GUIDELINES ON PROSTATE CANCER

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Introduction

Cancer of the prostate (PCa) is currently the second most common cause of cancer death in men. In developed countries PCa accounts for 15% of male cancers compared with 4% of male cancers in developing countries. Within Europe exist also large regional differences in the incidence rates of PCa.

There are three well-established risk factors for PCa: increasing age, ethnic origin, and genetic predisposition. Clinical data suggest that exogenous risk factors, such as diet, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, and occupational exposure may also play an important role in the risk of developing PCa.

The introduction of an effective blood test, prostate-specific antigen (PSA), has resulted in more early-stage prostate cancer diagnosis where potentially curative treatment options

can be provided. However, if effective diagnostic procedures are inappropriately used in elderly men with a short life span, the issue of over-diagnosis and over-treatment may occur. Consequently, the same stage of prostate cancer may require different treatment strategies depending on an individual patient's life expectancy.

Staging system

The 7th edition Union Internationale Contre le Cancer (UICC) 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)

T3b Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphinter, rectum, levator ani 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]

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

The most commonly used system for grading PCa is the Gleason grading system.

Diagnosis and staging

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 and two examples are presented here.

Checklist for pathology reporting of prostate biopsies

1. Histological type of carcinoma
2. Histological grade (global or highest)
   - Primary grade
   - Secondary (= highest) grade
3. Fraction of involved cores
   - Number of cores involved by carcinoma
   - Total number of cores
4. Tumour quantification
   - Percentage of prostatic tissue involved by carcinoma or total mm of cancer length
5. Tumour extent
   - Identification of perineural invasion
   - Identification of extra-prostatic extension
   - Identification of seminal vesicle invasion

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

1. Processing of RP specimens
   - Total embedding of a prostatectomy specimen is preferred, either by conventional (quadrant sectioning) or by whole-mount sectioning
   - The entire surface of RP specimens should be inked before cutting in order to evaluate the surgical margin status
   - The apex should be separately examined using the cone method with sagittal or radial sectioning
2. Histological type
3. Histological grade
   - Primary (predominant) grade
   - Secondary grade
   - Tertiary grade (if exceeding > 5% of PCA volume)
   - Global Gleason score
   - Approximate percentage of Gleason grade 4 or 5 (optional)
4. Tumour quantification (optional)
   - Percentage of prostatic tissue involved
   - Tumour size of dominant nodule (if identified), greatest dimension in mm
5. Pathological staging (pTNM)
   - Presence of extraprostatic extension (focal or extensive), specify sites
   - Presence of seminal vesicle invasion
   - Presence of lymph node metastases, number of retrieved lymph nodes and number of positive lymph nodes
6. Surgical margins
   - Presence of carcinoma at margin

- If present, specify site(s) and extra- or intra-prostatic invasion

7. Other
   - If identified, presence of angioinvasion
   - Location (site, zone) of dominant tumour (optional)
   - Perineural invasion (optional)
   - If present, specify extra- or intra-prostatic invasion

A short summary of the guidelines on diagnosis and staging of PCa are presented in Table 2.

Table 2: Guidelines for the diagnosis and staging of PCa

	Diagnosis of PCa	GR
1.	An abnormal digital rectal examination (DRE) result or elevated serum PSA measurement could indicate PCa. The exact cut-off level of what is considered to be a normal PSA value has yet to be determined, but values of approximately < 2-3 ng/mL are often used for younger men.	C
2.	The diagnosis of PCa depends on histopathological (or cytological) confirmation.	B
	Biopsy and further staging investigations are only indicated if they affect the management of the patient.	C

3.	Transrectal ultrasound (TRUS)-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 10 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volume prostates.	B
	Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates.	C
	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).	B
	Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	C
4.	Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies.	A
	Staging of PCa	
1.	Local staging (T-staging) of PCa is based on findings from DRE and possibly magnetic resonance imaging (MRI). Further information is provided by the number and sites of positive prostate biopsies, the tumour grade and the level of serum PSA.	C

	Despite its high specificity in the evaluation of extra-capsular extension (ECE) and seminal vesicle invasion or involvement (SVI), TRUS is limited by poor contrast resolution, resulting in low sensitivity and a tendency to understage PCa. Even with the advent of colour- and power Doppler to assist in identifying tumour vascularity, the accuracy of TRUS in local staging remains inadequate. In comparison with DRE, TRUS and computed tomography (CT), MRI demonstrates higher accuracy for the assessment of uni- or bi-lobar disease (T2), ECE and SVI (T3), as well as the invasion of adjacent structures (T4). However, the literature shows a wide range in the accuracy of T-staging by MRI, from 50-92%. The addition of dynamic contrast-enhanced MRI (DCE-MRI) can be helpful in equivocal cases. The addition of magnetic resonance spectroscopic imaging (MRSI) to MRI also increases accuracy and decreases inter-observer variability in the evaluation of ECE.	C
2.	Lymph node status (N-staging) is only important when potentially curative treatment is planned. Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score ≤ 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation.	B
	Given the significant limitations of pre-operative imaging in the detection of small metastases (< 5 mm), pelvic lymph node dissection (PLND) remains the only reliable staging method in clinically localised PCa.	

	Currently, it seems that only methods of histological detection of lymph node metastases with high sensitivity, such as sentinel lymph node dissection or extended PLND, are suitable for lymph node staging in PCa.	C
3.	Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is < 20 ng/mL in the presence of well or moderately differentiated tumours.	B
	In equivocal cases, ^{11}C-choline-, ^{18}F-flouride-PET/CT or whole body MRI could be of value in individual patients.	C

CT = computed tomography; DCE-MRI = dynamic contrast-enhanced MRI; DRE = digital rectal examination; ECE = extracapsular extension; MRI = magnetic resonance imaging; MRSI = magnetic resonance spectroscopic imaging; PCa = prostate cancer; PET = positron emission tomography; PLND = pelvic lymph-node dissection; PSA = prostate-specific antigen; SVI = seminal vesicle invasion; TRUS = transrectal ultrasound.

Treatment of prostate cancer

An overview of the treatment options for patients with PCa, subdivided by stage at diagnosis, is presented in Table 3. Due to a lack of randomised controlled trials in PCa, one therapy option cannot be considered superior to another. However, based on the currently available literature, the recommendations presented in Table 3 can be made.

Table 3: Guidelines for the primary treatment of PCa			
Stage	**Treatment**	**Comment**	**GR**
T1a	Watchful waiting	Standard treatment for Gleason score ≤ 6 and 7 adenocarcinomas and < 10-year life expectancy.	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 of each biopsy.	B
		Patients with a life expectancy < 10 years.	

		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	Radical prostatectomy	Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.	A
	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 'active surveillance' 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, well-differentiated and moderately-differentiated tumours, 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 (see below).	A
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSA-Doubling Time (DT) < 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), PSA DT > 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 adjuvant therapy in more than 1 positive node to radiation therapy or radical prostatectomy as primary local therapy. 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 an 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

Determination of serum PSA, disease-specific history and DRE are the cornerstones in the follow-up of PCa patients. Routine imaging procedures in stable patients are not recommended and should only be used in specific situations.

Table 4: 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 persistent or 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

Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be omitted if the serum PSA level is < 20 ng/mL but data on this topic are sparse.	C
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

CT = computed tomography; DRE = digital rectal examination; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

Table 5: Guidelines for follow-up after hormonal treatment

	GR
Patients should first be evaluated at 3 and 6 months after treatment initiation. Tests should at least include serum PSA measurement, DRE, serum testosterone and careful evaluation of symptoms in order to assess the treatment response and side-effects.	B
If patients undergo intermittent androgen deprivation, PSA and testosterone should be monitored at 3 month intervals during the treatment pause.	C
Follow-up should be tailored to the individual patient, according to symptoms, prognostic factors and the treatment given.	C
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.	C

In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. Follow-up should include at least a disease-specific history, DRE and serum PSA measurement, frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements.	C
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
Where disease progression occurs, or if the patient does not respond to the treatment given, follow-up needs to be individualised.	C
Routine imaging of stable patients is not recommended.	B
DRE = digital rectal examination; GR = grade of recommendation; PSA = prostate specific antigen.	

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.

Table 6: Guidelines for second-line therapy after curative treatments

		GR
Presumed local failure after radical prostatectomy	Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64-66 Gy and preferably before PSA has risen above 0.5 ng/mL. Other patients are best offered a period of active surveillance (active monitoring), with possible hormonal therapy later on.	B
Presumed local failure after radiotherapy	Selected patients may be candidates for salvage radical prostatectomy and they should be informed about the high risk of complications, such as incontinence and erectile dysfunction. Salvage prostatectomy should only be performed in experienced centres.	C
	Cryosurgical ablation of the prostate represents another local treatment option in patients not suitable for surgery.	
	Other patients are best offered a period of active surveillance (active monitoring), with possible hormonal therapy later on.	

Presumed distant failure	There is some evidence that early hormonal therapy may be of benefit in distant (+/- local) failure delaying progression, and possibly achieving a survival benefit in comparison with delayed therapy. The results are controversial. Local therapy is not recommended except for palliative reasons.	B

Treatment of relapse after hormonal therapy

Castration-refractory PCa (CRPCa) 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.

Table 7: Guidelines for secondary hormonal management in patients with CRPCa

	GR
Anti-androgen therapy should be stopped once PSA progression is documented.	B
No clear-cut recommendation can be made for the most effective drug for secondary hormonal manipulations because data from randomised trials are scarce. However, abiraterone and MDV3100 may address this issue once final data from the prospective randomized Phase III clinical trials are analysed.	C

PSA = prostate specific antigen.

Comment: An eventual anti-androgen withdrawal effect should become apparent 4-6 weeks after the discontinuation of flutamide or bicalutamide.

Table 8: Guidelines for cytotoxic therapy in patients with CRPCa

	GR
Patients with CRPCa should be counselled, managed and treated in a multidisciplinary team.	
In non-metastatic CRPCa, cytotoxic therapy should only be used in clinical trials.	B
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	B
Prior to treatment, testosterone serum levels should be below 32 ng/dL.	B
Prior to treatment, PSA serum levels should be > 2 ng/mL to assure correct interpretation of therapeutic efficacy.	B
Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient.	C
In patients with metastatic CRPCa who are candidates for cytotoxic therapy, docetaxel at 75 mg/m^2 every 3 weeks is the drug of choice since it has shown a significant survival benefit.	A

In patients with symptomatic osseous metastases due to CRPCa, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options. If not contraindicated, docetaxel is the preferred agent based on the significant advantage in pain relief.	A
In patients with relapse following first-line docetaxel chemotherapy, based on the results of prospective randomised clinical phase III trials, Cabazitaxel and Abiraterone are regarded as first-choice option for second-line treatment.	A
Second-line docetaxel may be considered in previously responding docetaxel-treated patients. Otherwise treatment is to be tailored to the individual patients. In case patients are not eligible for cabazitaxel or abiraterone, docetaxel is an option.	A

Table 9: Guidelines for palliative management of patients with CRPCa

	GR
Patients with symptomatic and extensive osseous metastases cannot benefit from medical treatment with regard to life prolongation.	A
Management of these patients has to be directed at improving quality of life and providing pain reduction.	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.	A

Bisphosphonates (e.g., zoledronic acid) should be offered to patients with skeletal masses to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, in particular, jaw necrosis must be avoided.	A
Palliative treatments, such as radionuclides, external beam radiotherapy and adequate use of analgesics, should be considered early on in the management of painful osseous metastases.	B
Spinal surgery or decompressive radiotherapy are emergency surgeries which have to be considered for patients with neurological symptoms thought to be critical.	A
CRPCa = castration-resistant prostate cancer.	

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 978-90-79754-96-0), available to all members of the European Association of Urology at their website - http://www.uroweb.org/guidelines/online-guidelines/.