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 seems to support 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 with over diagnosis and over treatment might occur. Thus the same stage of prostate cancer may need different treatment strategies, pending on the patient's life expectancy. This, and many other issues regarding the disease, is the subject of the EAU guidelines on prostate cancer.

Staging system

The UICC 1997 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 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 level)
T2	Tumour confined within the prostate[1]
T2a	Tumour involves one lobe
T2b	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 sphincter, 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 prostate capsule, is not classified as T3, but as T2.*

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. 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 used system for grading of adenocarcinoma of the prostate is the Gleason grading system. The system describes patterns of tumour growth (grade 1-5). Grade 1 is the pattern with least aggressive pattern of growth (well differentiated) and grade 5 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 written first; i.e. Gleason 3+4=7. To be counted, a pattern (grade) needs to occupy more than 5% of the biopsy specimen. The scoring system needs biopsy material (core biopsy or operative specimens) in order to be helpful; 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. Procedures that do not affect the treatment decision can usually be avoided. Below is a short summary of the guidelines.

- An abnormal DRE result or elevated serum PSA measurement may indicate CaP.
- The diagnosis of CaP depends on histopathological (or cytological) confirmation. Biopsy and further staging investigations are only indicated if they do affect the management of the patient.
- Local staging (T-staging) of CaP is based on findings from DRE and imaging studies. The number and sites of positive prostate biopsies, tumour grade and level of serum PSA provide further information.
- Lymph node status (N-staging) is only important when treatment with curative intent is planned. Patients with Stage T2 or less, PSA < 20 ng/ml and a Gleason sum of 6 or less have less than 10% likelihood of having node metastases and may be spared nodal evaluation. Accurate lymph node staging can only be determined by bilateral pelvic lymphadenectomy; CT/MRI are of limited value due to low sensitivity.
- 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.

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, a few recommendations can be made based on the available literature and they are summarized below, divided by stage at diagnosis.

Stage	Treatment	Comment
T1a	Watchful waiting	Standard treatment for well and moderately differentiated tumours and a < 10-year life expectancy. In patients with > 10-year life expectancy, a restaging with TRUS and biopsy is advised.
	Radical prostatectomy	Optional in young patients with a long life expectancy, especially for poorly differentiated tumours.
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.
	Hormonal	Not an option.
	Combination	Not an option.
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.
	Radical prostatectomy	Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications.
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contra-indications for surgery. Unfit patients with a 5-10 year life expectancy and poorly differentiated tumours(combination therapy is recommended, see below).
	Hormonal	Symptomatic patients unfit for curative treatment.
	Combination	NHT + radical prostatectomy: no proven benefit. NHT + radiotherapy: better local control. No proven survival benefit. Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumours.
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well and moderately differentiated tumours and a life expectancy < 10 years.
	Radical prostatectomy	Optional for selected patients with 'small T3', PSA < 20 ng/mL, Gleason score < 8 and a life expectancy > 10 years.
	Radiotherapy	T3 (N0) with > 5–10 years of life expectancy. Dose escalation >70 Gy seems to be of some benefit. If this is not available, a combination with hormonal therapy could be recommended (see below)
	Hormonal	Symptomatic patients, extensive T3-T4,

		high prostate- specific antigen level (> 25 ng/mL), unfit patients.
	Combination	Radiotherapy + hormonal seems better than radiotherapy alone. NHT + radical prostatectomy: no proven benefit.
N+, M0	Watchful waiting	Asymptomatic patients. Patient driven.
	Radical prostatectomy	No standard option.
	Radiotherapy	No standard option.
	Hormonal	Standard therapy.
	Combination	No standard option. Patient driven.
M+	Watchful waiting	No standard option
	Radical prostatectomy	Not an option.
	Radiotherapy	Not an option (given for cure).
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment.
	Combination	Not an option.

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 about second-line therapy, please see the full text version of the guidelines.

Follow-up of prostate cancer patients

The determinations of serum PSA, together with a disease specific history and supplemented by DRE, are the corner-stones in the follow-up of prostate cancer patients. Routine imaging procedures in stable patients are not recommended and should only be conducted 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.
2. After radical prostatectomy a serum PSA level of more than 0.2 ng/mL is mostly associated with residual or recurrent disease.
3. After radiation therapy a rising PSA level, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.
4. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.
5. Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the plan of treatment. In most cases this is not necessary.
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 subject is sparse.
7. Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If the patient has

bone pain, a bone scan should be considered irrespective of the serum PSA level.

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.
2. Follow-up should be tailored for the individual patient according to symptoms, prognostic factors and the treatment given.
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.
4. In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3–6 months. This follow-up should minimally include a disease-specific history, DRE and serum PSA determination, frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements.
5. When disease progression occurs or if the patient does not respond to the treatment given, the follow-up needs to be individualized.
6. Routine imaging in stable patients is not recommended.

Summary:

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

This short booklet is based on the more comprehensive EAU guidelines (ISBN 90-806179-8-9), available to all members of the European Association of Urology at their website - www.uroweb.org.