GUIDELINES ON PROSTATE CANCER

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Introduction

Cancer of the prostate is now recognized as one of the principal medical problems facing the male population. The disease accounts for 9% of all cancer deaths among men.

As men live longer, an increase in both incidence and mortality of prostate cancer can be observed. Apart from age, the primary risk factor is hereditary, and clinical data seem to support the idea that exogenous factors may have an important impact on the risk of developing CaP (race, diet containing a high content of animal fat, exposure to heavy metals, etc.).

The introduction of an effective blood test, prostate-specific antigen (PSA), has made it possible to diagnose more and more men in an earlier stage where they can be offered potentially curative treatments. The other side of the coin is that if effective diagnostic procedures are used unselectively in elderly men with a short life expectancy, a problem of over-diagnosis and over-treatment might occur. Thus the same stage of prostate cancer may need different treatment strategies

depending on a patient's life expectancy. This, and many other issues related to the disease, are the subject of the EAU guidelines on prostate cancer.

Staging system

The UICC 2002 TNM (Tumour Node Metastasis) 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 prostate-specific antigen 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: bladder neck, 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]

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

The most commonly used system for grading of adenocarcinoma of the prostate is the Gleason grading system. This system

describes patterns of tumour growth (grade 1-5). Grade 1 relates to the least aggressive pattern of growth (well differentiated) and grade 5 to the most aggressive pattern (poorly differentiated). The two most common patterns are then combined to a score (2-10). The most common pattern of growth is to be mentioned first; i.e. Gleason 3+4=7. To be counted, a pattern (grade) needs to occupy more than 5% of the biopsy specimen. Biopsy material (core biopsy or operative specimens) is required to be able to assess the Gleason score; cytological preparations cannot be used.

Diagnosis and staging

The decision to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking age and comorbidity into consideration. Procedures that will not affect the treatment decision can usually be avoided. Below is a short summary of the guidelines on diagnosis and staging.

Guidelines on the diagnosis and staging of prostate cancer

1. An abnormal DRE result or elevated serum PSA measurement may indicate CaP. The exact cut-off level of what is considered to be a normal PSA value has not yet been determined, but values around < 2.5-3 ng/mL are often used for younger men (grade C recommendation).
2. The diagnosis of CaP depends on histopathological (or cytological) confirmation (grade B recommendation). Biopsy and further staging investigations are only indicated if they affect the management of the patient (grade C recommendation).

3. Transrectal ultrasound guided systemic biopsies is the recommended method in most cases where prostate cancer is suspected. A minimum of 6-10 systemic laterally directed cores are recommended, perhaps more cores in larger glands (grade B recommendation).
    - Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates (grade C recommendation).
    - One set of repeat biopsies is warranted in cases with persistent indication (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the first biopsy) for prostate biopsy (grade B recommendation).
    - Overall recommendations for further (third or more) sets of biopsies cannot be made; the decision has to be made based on an individual patient (grade C recommendation).
4. Transrectal periprostatic injection with a local anaesthetic may be offered to patients as effective analgesia when undergoing prostate biopsies (grade A recommendation).
5. Local staging (T-staging) of CaP is based on findings from DRE and possibly MRI. Further information is provided by the number and sites of positive prostate biopsies, tumour grade and level of serum PSA (grade C recommendation).
6. 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 of 6 or less have less than a 10% likelihood of having node metastases and may be spared nodal evaluation. Accurate lymph node staging can only be determined by operative lymphadenectomy (grade B recommendation).
7. Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if

the serum PSA level is less than 20 ng/mL in the presence of well-, or moderately, differentiated tumours (grade B recommendation).

Treatment of prostate cancer

This summary is an overview of the treatment options in patients with prostate cancer. It is usually impossible to state that one therapy is superior to another as there is a profound lack of randomized controlled trials in this field. However, based on the available literature, some recommendations can be made. A summary, subdivided by stage at diagnosis, is found below.

Guidelines for the primary treatment of prostate cancer

Stage	Treatment	Comment
T1a	Watchful waiting	Standard treatment for well-, and moderately, differentiated tumours and < 10-year life expectancy. In patients with > 10-year life expectancy, restaging with TRUS and biopsy is advised (grade B recommendation).
	Radical prostatectomy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours (grade B recommendation).
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP,

		especially for interstitial radiation (grade B recommendation).
	Hormonal	Not an option (grade A recommendation).
	Combi-nation	Not an option (grade C recommendation).
T1b-T2b	Watchful waiting	Asymptomatic patients with well-, and moderately, differentiated tumours and a life expectancy < 10 years. Patients who do not accept treatment-related complications (grade B recommendation).
	Radical prostatec-tomy	Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications (grade A recommendation).
	Radio-therapy	Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with a 5-10 year life expectancy and poorly differentiated tumours (combination therapy is recommended; see below) (grade B recommendation).
	Hormonal	Symptomatic patients who need palliation of symptoms and who are unfit for curative treatment. (grade C recommendation). Antiandrogens are associated with a poorer outcome compared with watch-

		ful waiting and are not recommended (grade A recommendation).
	Combination	NHT + radical prostatectomy: no proven benefit (grade A recommendation). NHT + radiotherapy: better local control. No proven survival benefit (grade B recommendation). Hormonal (2-3 years) + radiotherapy: better than radiotherapy alone for poorly differentiated tumours (grade A recommendation).
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumours, and a life expectancy < 10 years (grade C recommendation).
	Radical prostatectomy	Optional for selected patients with T3a and a life expectancy > 10 years (grade C recommendation).
	Radiotherapy	T3 with a life expectancy > 5-10 years. Dose escalation > 70 Gy seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (see below) (grade A recommendation).
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25 ng/mL), unfit patients. Better than watchful waiting. (grade A recommendation).
	Combination	Radiotherapy + hormonal treatment seems better than radiotherapy alone

		(grade A recommendation) NHT + radical prostatectomy: no proven benefit (grade B recommendation).
N+, M0	Watchful waiting	Asymptomatic patients. Patient driven. May have a negative influence on survival (grade C recommendation).
	Radical prostatectomy	No standard option (grade C recommendation).
	Radiotherapy	No standard option (grade C recommendation).
	Hormonal	Standard therapy (grade A recommendation).
	Combination	No standard option. Patient driven (grade B recommendation).
M+	Watchful waiting	No standard option. May result in worse survival/more complications than with immediate hormonal therapy (grade B recommendation).
	Radical prostatectomy	Not an option (grade C recommendation).
	Radiotherapy	Not an option (given for cure) (grade C recommendation).
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment (grade A recommendation).
	Combination	Not an option (grade C recommendation).

Hormonal = all forms of hormonal therapy;
Combination = hormonal therapy given prior to and/or after radical prostatectomy or radiotherapy;
NHT = neoadjuvant therapy;
TRUS = transurethral ultrasonography;
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, together with a disease-specific history and supplemented by DRE, are the cornerstones in the follow-up of prostate cancer patients. Routine imaging procedures in stable patients are not recommended and should only be used in specific situations.

Guidelines for follow-up after treatment with curative intent

1. 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 (grade B recommendation).
2. After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease (grade B recommendation).
3. After radiation therapy, a rising PSA level, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease (grade B recommendation).

4. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence (grade B recommendation).
5. 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 (grade B recommendation).
6. 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 less than 30 ng/mL, but data on this topic are sparse (grade C recommendation).
7. 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 (grade B recommendation).

Guidelines for follow-up after hormonal treatment

1. Patients should be evaluated at 3 and 6 months after initiating treatment. Tests should include at least serum PSA measurement, DRE and careful evaluation of symptoms in order to assess the treatment response and the side-effects of treatments given (grade B recommendation).
2. Follow-up should be tailored to the individual patient, according to symptoms, prognostic factors and the treatment given (grade C recommendation).
3. 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 determination (grade C recommendation).

4. In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3-6 months. A minimal follow-up should include a disease-specific history, DRE and serum PSA determination, frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements (grade C recommendation).
5. When disease progression occurs or if the patient does not respond to the treatment given, the follow-up needs to be individualized (grade C recommendation).
6. Routine imaging in stable patients is not recommended (grade B recommendation).

Treatment of relapse after curative therapies

An effort is 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 fast rising PSA 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 on second-line therapy after curative treatments

Recommendations:

Presumed local failure after RP:	Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably before PSA has risen above 1.5 ng/mL. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade B recommendation).
Presumed local failure after RT:	Selected patients may be candidates for salvage radical prostatectomy (or other curative efforts) although patients should be informed about the comparatively high risk of complications. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade C recommendation).
Presumed distant +/- local failure:	There is some evidence that early hormonal therapy may be of benefit in delaying progression and possibly achieve a survival benefit in comparison with delayed therapy. The results are not without controversy. Local therapy is not recommended except for palliative reasons (grade B recommendation).

RP = radical prostatectomy
RT = radiotherapy

Treatment of relapse after hormonal therapy

Many of these patients are affected by their disease and maintaining or improving quality of life should be the main goal. In most cases the decision to treat, or not to treat, is made based on counselling of the individual patient, which limits the role of guidelines.

Guidelines for secondary hormonal management

1. It is recommended to cease antiandrogen therapy once PSA progression is documented (grade B recommendation).
2. Four to six weeks after discontinuation of flutamide or bicalutamide, an antiandrogen withdrawal (AAW) effect might become apparent (grade B recommendation).
3. No clear cut recommendation can be made regarding the most effective drug for secondary hormonal manipulations since data from randomized trials are scarce (grade C recommendation).

Guidelines for cytotoxic therapy in HRPCA

1. In patients with a PSA rise only, 2 consecutive increases of PSA serum levels above a previous reference level should be documented (grade B recommendation).
2. Prior to treatment, PSA serum levels should be > 5 ng/mL to assure correct interpretation of therapeutic efficacy (grade B recommendation).
3. Potential benefits of cytotoxic therapy and expected side effects should be discussed with each individual patient (grade C recommendation).

4. In patients with metastatic HRPCA, and who are candidates for cytotoxic therapy, docetaxel at 75 mg/m^2 every 3 weeks has shown a significant survival benefit (grade A recommendation).
5. In patients with symptomatic osseous metastases due to HRPCA, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options (grade A recommendation).

Recommendations for palliative management of HRPCA

1. Bisphosphonates may be offered to patients with skeletal metastases (mainly zoledronic acid has been studied) to prevent osseous complications (grade A recommendation).
2. Palliative treatments such as radionuclids, external beam radiotherapy, and adequate use of analgesics should be considered early on in the management of painful osseous metastases (grade B recommendation).

Summary

Prostate cancer is often a complex disease and one in which many aspects of the disease and the affected patient must be taken into consideration before decisions about diagnostic work-up, treatments, follow-up etc. can be made.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-29-2), available to all members of the European Association of Urology at their website - http://www.uroweb.org.