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EAU Guidelines on Prostate Cancer

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Key Words

Prostatic neoplasm · EAU Guidelines · Diagnosis · Treatment · Follow-up

Abstract

Objectives: To develop clinical guidelines for the management of patients with prostate cancer.

Methods: Guidelines were compiled by a working panel based on current literature following a literature review using MEDLINE. Already published structured analysis from national and international guidelines was used, and panel consensus was employed when literature evidence was absent or of poor quality.

Results: The full text of the guidelines is available through the EAU Central Office and the EAU website (www.uroweb.org). This article summarizes the main conclusions from the guidelines concerning the diagnosis and staging, treatment and follow-up of patients with prostate cancer. The diagnosis of prostate cancer should be based on histopathological or cytological examinations. N- and M-staging may be omitted in selected patients with a low serum prostate-specific antigen due to low risk of metastasis. Active treatment is warranted in most stages of prostate cancer but active monitoring is recommended for elderly patients with early stage tumours and is still optional in some other situations. Follow-up is based on a disease-specific history, serum-prostate-specific antigen supplemented by a digital rectal examination. Routine imaging is not necessary in asymptomatic patients.

Conclusions: Prostate cancer is one of the most common malignancies in men. These guidelines have been drawn up to provide support in the management of this large group of patients.

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Table 1. Guidelines for the diagnosis and staging of CaP

1	An abnormal DRE result or elevated serum PSA measurement may indicate CaP
2	The diagnosis of CaP depends on histopathological (or cytological) confirmation. Biopsy and further staging investigations are not indicated if they do not affect the management of the patient
3	Local staging (T-staging) of CaP is based on findings from DRE and imaging studies. Further information is provided by the number and sites of positive prostate biopsies, tumour grade and level of serum PSA
4	Lymph node status (N-staging) is only important when treatment with curative intent is planned. Accurate lymph node staging can only be determined by bilateral pelvic lymphadenectomy; CT/MRI are of limited value due to low sensitivity. However, in patients with a high risk of node metastases, CT/MRI may be useful in recognizing enlarged lymph nodes and in guiding aspiration biopsy, thus avoiding an operative procedure
5	Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is <10 ng/ml in the absence of a poorly differentiated cancer

Epidemiology

Cancer of the prostate (CaP) is now recognized as one of the principal medical problems facing the male population. In the European Union, an estimated 85,000 new cases of CaP are diagnosed each year, accounting for 9% of all cancer deaths among men [1]. As more men live longer, both the incidence and mortality of CaP are increasing.

Classification

The 1997 Tumour, Node, Metastasis (TNM) Classification for CaP is used throughout these guidelines [2].

Risk Factors

The factors that determine the risk of developing clinical CaP are not well known; however, a few have been identified. The most important risk factor seems to be heredity – if 1 first-line relative (brother or father) has the disease, the risk for an individual is doubled. If 2 or more first-line relatives are affected the risk increases to 5- to 11-fold [3]. A small subpopulation of men with CaP (about 9%) has true hereditary CaP, defined as 3 or more relatives affected or at least 2 who develop early-onset disease (before age 55 years).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world. This finding is in sharp contrast with the incidence of clinical CaP, which differs widely between different geographical areas, being high in the USA and Northern Europe and low in South-East Asia. However, if Japanese men move from Japan to Hawaii their risk of CaP increases, and if they move further on to California their risk approaches that of American men.

These findings indicate that exogenous factors affect the risk of progression from so-called latent CaP to clinical CaP. The identity of these factors is still under debate, but a high content of animal fat in the diet may be important in increasing the risk of developing CaP. Other factors include low intakes of vitamin E, lignans and isoflavonoids [4].

In summary, hereditary factors are important in determining the risk of developing clinical CaP and exogenous factors may also have an important impact on this risk. The key question is whether or not there is enough evidence to recommend lifestyle changes (lowered intake of animal fat and increased intake of fruit, cereals, vegetables and red wine) in order to decrease the risk. There is some, albeit weak, evidence for this, and such information could be given to male relatives of CaP patients who ask about the impact of diet.

Diagnosis of CaP

The diagnosis of CaP may be suspected from symptoms, a suspicious digital rectal examination (DRE) finding or an elevated level of serum prostate-specific antigen (PSA). However, the diagnosis of CaP demands the presence of adenocarcinoma in tissue obtained at operation, prostate biopsy cores or aspiration needle cytology.

In most cases today, the diagnosis is made by transrectal ultrasound (TRUS)-guided core biopsies. The likelihood of finding CaP in these biopsies is related to the findings at DRE and TRUS and the level of serum PSA. If a result using any one of these three modalities is abnormal, the positive biopsy rate is 6–25%; with two abnormalities it is 18–60%; and with all three modalities it is 56–72% [5, 6]. The wide variation is most probably due to differences in the populations studied. In diagnosis of early-stage CaP in young men, PSA level is by far the most sensitive test [7, 8].

Staging of CaP

Although T-stage is determined by DRE and imaging modalities, a combination of serum PSA level, Gleason

Table 2. Guidelines for the treatment of CaP

Stage	Treatment	Comment
T1a	WW	Standard treatment for patient with well and moderately differentiated tumours and a <10-year life expectancy. In patients with >10-year life expectancy, restaging with TRUS and biopsy is advised
	RP	Optional in young patients with a long life expectancy, especially for those with poorly differentiated tumours
	RT	Optional in younger patients with a long life expectancy, especially for those with poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation
	Hormonal	Not recommended option
	Combination	Not recommended option
T1b–T2b	WW	Asymptomatic patients with well and moderately differentiated tumours and a life expectancy <10 years. Patients who do not accept treatment-related complications
	RP	Patients with life expectancy >10 years who accept treatment-related complications
	RT	Patients with a life expectancy >10 years who prefer radiation treatment and accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with a 5–10-year life expectancy and poorly differentiated tumours
	Hormonal	Symptomatic patients unfit for curative treatment
	Combination	NHT + RP: no better NHT + RT: better local control. No proven survival benefit Hormonal (3 years) + RT: better than RT in patients with poorly differentiated tumours
T3–T4	WW	Option in asymptomatic patients with T3, well and moderately differentiated tumours and a life expectancy <10 years
	RP	Optional for selected patients with 'small T3', PSA <20 ng/ml, Gleason score <8 and a life expectancy >10 years
	RT	T3 (N0) with >5–10 years of life expectancy. Dose escalation >70 Gy seems to be of some benefit
	Hormonal	Symptomatic patients, extensive T3–T4, high PSA level (>25 ng/ml), unfit patients
	Combination	RT + hormonal seems better than RT alone. NHT + RP: no proven benefit
N+, M0	WW	Asymptomatic patients. Driven by the patient
	RP	Not standard option
	RT	Not standard option
	Hormonal	Standard therapy
	Combination	Not standard option. Patient driven
M+	WW	Not standard option (requires asymptomatic informed patient, good compliance and good access to health care)
	RP	Not recommended option
	RT	Not recommended option (given for cure)
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment
	Combination	Not recommended option

WW = Watchful waiting; RP = radical prostatectomy; RT = radiotherapy; hormonal = all forms of hormonal therapy; combination = hormonal therapy given prior to and/or after RP or RT; TURP = transurethral resection of the prostate; NHT = neoadjuvant hormonal therapy.

score on prostate biopsy and clinical T-stage has proved to be more useful in predicting the final pathological stage of CaP than the individual parameters per se [9].

N-staging should only be performed when the findings would directly influence a treatment decision. This is usually the case in patients for whom treatments with curative intent are planned. The gold standard for N-staging is operative lymphadenectomy, using either open or laparoscopic techniques. Both computed tomography (CT) and magnetic resonance imaging (MRI) are considered to be of limited use due to their low sensitivity, which varies from 0 to 70%, although CT accuracy increases when fine-needle aspiration biopsies are applied to virtually all visible and asymmetrical lymph nodes. CT scanning may be warranted in patients with a very high risk of harbouring lymph node metastases as the specificity of a positive scan is high and is in the range 93–96%. Patients with nodal metastasis on CT or with a positive aspiration biopsy may thus be spared op-

Table 3. Guidelines for the follow-up of CaP after treatment with curative intent

1	1. In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented with 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 >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 recommended if it will affect the plan of treatment, i.e. second-line treatment with curative intent
6	Metastasis may be detected by a pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be delayed until the serum PSA level exceeds 4 or 20 ng/ml, respectively
7	If the patient has bone pain, a bone scan should be considered irrespective of serum PSA level

Table 4. Guidelines for follow-up of CaP 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 evaluation of symptoms in order to assess the treatment response and the side effects of treatments given
2	Follow-up should be tailored to 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 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

erative lymphadenectomy. At the other end of the scale, Partin nomograms may be used to define a group of patients with a low risk of nodal metastasis (<10%) [9]. Those with a serum PSA level <20 ng/ml, stage T2a disease or less and a Gleason score of 6 or less may be spared N-staging procedures before treatment with curative intent.

M-staging is best carried out using bone scintigraphy. This remains the most sensitive method of assessing bone metastases, being superior to clinical evaluation, bone radiographs, serum alkaline phosphatase measurement and prostatic acid phosphatase determination [10]. A staging bone scan may be unnecessary if the serum PSA concentration is <10 ng/ml in asymptomatic patients with well or moderately differentiated tumours. A summary of the guidelines for diagnosis and staging of CaP is presented in table 1.

Treatment of CaP

Treatment alternatives for patients with CaP are related to tumour stage, grade, serum PSA level, life expectancy and the presence of symptoms. Patients with a life expectancy of >10 years and localized CaP should have the option to discuss curative treatments in relation to the outcome after watchful waiting [11–14].

The timing of eventual hormonal therapy in patients in whom this is indicated is controversial. Should treatment be initiated immediately or postponed until symptoms occur? Although no definitive answer can be given, some studies indicate that early hormonal therapy might provide survival advantages in both localized [15], node-positive [16] and metastatic [17] disease. These potential benefits should be judged against the side effects of early hormonal therapy.

No second-line treatment of hormone-refractory CaP may be recommended before any other. A summary of the guidelines for treatment of CaP in relation to clinical stage is presented in table 2.

Follow-Up of Patients with CaP

In most cases, patients with CaP will need very long or lifelong follow-up. With palliative therapy, disease progression may occur at any time, and after treatment with curative intent, relapse is common, even a long time after the treatment/operation. The follow-up scheme must be tailored to the individual patient's needs.

Follow-up after treatment with curative intent is mostly directed at finding early signs of relapse and detecting treatment-related complications that may affect quality of life. The recommendations are summarized in table 3. Follow-up after hormonal therapy needs to be more closely individualized and is mainly directed at finding signs of hormonal escape, complications of the disease and control of the side effects of the treatment given. Many of these patients will require psychological support. The guidelines for follow-up of CaP after hormonal therapy are summarized in table 4.

Conclusions

Today, CaP is one of the most common malignancies in the male. Making decisions in CaP management is complicated by the fact that many treatments directly affect the quality of life of the patients (sexual function, urinary control, side effects of hormonal therapy, etc.). The aim of these guidelines is to provide help for the practising urologist in the everyday management of CaP patients.

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For more extensive information consult the EAU Guidelines presented at the XVIth EAU Annual congress, Geneva, Switzerland (ISBN 90–806179–3–9) or the EAU website (www.uroweb.org).