

## Editorial and EAU Guideline

## EAU Guidelines on Prostate Cancer

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**Abstract**

**Objectives:** The first summary of the European Association of Urology (EAU) guidelines on prostate cancer was published in 2001. These guidelines have been continuously updated since many important changes affecting the clinical management of patients with prostate cancer have occurred over the past years. The aim of this paper is to present a summary of the 2005 update of the EAU guidelines on prostate cancer.

**Methods:** A literature review of the new data has been performed by the working panel. The guidelines have been updated and level of evidence/grade of recommendation added to the text. This enables readers to better understand the quality of the data forming the basis of the recommendations.

**Results:** A full version is available at the EAU Office or at [www.uroweb.org](http://www.uroweb.org). Systemic prostate biopsies under ultrasound guidance is the preferred diagnostic method and the use of periprostatic injection of a local anaesthetic can significantly reduce pain/discomfort associated with the procedure. Active treatment (surgery or radiation) is mostly recommended for patients with localized disease and a long life expectancy with radical prostatectomy being the only treatment evaluated in a randomized controlled trial. Follow-up is at large based on prostate specific antigen (PSA) and a disease-specific history with imaging only indicated when symptoms occur. Cytotoxic therapy has become an option for selected patients with hormone refractory prostate cancer.

**Conclusion:** The knowledge in the field of prostate cancer is rapidly changing. These EAU guidelines on prostate cancer summarize the most recent findings and put them into clinical practice.

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**Keywords:** Prostate cancer; EAU guidelines; Review; Diagnosis; Treatment; Follow-up

**1. Introduction**

The first summary of the European Association of Urology (EAU) guidelines on prostate cancer was published in 2001 [1]. The long version of these guidelines has been continuously updated since many important

changes affecting the clinical management of patients with prostate cancer have occurred over the past years. The aim with this paper is to present a summary of the 2005 update of the EAU guidelines on prostate cancer.

To facilitate evaluating the quality of the information provided, evidence levels and grade of recommendation have been inserted in this updated guidelines text according to the general principles of evidence-based medicine (EBM) [2].

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## 2. Epidemiology

Cancer of the prostate (CaP) is now recognized as one of the major medical problems facing the male population. In Europe, an estimated 2.6 million new cases of cancer are diagnosed each year. Prostate cancer constitutes about 11% of all male cancers in Europe [3], and accounts for 9% of all cancer deaths among men within the European Union (EU) [4].

## 3. Risk factors

The factors that determine the risk of developing clinical CaP are not well known; however, a few have been identified. Age is the most obvious risk factor with the incidence of the disease increasing with increasing age. Another important risk factor seems to be heredity. If one first-line relative has the disease, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases 5- to 11-fold [5]. A small subpopulation of individuals with CaP (about 9%) has true hereditary CaP, defined as three or more relatives affected or at least two who have developed early-onset disease, i.e. before the age of 55 [6]. The frequency of autopsy-detected cancers is roughly the same in different parts of the world [7]. This finding is in sharp contrast with the incidence of clinical CaP, which varies widely between different geographical areas and ethnic groups, being high in the USA and Northern Europe and low in South-East Asia.

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, selenium, lignans and isoflavonoids [8].

In summary, hereditary factors are important in determining the risk of developing clinical CaP and exogenous factors may 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 and vegetables) in order to decrease the risk. There is some evidence for this, and this information could be given to male relatives of CaP patients who ask about the impact of diet (level of evidence: 3–4).

## 4. Classifications

The UICC 2002 Tumour Node, Metastasis (TNM) classification is used throughout these guidelines [9]. The most commonly used system for grading of adenocarcinoma of the prostate is the Gleason score [10]. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. This score is the sum of the two most common patterns (grades 1–5) of tumour growth found. 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.

**Table 1**

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 <math>2.5\text{--}3\text{ ng/ml}</math> 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 diagnostic method in most cases with the suspicion of prostate cancer. A minimum of 6–10 systemic, laterally directed, cores are recommended, eventually with 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 are 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 an 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, the % of core involvement, 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 for. Patients with Stage T2 or less, PSA <math><20\text{ ng/mL}</math> 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).

## 5. Prostate cancer screening

*Population or mass screening* is defined as the examination of asymptomatic men (at risk). Usually, screening takes place within the framework of a trial or study and is initiated by a screener. Contrary to that, *early detection or opportunistic screening* represents individual case findings. It is initiated by the screenee (patient) and/or his physician.

To evaluate the efficacy of CaP screening, two large randomized trials are underway, the PLCO (Prostate, Lung, Colorectal and Ovary) trial in the USA and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe [11]. The first analysis of the main endpoint of these trials – differences in CaP mortality – is scheduled for 2008 (level of evidence: 1b).

Thus, at the present time, there is a lack of evidence to support or disregard widely adopted, population-

**Table 2**

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, re-staging 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 Combination	Not an option (grade A recommendation) 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 prostatectomy	Standard treatment for patients with a life expectancy >10 years who accept treatment-related complications (grade A recommendation)
	Radiotherapy	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 Combination	Symptomatic patients who need palliation of symptoms and who are unfit for curative treatment (grade C recommendation). Pure antiandrogens are associated with poorer outcome compared to watchful waiting and are not recommended (grade A recommendation) Neoadjuvant Hormonal Treatment (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 limited T3a, G1 5–7 and low PSA 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 Combination	Symptomatic patients, extensive T3-T4, high PSA level (>25 ng/mL), unfit patients. Better than watchful waiting (grade A recommendation) 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 Combination	Standard therapy (grade A recommendation) 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 Combination	Standard therapy. Symptomatic patients should not be denied treatment (grade A recommendation) 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 = transrectal 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.

based screening programmes for early detection of CaP aimed at all men in a given population (level of evidence: 3). The use of PSA in combination with digital rectal examination (DRE) as an aid to early diagnosis in well informed patients is less controversial and widely used in clinical practice [12] (level of evidence: 3).

## 6. Diagnosis and staging of prostate cancer

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. A short summary of the guidelines on diagnosis and staging are presented in Table 1.

## 7. Treatment of prostate cancer

An overview of the primary treatment options in patients with prostate cancer is provided in Table 2. It is

usually impossible to state that one therapy is clearly superior over 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 in the table.

## 8. Follow-up of prostate cancer patients

Patients diagnosed with prostate cancer are usually followed lifelong or until high age makes follow-up superfluous. 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. The follow-up intervals and which tests are needed is not well studied and often this needs to be individualized. In Table 3 are the guidelines for follow-up after therapy with curative intent summarized and in Table 4 follow-up after hormonal therapy. Patients initially managed by active monitoring (no active therapy) need individual follow-

**Table 3**

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 (3 consecutive rises measured at 3-month intervals), 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 (salvage, radiotherapy or surgery). 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).

**Table 4**

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). Serum testosterone level determination is an optional test
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).

**Table 5**

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 64Gy 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 concerning 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 $\pm$ 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).

up depending on the future aims of therapy and tumour characteristics.

## 9. Treatment of relapse after curative therapies

### 9.1. Definition of recurrence

- Following radical prostatectomy, two consecutive PSA values  $\geq$  above 0.2 ng/mL represent recurrent cancer.
- Following radiation therapy, three consecutive increasing PSA values measured by 3-month intervals above a previous nadir represent recurrent cancer.

An effort is made to distinguish between the probability of local failure only, versus distant ( $\pm$ local) failure. Initial pathology, how long after primary therapy the PSA-relapse occur 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 (systemic disease) while patients with moderately differentiated tumours, late PSA-relapse and a slow doubling time ( $>10$ – $12$  months) can be presumed to have local failure only. Treatment can then be guided by the presumed site of failure, the patient's general condition and personal preferences (Table 5). Imaging studies to determine the site of recurrence are of very limited value in patients with early PSA-relapse only and can thus usually be avoided.

## 10. Treatment of relapse after hormonal therapy

Patients experiencing relapse after hormonal therapy are usually in a more advanced disease stage and

**Table 6**

Guidelines for secondary hormonal, cytotoxic and palliative management in patients with hormone refractory prostate cancer

**Hormonal manipulations**

1. Castration levels of testosterone should be maintained also in hormone refractory patients (grade C recommendation)
2. Administration of all antiandrogens has to cease once PSA progression is documented (grade B recommendation)
3. After discontinuation of flutamide or bicalutamide, after 4 weeks and 6 weeks, respectively, an eventual anti-androgen withdrawal (AAW) effect may become apparent (grade B recommendation)
4. No clear cut recommendation can be made regarding the most effective drug for secondary hormonal manipulations since no data from randomized trials are available (grade C recommendation).

**Cytotoxic therapy**

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)
3. In patients with metastatic HRPc docetaxel at 75 mg/m<sup>2</sup> every 3 weeks results in a significant survival benefit and represents the reference treatment (grade A recommendation)
4. In patients with symptomatic osseous metastases due to HRPc either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options (grade A recommendation).

**Palliative management**

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, adequate use of analgesics should be considered early on in the management of painful osseous metastases (grade B recommendation).

will generally become symptomatic within a relatively short time after the onset of the PSA rise. Patients with hormone refractory prostate cancer are not curable and maintaining or improving quality of life should be a 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. The recommendations for management of patients who fail hormonal therapy are summarized in Table 6.

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## 11. Summary

The present text represents a summary and for more detailed information and a full list of references, we refer to the full text version. These EAU guidelines (ISBN 90-70244-27-6), are available at the website of the European Association of Urology: <http://www.uroweb.org>.