 adenocarcinomas.	B
	Radiotherapy	Optional in younger patients with a long life-expectancy, in particular in poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.	B

	Hormonal	Not an option.	A
	Combination	Not an option.	C
T1b-T2b	Active surveillance	Treatment option in patients with cT1c-cT2a, PSA < 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 biopsies positive, ≤ 50% cancer involvement in each biopsy.	B
		Patients with a life expectancy > 10 years once they are informed about the lack of survival data beyond 10 years.	
		Patients who do not accept treatment-related complications.	
T1a-T2c	Watchful waiting	Patients with life expectancy < 10 years and Gleason score < 7.	A
		Patients with life expectancy < 10 years and Gleason score = 7.	B
	Radical prostatectomy	Optional in patients with pT1a PCa.	A
		Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.	

	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications.	B
		Patients with contraindications for surgery.	
		Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below).	
	Brachytherapy	Low-dose rate brachytherapy can be considered for low-risk PCa patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.	B
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.	C
		Anti-androgens are associated with a poorer outcome compared to 'watchful waiting' and are not recommended.	A
	Combination	For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A

T3- T4	Watchful waiting	Option in asymptomatic patients with T3, Gleason score ≤ 7, and a life expectancy < 10 years who are unfit for local treatment.	C
	Radical prostatectomy	Optional for selected patients with T3a, PSA < 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy > 10 years.	C
		Patients have to be informed that RP is associated with an increased risk of positive surgical margins, unfavourable histology and positive lymph nodes and that, therefore, adjuvant or salvage therapy such as radiation therapy or androgen deprivation might be indicated.	
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation of > 74 Gy seems to be of benefit. A combination with hormonal therapy can be recommended.	A

	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSADT < 1 year.	A
		Patient-driven, unfit patients.	
		Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.	
	Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation.	A
		NHT plus radical prostatectomy: no indication.	B
N+, M0	Watchful waiting	Asymptomatic patients. Patient-driven (PSA < 20-50 ng/mL), PSADT > 12 months. Requires very close follow-up.	B
	Radical prostatectomy	Optional for selected patients with a life expectancy of > 10 years as part of a multimodal treatment approach.	C
	Radiotherapy	Optional in selected patients with a life expectancy of > 10 years, combination therapy with adjuvant androgen deprivation for 3 years is mandatory.	C

	Hormonal	Standard treatment after extended node dissection if > 2 positive nodes (irrespective of the local treatment: surgery or radiotherapy). Hormonal therapy should only be used as monotherapy in patients who are unfit for any type of local therapy.	A
	Combination	No standard option. Patient-driven.	B
M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.	B
	Radical prostatectomy	Not a standard option.	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.	C
	Hormonal	Standard option. Mandatory in symptomatic patients.	A

DT = doubling time; NHT = neoadjuvant hormonal treatment; IPSS = International Prostatic Symptom Score; PSA = prostate specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate.

For more detailed information and discussion on second-line therapy, please see the full text version of the guidelines.

Follow-up of Prostate Cancer Patients

Reasons for follow-up may vary depending on the treatment given, patient age, co-morbidity and the patient's own wishes. In general, patients who receive curative therapy are followed up to assess:

- The possibility of second-line treatment with curative intent;
- The possibility of early hormonal therapy after failure.

Guidelines for follow-up after treatment with curative intent	GR
In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	B
After RP, a serum PSA level > 0.2 ng/mL can be associated with residual or recurrent disease.	B
After radiation therapy, a rising PSA level > 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of recurrent disease.	B
Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.	B
Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases TRUS and biopsy are not necessary before second-line therapy.	B
Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.	B

DRE = digital rectal examination; RP = radical prostatectomy.

Guidelines for follow-up after hormonal treatment	GR
Patients should first be evaluated at 3 and 6 months after treatment initiation.	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 set intervals during the treatment pause (one or three months).	A
Follow-up should be tailored to 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 months, and should include at least a disease-specific history, DRE and serum PSA measurement.	A
In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. 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 the treatment given, follow-up needs to be individualised.	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/dL.	B
Routine imaging of stable patients is not recommended.	B

CRPC = castration-resistant prostate cancer; DRE = digital rectal examination.

Treatment of relapse after curative therapies

An effort should be made to distinguish between the probability of local failure only, versus distant (+/- local) failure. Initial pathology, how long after primary therapy the PSA-relapse occurs and how fast the PSA-value is rising can all aid in the distinction between local and distant failure. Poorly differentiated tumour, early PSA-relapse and a short PSA-doubling time are all signs of distant failure. Treatment can then be guided by the presumed site of failure, the patient's general condition and personal preferences. Imaging studies are of limited value in patients with early PSA-relapse only.

Guidelines for imaging and second-line therapy after treatment with curative intent	**LE**	**GR**
Biochemical failure (BCF) after RP		
In case of BCF, bone scan and abdominopelvic CT should be performed only in patients with a PSA level > 10 ng/mL, or with high PSA kinetics (PSA doubling time < 6 months or a PSA velocity > 0.5 ng/mL/month) or in patients with symptoms of bone disease.	3	A
A choline PET/CT is not recommended in patients with BCF and a PSA-level < 1 ng/mL.	3	A

For patients with a PSA rising out of the undetectable range and favourable prognostic factors (PSADT > 1 year and Gleason ≤ 7) surveillance and possibly delayed salvage RT (SRT) can be offered.	3	B
Patients with a PSA rising out of the undetectable range should be treated with SRT to the prostatic bed at least. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Patients with persistent PSA should be treated with SRT to the prostatic bed at least. The total dose of SRT should be at least 66 Gy and has to be given early (PSA < 0.5 ng/mL).	3	C
Biochemical failure after RT		
In patients with BCF who are candidates for local salvage therapy, prostate multiparametric MRI can guide biopsy.	3	C
Selected patients with localized PCa at primary treatment and histologically proven recurrence without evidence of metastatic disease should be treated with SRP.	3	B
Due to the increased rate of side effects, SRP and salvage brachytherapy should be performed in experienced centres.	3	A
HIFU and cryosurgical ablation are treatment options for patients without evidence of metastasis and with histologically proven local recurrence. However, patients must be informed about the experimental nature of these approaches.	3	B

BCF = biochemical failure; CT = computed tomography; HIFU = high-intensity focused ultrasound; MRI = magnetic resonance imaging; PET = positron emission tomography; PSADT = pros-

tate-specific antigen doubling-time; RP = radical prostatectomy; RT = radiotherapy; SRP = salvage radical prostatectomy.

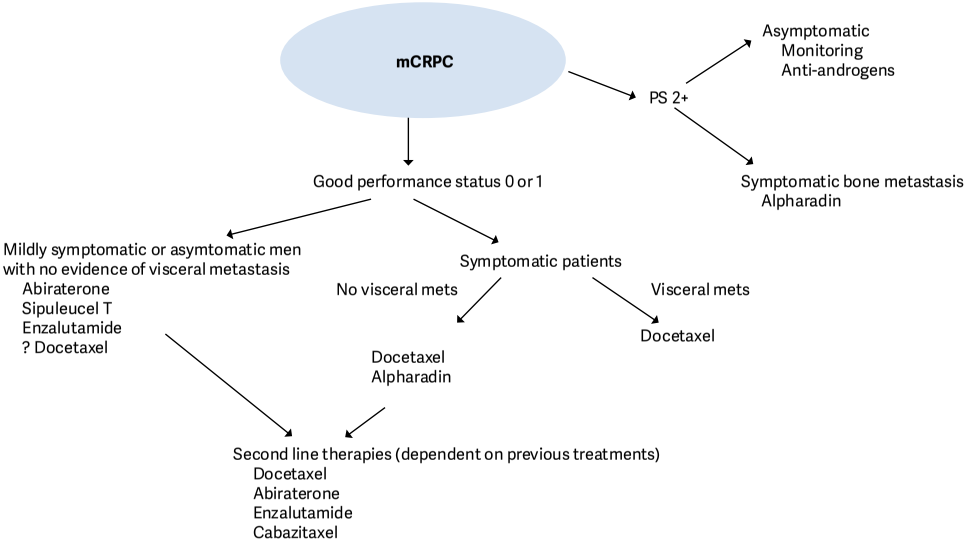
Treatment of relapse after hormonal therapy

Castration-refractory PCa (CRPC) is usually a debilitating disease, often affecting elderly patients. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers. In most cases the decision whether to treat or not is made based on counselling of the individual patient, which limits the role of guidelines.

Guidelines for the treatment after hormonal therapy (first second-line modality) in metastatic CRPC	**LE**	**GR**
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	2b	B
Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.		B
Patients should not be started on second-line therapy unless their PSA serum levels are > 2 ng/mL to ensure correct interpretation of therapeutic efficacy.		A
Men 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.*	1	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.	3	A
Cabazitaxel, abiraterone and enzalutamide are effective in the management of progressive CRPC following docetaxel therapy.	1b	A
Second-line salvage hormonal treatment using abiraterone acetate is considered to be a valid option. It must be remembered that one of the 2 coprimary end-points of the pivotal trial has not yet been met.	2b	A
Second-line salvage hormonal treatment using enzalutamide might become a valid option, but a full paper is awaited.	2b	C
In non-metastatic CRPC, secondary hormonal treatment (AA, Enza) should only be used in a clinical trial setting	3	A
Ra223 improves survival in men with bone predominant disease without visceral metastasis	1b	A

CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen; MAB = maximal androgen blockade.


mCRPC
PS 2+
Asymptomatic
Monitoring
Anti-androgens
Symptomatic bone metastasis
Alpharadin
Good performance status 0 or 1
Mildly symptomatic or asymtomatic men with no evidence of visceral metastasis
Abiraterone
Sipuleucel T
Enzalutamide
? Docetaxel
Symptomatic patients
No visceral mets
Visceral mets
Docetaxel
Docetaxel
Alpharadin
Second line therapies (dependent on previous treatments)
Docetaxel
Abiraterone
Enzalutamide
Cabazitaxel

Management of PCa in senior Adults*

Conclusions and recommendations	LE	GR
Evaluation of health status		
Senior adults with localized PCa should systematically undergo health status screening.	1b	A
Health status screening should be performed using the G8 screening tool.	2a	A
Patients with a G8 score ≤ 14 should undergo a full geriatric evaluation, preferably by a medical team specialized in geriatric medicine.	2a	A
Based on this evaluation, senior adults can be classified into one of four groups: 1. **'Fit'** or 'healthy' older men, should receive standard treatment; 2. '**Vulnerable**' patients (i.e. reversible impairment), may be given standard treatment after resolution of any geriatric problems through geriatric interventions; 3. '**Frail**' patients (i.e. irreversible impairment), should receive an adapted treatment; 4. Patients who are '**too sick**' with have a '**terminal illness**' should receive only symptomatic palliative treatment.	3	B
Treatment		
Localized disease		
'Fit' and 'vulnerable' senior adults with a life expectancy of > 10 years, diagnosed with high-risk disease, should be offered standard treatment.	2b	A
In 'frail' patients or patients who are 'too sick', immediate ADT should only be used for symptom palliation.	1b	A

Minimally invasive therapies should not be applied routinely in senior adults. These therapies have a role only in highly selected fit and vulnerable senior adults with intermediate-risk disease.	3	B
Advanced 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 successfully in senior adults.	1b	B

**Prof.Dr. J-P. Droz provided considerable expertise for this section.*

Summary

Prostate cancer is a complex disease, in which many aspects of the disease itself and the affected patient must be considered before decisions regarding diagnostic work-up, treatment and follow-up can be made.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-65-6), available to all members of the European Association of Urology at their website, http://www.uroweb.org.