available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Guidelines

EAU Guidelines on Prostate Cancer

Axel Heidenreich [a,*], *Gunnar Aus* [b], *Michel Bolla* [c], *Steven Joniau* [d], *Vsevolod B. Matveev* [e], *Hans Peter Schmid* [f], *Filliberto Zattoni* [g]

[a] *Department of Urology, University Hospital Cologne, Cologne, Germany*
[b] *Department of Urology, Sahlgrens University Hospital, Göteborg, Sweden*
[c] *Department of Radiation Therapy, C.H.U. Grenoble, Grenoble, France*
[d] *Department of Urology, University Hospital Gasthuisberg, Leuven, Belgium*
[e] *Department of Urology, Russian Academy of Medical Science, Cancer Research Center, Moscow, Russia*
[f] *Department of Urology, Kantonspital St. Gallen, St. Gallen, Switzerland*
[g] *Department of Urology, Santa Maria Della Misericordia Hospital, Udine, Italy*

Article info

Article history:
Accepted September 7, 2007
Published online ahead of print on September 19, 2007

Keywords:
Androgen deprivation
Chemotherapy
Diagnosis
EAU guidelines
Follow-up
Prostate cancer
Radiation therapy
Radical prostatectomy
Review
Treatment

EU✱ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Objectives: To present a summary of the 2007 version of the European Association of Urology (EAU) guidelines on prostate cancer (PCa).
Methods: A literature review of the new data emerging from 2004 to 2007 was performed by the working panel. The guidelines have been updated, and the level of evidence/grade of recommendation was added to the text based on a systematic review of the literature, which included a search of online databases and bibliographic reviews.
Results: A full version is available at the EAU Office or at www.uroweb.org. Systemic prostate biopsy under ultrasound guidance is the preferred diagnostic method. Active treatment is mostly recommended for patients with localized disease and a long life expectancy, with radical prostatectomy being shown to be superior to watchful waiting in a prospective randomized trial. Nerve-sparing radical prostatectomy represents the approach of choice in organ-confined disease; neoadjuvant androgen deprivation demonstrates no improvement of outcome variables. Radiation therapy should be performed with at least 72 and 78 Gy in low-risk and intermediate- to high-risk PCa, respectively. Monotherapeutic androgen deprivation is the standard of care in metastatic PCa; intermittent androgen deprivation might be an alternative treatment option for selected patients. Follow-up is largely based on prostate-specific antigen and a disease-specific history with imaging only indicated when symptoms occur. Cytotoxic therapy with docetaxel has emerged as the reference treatment for metastatic hormone-refractory PCa.
Conclusions: The knowledge in the field of PCa is rapidly changing. These EAU guidelines on PCa summarize the most recent findings and put them into clinical practice.

* Corresponding author. Department of Urology, Division of Oncological Urology, University of Köln, Kerpener Strasse 62, 50924 Köln, Germany. Tel. +49 221 478 86577; Fax: +49 221 478 87901.
E-mail address: axel.heidenreich@uk-koeln.de (A. Heidenreich).

0302-2838/$ – see back matter doi:10.1016/j.eururo.2007.09.002

1. Introduction

The most recent summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2005 [1]. The long version of these guidelines has been continuously updated because many important changes affecting the clinical management of PCa have occurred over the past few years. The aim of this paper is to present a summary of the 2007 update of the EAU guidelines on PCa. To facilitate evaluating the quality of the information provided, evidence levels and grade of recommendation have been inserted according to the general principles of evidence-based medicine [2].

2. Epidemiology

PCa is 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. PCa constitutes about 11% of all male cancers in Europe [3], and accounts for 9% of all cancer deaths among men within the European Union [4].

3. Risk factors

Hereditary factors are important in determining the risk of developing clinical PCa, and exogenous factors may have an important impact on this risk. The key question is whether there is enough evidence to recommend lifestyle changes in order to decrease the risk. There is some evidence for this, and such information could be given to male relatives of PCa patients who ask about the impact of diet (level of evidence: 3–4).

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 PCa (about 9%) has true hereditary PCa, defined as three or more relatives affected or at least two who have developed early-onset disease, that is, before the age of 55 yr [6].

4. Classifications

The Union International Contra Cancer 2002 tumour, node, metastasis (TNM) classification is used throughout these guidelines [7]. The most commonly used system for grading of adenocarcinoma of the prostate is the Gleason score [8]. 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.

5. Prostate cancer screening

Population or mass screening is defined as the systematic examination of asymptomatic men (at risk). Usually, screening takes place within the framework of a trial or study and is initiated by a screener. In contrast, opportunistic screening aims at early detection of PCa in individual cases, and it is initiated by the patient and/or his physician. To evaluate the efficacy of PCa screening, two large randomized trials are underway, the Prostate, Lung, Colorectal, and Ovary Trial in the United States and the European Randomized Screening for Prostate Cancer [9]. The first analyses of the main endpoint of these trials—differences in PCa mortality—are scheduled for 2013 and 2008, respectively (level of evidence: 1b).

Thus, at the present time, there is a lack of evidence to support or disregard widely adopted, population-based screening programmes for early detection of PCa aimed at all men in a given population (level of evidence: 3). The use of prostate-specific antigen (PSA) in combination with digital rectal examination as an aid to early diagnosis in well informed patients is less controversial and widely used in clinical practice [10,11] (level of evidence: 3).

6. Diagnosis and staging of prostate cancer

The main diagnostic tools used to look for evidence of PCa include digital rectal examination, serum concentration of PSA, and transrectal ultrasound-guided biopsies [11]. Diagnosis depends on the presence of adenocarcinoma in operative specimens and prostate biopsy cores.

A threshold level of PSA that indicates the highest risk of PCa needs to be defined [10]. Extrapolating data from the curves, the cumulative 7-yr risk of being diagnosed with PCa in a screening programme based on PSA measurement was only 34% for men with PSA values between 3 and 6 ng/ml, 44% for those with PSA values between 6 and 10 ng/ml, and 71% for those with PSA values >10 ng/ml [12]. In younger men (50–66 yr) the PCa detection rate was

13.2% in the PSA range 3–4 ng/ml [12]. The finding that many men may harbour PCa despite low levels of serum PSA has been underscored by recent results from a prevention study conducted in the United States [13].

In routine clinical practice, a free-to-total PSA ratio of $<$ 20% and PSA velocity $>$ 0.75 ng/ml/yr in men with elevated PSA levels have been accepted as valid parameters, which are associated with a higher risk of PCa and which facilitate the indication to perform a prostate biopsy. In a recent retrospective study of 12,078 men undergoing a prostate biopsy [14], threshold values of PSA and PSA velocity were identified to improve the assessment of PCa risk in men aged $<$ 50 yr. The prevalence of PCa was 4.4% and 14.2% in men aged $<$ 50 yr and $\geq$ 50 yr, respectively. Although the study might be biased by assignment or by assessment, a PSA threshold level of $\geq$ 2.5 ng/ml and a PSA velocity threshold level $>$ 0.60 ng/ml/yr appear to be appropriate for clinical practice.

Ultrasound-guided transrectal, laterally directed 18G core biopsy has become the standard way to obtain material for histopathological examination. The number of biopsies required for the optimal detection of PCa is controversial. Nearly all studies have shown a higher cancer detection rate with a greater number of biopsies in comparison with the standard sextant technique [15]. Currently, at least 10 biopsy cores or the use of the Vienna nomograms are recommended for routine use; adaptations have to be made considering age, PSA serum level, and prostate volume. Studies clearly show that the transition zone should not be the target area for a first set of prostate biopsies because of a consistently low cancer detection rate of $\leq$ 2% [16]. If the first set of biopsies is negative, repeated biopsies can be recommended. In the second set of biopsies, a detection rate of about 10–35% has been reported in cases with a negative first set of biopsies [17]. In cases where high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation is present, as many as 30–50% of prostates harbour a concomitant cancer and another biopsy is indicated.

The decision to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking his preference, 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. Primary local treatment of prostate cancer

It is not possible to state that one therapy is clearly superior over another, as randomized controlled trials are lacking in this field. However, based on the available literature, some recommendations can be made. A summary, subdivided by stage at diagnosis, is provided in Table 2; below a few suggestions are made with regard to the different treatment options available. In general, it is recommended to integrate recently developed and validated nomograms into the counselling process.

Table 1 – Guidelines on the diagnosis and staging of prostate cancer

1.	An abnormal digital rectal exam result or elevated serum PSA measurement may indicate PCa. 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 PCa 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 PCa. A minimum of 10 systematic, laterally directed cores or the use of the Vienna nomograms 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 digital rectal exam, 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 PCa is based on findings from digital rectal exam and possibly magnetic resonance imaging. Further information is provided by the number and sites of positive prostate biopsies, the percent 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 intermediate- or high-risk PCa have a $>$ 10% likelihood of having node metastases and should undergo pelvic lymphadenectomy. Accurate lymph node staging can only be determined by operative extended 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 $<$ 20 ng/ml in the presence of well- or moderately differentiated tumours (grade B recommendation).

Table 2 – Guidelines for the primary treatment of prostate cancer

Stage	Treatment	Comment
T1a	watchful waiting	Standard treatment for PCa with biopsy Gleason score ≤ 7 and < 10-yr life expectancy. In patients with > 10-yr 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 Gleason score 8–10 (grade B recommendation)
	radiotherapy	Optional in younger patients with a long life expectancy, especially for Gleason score 8–10. Higher complication risks after TURP, especially for interstitial radiation (grade B recommendation)
	hormonal	Not an option (grade A recommendation)
	combination	Not an option (grade C recommendation)
T1b–T2b	watchful waiting	Asymptomatic patients with biopsy Gleason score ≤ 7 and a life expectancy < 10 yr. Patients who do not accept treatment-related complications (grade B recommendation)
	radical prostatectomy	Standard treatment for patients with a life expectancy > 10 yr who accept treatment-related complications (grade A recommendation)
	radiotherapy	Patients with a life expectancy > 10 yr who accept treatment-related complications. Patients with contraindications for surgery. Unfit for patients with a 5–10 yr life expectancy and Gleason score 8–10 (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). Pure anti-androgens are associated with poorer outcome compared to watchful 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 yr) + radiotherapy: better than radiotherapy alone for poorly differentiated tumours (grade A recommendation)
T3–T4	watchful waiting	Option in asymptomatic patients with T3, biopsy Gleason score ≤ 7, and a life expectancy < 10 yr (grade C recommendation)
	radical prostatectomy	Optional for selected patients with limited ≤ T3a, Gleason ≤ 8, PSA < 20 ng/ml, and a life expectancy > 10 yr (grade C recommendation)
	radiotherapy	T3 with a life expectancy > 5–10 yr. 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; TRUS: transrectal ultrasonography; TURP: transurethral resection of the prostate; NHT: neoadjuvant hormonal therapy. For more detailed information and discussion on second-line therapy, please see the full text version of the guidelines.

7.1. *Active surveillance*

The terms ''deferred treatment'' or ''watchful waiting'' are used to describe a treatment strategy that includes an active standpoint to postpone treatment until it is required. Patients who are offered watchful waiting must be followed-up carefully. Active surveillance has emerged as a therapeutic alternative in men with PCa and a low risk of disease progression based on the early data of Chodak et al.

[18] and Albertsen et al. [19] demonstrating that men with well-differentiated PCa have a 20-yr PCa-specific survival rate of 80–90%. Today, Gleason score, clinical stage, and PSA are widely accepted risk factors that predict the likelihood of progression. According to recent data, men with good-risk PCa (PSA $<$ 10 ng/ml, biopsy Gleason score $\leq$ 6, cT1c–cT2a, life expectancy $<$ 10 yr) are good candidates for active surveillance [20]. Men with a life expectancy $>$ 15 yr might be eligible if fewer than three biopsy cores are involved with $<$ 50% involvement of each core. A recent update on 299 patients and a median follow-up of 64 mo showed that 34% of men came off active surveillance due to rapid biochemical progression, clinical or histologic progression, or patient's preference [21]. At 8 yr, overall survival is 85% and disease-specific survival is 99%. PSA doubling time $>$ 3 yr and repeat biopsy appear to be useful tools to guide treatment intervention for good-risk and screen-identified patients initially managed expectantly.

7.2. *Radical prostatectomy*

Currently, radical prostatectomy (RP) is the only treatment for localized PCa that has shown a cancer-specific survival benefit when compared to conservative management in a prospective, randomized trial [22]. Nerve-sparing RP represents the approach of choice in all men with normal erectile function and organ-confined disease improving quality of life without compromising oncological outcome [23]. The need and the extent of pelvic lymphadenectomy is currently controversial. However, the risk of lymph node involvement is low in men with low-risk PCa (cT1c, PSA $<$ 10 ng/ml, biopsy Gleason score $\leq$ 6) and $<$ 50% positive biopsy cores. In men with intermediate (cT2a, PSA 10–20 ng/ml, biopsy Gleason score = 7) or high-risk PCa ($>$ cT2b, PSA $>$ 20 ng/ml, biopsy Gleason score $\geq$ 8) an extended pelvic lymphadenectomy should always be performed due to the relatively high risk of lymph node involvement [24].

Management of cT3 PCa primarily has to be a multimodal approach due to the high likelihood of positive lymph nodes and/or positive resection margins. Overstaging of cT3 PCa is relatively frequent and occurs in 13–27% of cases. Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease with excellent 5-, 10-, and 15-yr overall and cancer-specific survival rates of 95%, 90% and 79%, respectively [25,26].

Neoadjuvant androgen deprivation before RP does not provide a significant advantage in overall survival and progression-free survival according to a recent Cochrane meta-analysis [27]. Furthermore, it is not associated with an improvement of local pathologic variables.

Adjuvant androgen deprivation therapy (ADT) following RP has always been controversial [28]. Although the only prospective randomized trial demonstrated a significant survival advantage for immediate ADT in N+ disease [29], it must be acknowledged that most patients had gross nodal disease and that 70% also had positive margins and/or seminal vesicle invasion. It is unclear whether adjuvant androgen deprivation in patients with minimal nodal involvement would result in the same positive results. The most recent update on the Early Prostate Cancer Trial has shown that there is no benefit to progression-free survival by adding bicalutamide 150 mg/die to standard care, whereas a benefit in overall survival was identified in men with locally advanced PCa [28]. In patients with microscopic lymph node involvement only, no final recommendations can be made.

7.3. *Radiation therapy*

For external radiotherapy, at least 72 Gy are recommended for the management of low-risk PCa as it has been shown that the biochemical disease-free survival is significantly higher with a radiation dose $\geq$ 72 Gy as compared to $<$ 72 Gy (69% vs 63%, $p = 0.046$) [30].

For intermediate-risk PCa, many series have shown a significant impact of dose escalation on 5-yr survival without biochemical relapse for patients classified as cT1c–T3, with a dose ranging from 76 to 81 Gy [31]. In daily practice, although a consensus has not been reached concerning the level of dose escalation, 78 Gy seems to represent a good compromise. A short course of androgen deprivation for 6 mo is beneficial for patients receiving up to 72 Gy of radiation, but its role in high-dose radiation therapy is unclear.

In patients with high-risk disease, external irradiation with dose escalation improves 5-yr biochemical disease-free survival [32], but seems insufficient to cover the risk of relapse outside the pelvis. Therefore, neoadjuvant and adjuvant androgen deprivation for 2 yr is mandatory to significantly improve overall and cancer-specific survival [33,34].

7.4. *Transperineal brachytherapy*

Transperineal low-dose brachytherapy is a safe and efficient technique that can be applied to patients with the following eligibility criteria: stage cT1b–T2a N0, M0, a Gleason score $\leq$ 6 assessed on a sufficient number of random biopsies, an initial PSA level

of ≤ 10 ng/ml, ≤ 50% of biopsy cores involved with cancer, and a prostate volume of < 50 cm^3 and a good International Prostatic Symptom Score [35]. Results of permanent implants have been reported from different institutions with a median follow-up ranging between 36 and 120 mo [36]. Recurrence-free survival after 5 and 10 yr was reported to range from 71% to 93% and from 65% to 85%, respectively. There is no benefit in adding neoadjuvant or adjuvant androgen deprivation to transperineal low-dose brachytherapy [36]. Most patients experience acute urinary symptoms shortly after implantation, such as urinary retention (1.5–22%) resulting in post-implant transurethral resection of the prostate (up to 8.7%) and incontinence (0–19%). Chronic urinary morbidity can occur in up to 20% of patients depending on the severity of symptoms prior to brachytherapy.

7.5. *Adjuvant external beam radiation therapy for pT3 or pTxR1 prostate cancer*

Three prospective randomized trials have assessed the role of immediate postoperative radiotherapy [37]. EORTC study 22911 compared immediate post-operative radiotherapy (60 Gy) to radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 after retropubic RP. Immediate postoperative radiotherapy proved to be well tolerated with a risk of grade 3–4 urinary toxicity in ≤ 3.5%. All trials conclude that immediate post-operative radiotherapy after surgery significantly improves 5-yr clinical or biological survival by approximately 20%. However, it has not been demonstrated that immediate radiation therapy improves metastasis-free survival and cancer-specific survival in this cohort of patients. Most suitable candidates for immediate radiation therapy may be those with multifocal positive surgical margins, a Gleason score > 7, or a PSA nadir of ≥ 0.1 ng/ml after RP.

8. Alternative local treatment options of prostate cancer

Besides RP, external beam radiation therapy, and/or brachytherapy, cryosurgical ablation of the prostate and high-intensity focused ultrasound have emerged as alternative therapeutic options in patients with clinically localized PCa who are not suitable for RP [38]. Patients ideally suitable for cryosurgical ablation of the prostate are those with organ-confined PCa, prostate size ≤ 40 ml, PSA serum level < 20 ng/ml, and a biopsy Gleason score < 7. Because there are only very few data on the long-term outcome in terms of cancer control, patients with a life expectancy > 10 yr should be informed accordingly.

9. Hormonal therapy

Today, luteinising hormone-releasing hormone (LHRH) agonists have become the standard of care in hormonal therapy because they avoid the physical and psychological discomfort associated with orchiectomy and lack the potential cardiotoxicity associated with DES [39,40]. As primary anti-androgen monotherapy, bicalutamide 150 mg/d has been compared to medical or surgical castration in two large prospective randomized trials with an identical study design, including a total of 1435 patients with locally advanced M0 or M1 PCa [41]. In M1 patients, an improvement in overall survival with castration was demonstrated, although the difference in median survival between the groups was only 6 wk. Nonsteroidal anti-androgens might be a therapeutic alternative in the M1 subgroup if PSA serum level is ≤400 ng/ml, whereas steroidal anti-androgens are not [42]. In M0 patients, no significant survival difference was noted in overall survival. The current indications for androgen deprivation are summarized in Table 3.

9.1. *Complete androgen blockade*

From the most recent systematic reviews and meta-analyses, at a 5-yr follow-up complete androgen blockade appears to provide a small survival advantage (< 5%) when compared to monotherapy [39,41]. It remains debatable whether this small advantage, if any, can be meaningful when applied to everyday clinical practice.

9.2. *Intermittent androgen blockade*

The idea of intermittent androgen blockade is to preserve quality of life and to reduce treatment-associated costs without compromising the therapeutic efficacy of endocrine manipulation. Several phase II trials have demonstrated the feasibility of intermittent androgen blockade in metastatic or biochemically recurrent disease, with PSA response rates and symptom improvement similar to that of complete androgen blockade. The largest trial (SWOG 9346) randomized 1134 men with stage D2 PCa to intermittent and continuous ADT after 7 mo of induction ADT, with PSA reduction < 4 ng/ml [43]. A PSA reduction to < 0.2, < 4, and > 4 ng/ml was

Table 3 – Indications for hormonal therapy

Castration indications	Comments
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis) (level of evidence: 3)
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious complications related to disease progression (level of evidence: 1b)
N+	Immediate castration for macroscopic metastases to prolong progression-free survival (level of evidence: 1b) and even overall survival (level of evidence: 3). For microscopic lymph node involvement no final recommendations can be made.
Locally advanced M0 Locally advanced symptomatic Locally advanced asymptomatic unfit for local definitive treatment	Immediate castration to improve overall survival (level of evidence: 1b) (level of evidence: 4)
Anti-androgens	
Short-term administration	To reduce the risk of the flare-up phenomenon in patients with advanced metastatic disease who are to receive an luteinising hormone-releasing hormone agonist (level of evidence: 1b)
Nonsteroidal anti-androgens	Primary monotherapy as an alternative to castration in patients with locally advanced PCa (level of evidence: 1b)

identified as a significant prognostic factor with regard to survival, achieving 75, 44, and 13 mo, respectively. Thus, it is possible to offer intermittent androgen blockade to selected patients, but results from randomized trials are still lacking. A minimum induction period of 7 mo with continuous hormonal therapy and a PSA response to < 4 ng/ml seems to be required for a successful intermittent regimen.

9.3. *Immediate versus deferred androgen deprivation*

The most appropriate time to introduce hormonal therapy in patients with advanced PCa is still controversial. It remains unclear whether immediate ADT for locally advanced and asymptomatic metastatic disease favourably influences survival and quality of life as compared to deferred ADT at the time of symptomatic disease. The dispute mainly derives from the lack of properly conducted randomized, controlled trials.

With regard to PSA rise after RP, there are also no prospective randomized clinical trials available. Only one retrospective analysis of 1352 men with PSA rise after RP is available for analysis [44]. Of these 1352 men, 355 with various PSA serum levels started ADT, whereas 997 remained without hormonal manipulation until detection of metastatic disease. Early ADT showed a benefit with regard to the bone metastasis-free interval only for patients with a Gleason score > 7 or a PSA-DT < 12 mo; there was no statistically significant difference in overall or cancer-specific survival.

10. Follow-up of prostate cancer patients

Patients diagnosed with PCa are usually followed lifelong or until advancing age makes follow-up superfluous. Determination of serum PSA, disease-specific history, and digital rectal examination are

Table 4 – Guidelines for follow-up after treatment with curative intent

1.	In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by digital rectal exam are the recommended tests for routine follow-up. These should be performed at 3, 6, and 12 mo after treatment, then every 6 mo until 3 yr, and then annually (grade B recommendation).
2.	After radical prostatectomy, a serum PSA level > 0.2 ng/ml can be associated with residual or recurrent disease (grade B recommendation).
3.	After radiation therapy, a rising PSA level 2.0 ng/ml above the nadir value, 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 transrectal ultrasonography and biopsy is only recommended if it will affect the treatment plan (salvage, radiotherapy, or surgery). In most cases, transrectal ultrasonography 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 < 20 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 5 – Guidelines for follow-up after hormonal treatment

1.	Patients should be evaluated at 3 and 6 mo after initiating treatment. Tests should include at least serum PSA measurement, digital rectal exam, 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 mo and should include at least a disease-specific history, digital rectal exam, 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 mo. A minimal follow-up should include a disease-specific history, digital rectal exam, 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).

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. The follow-up intervals and which tests are needed have not been well studied, and often these need to be individualized. Table 4 summarizes the guidelines for follow-up after therapy with curative intent, and in Table 5 are follow-up guidelines after hormonal therapy. Patients initially managed by active monitoring (no active therapy) need individual follow-up depending on the future aims of therapy and tumour characteristics.

11. Treatment of relapse after curative therapies

Following RP, PSA values $>$ 0.2 ng/ml represent recurrent cancer [45]. Following radiation therapy, a PSA value 2 ng/ml above the nadir after radiation therapy represents recurrent cancer [46].

An effort should be made to distinguish between the probability of local failure only versus distant and/or 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 (Table 6). Poorly differentiated tumour, early PSA relapse, and a quickly rising PSA are all signs of distant failure (systemic disease), whereas patients with moderately differentiated tumours, late PSA relapse, and a slow doubling time (>10–12 mo) 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 (Tables 7 and 8).

Imaging studies such as bone scintigraphy or computed tomography (CT) to determine the site of recurrence are of no additional diagnostic value unless the PSA serum level is $>$ 20 ng/ml or unless the PSA velocity is $>$ 2 ng/ml/yr. Endorectal coil imaging represents a useful technique to detect local recurrences after RP if the PSA serum level is $>$ 2 ng/ml.

Positron emission tomography (PET) with ^{11}C-choline has been successfully applied in many human cancers for early identification of local or systemic recurrences. However, in PCa there are only a few data published on the clinical efficacy of PET so that no final conclusions can be made. Clearly PET/CT is not indicated as a routine imaging study in the clinical situation of PSA rise after local treatment with curative intent.

Table 6 – Important clinical and pathohistological parameters predicting local and systemic relapse following radical prostatectomy

Parameter	Local recurrence	Systemic recurrence
Interval to PSA relapse		
≤1 yr	7%	93%
1–2 yr	10%	90%
>2 yr	61%	39%
>3 yr	74%	26%
PSA doubling time	11.7 mo	4.3 mo
Gleason score		
2–4	0%	0%
5–6	55%	45%
7	39%	61%
8–10	11%	89%
Pathological stage		
Organ confined (≤pT2b)	40%	60%
pT3a, R0	54%	46%
pT3a, R1	48%	52%
pT3b	16%	84%
pTxpN1	7%	93%

12. Treatment of relapse after hormonal therapy

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

Table 7 – Treatment options of second-line therapy after local treatment with curative intent

Management of PSA relapse after radical prostatectomy
1. Local recurrences are best treated by salvage radiation therapy with 64–66 Gy at a PSA serum level ≤1.5 ng/ml (grade B recommendation).
2. Expectant management is an option for patients with presumed local recurrence unfit for or unwilling to undergo radiation therapy (grade B recommendation).
3. PSA recurrence indicative of systemic relapse is best treated by early androgen deprivation therapy resulting in decreased frequency of clinical metastases (grade B recommendation).
4. Luteinising hormone-releasing hormone analogues/orchiectomy or bicalutamide at 150 mg/d can both be used when there is indication for hormonal therapy (grade A recommendation).
Management of PSA relapse after radiation therapy
1. Local recurrences may be treated by salvage radical prostatectomy in carefully selected patients with presumably organ-confined disease (grade C recommendation).
2. Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative experimental procedures in patients not suitable for surgery (grade C recommendation).
3. Androgen deprivation therapy is an option in patients with presumed systemic relapse (grade B recommendation).

Table 8 – Guidelines for second-line therapy after curative treatment

1.	*Presumed local failure:* Patients with presumed local failure only may be candidates for salvage after radical radiotherapy. This should be given with at least 64 Gy and preferably prostatectomy 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 (grade B recommendation).
2.	*Presumed local failure*: Selected patients may be candidates for salvage radical prostatectomy after radiotherapy. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later (grade C recommendation).
3.	*Presumed distant*: There is some evidence that early hormonal therapy may be of benefit in ±local failure 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).

and will generally become symptomatic within a relatively short time after the onset of the PSA rise. 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. However, there are some therapeutic algorithms available that have emerged based on the data of prospective clinical trials. The recommendations for management of patients who fail hormonal therapy are summarized in Table 9.

The precise definition of recurrent or relapsed PCa remains controversial. Recently, various groups have published practical recommendations that should be adhered to when defining hormone-refractory PCa

Table 9 – 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 anti-androgens has to cease once PSA progression is documented (grade B recommendation).
3. After discontinuation of flutamide or bicalutamide after 4 wk and 6 wk, respectively, an eventual anti-androgen withdrawal effect may become apparent (grade B recommendation).
4. No clear-cut recommendation can be made regarding the most effective drug for secondary hormonal manipulations, as no data from randomized trials are available (grade C recommendation).
Cytotoxic therapy
1. In patients with a PSA rise only two 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 patient (grade C recommendation).
4. In patients with metastatic hormone-refractory PCa, docetaxel at 75 mg/m^2 every 3 wk results in a significant survival benefit and represents the reference treatment (grade A recommendation).
5. In patients with symptomatic osseous metastases due to hormone-refractory PCa, docetaxel with prednisone is the treatment option of choice (grade A recommendation).
Palliative management
1. Zoledronate may be offered to patients with skeletal to prevent osseous complications (grade A recommendation).
2. 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 (grade B recommendation).

Table 10 – Definition of hormone-refractory prostate cancer

1.	Serum castration levels of testosterone
2.	Three consecutive rises of PSA 2 wk apart resulting in two 50% increases over the nadir
3.	Anti-androgen withdrawal for at least 4 wk*
4.	PSA progression despite secondary hormonal manipulations*
5.	Progression of osseous or soft tissue lesions (3)

* Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for hormone-refractory PCa.

[47]. Androgen-independent but hormone-sensitive PCa has to be differentiated from true hormone-refractory PCa from the outset. The first group still responds to secondary hormonal manipulations, such as anti-androgen withdrawal, oestrogens, and corticosteroids, whereas the latter is resistant to all hormonal measures. Table 10 lists key defining factors of hormone-refractory PCa.

12.1. *Secondary hormonal therapy*

For the patient with progressive disease after androgen deprivation, multiple therapeutic options are available. These include anti-androgen withdrawal, addition of anti-androgens, oestrogenic compounds, adrenolytic agents, and novel approaches [48]. The therapeutic algorithm given in Fig. 1 summarizes the various treatment modalities and the responses to be expected.

12.2. *Nonhormonal therapy (cytotoxic agents)*

Based on prospective randomized clinical phase III trials, docetaxel in combination with prednisone represents the cytotoxic regime of choice in men with hormone-refractory PCa, resulting in a survival benefit of 3 mo and a significant improvement of pain and quality of life as compared to mitoxantrone [49,50]. The beneficial effect of docetaxel is independent on age, pain, or performance status at initiation and the presence of symptomatic or asymptomatic metastatic disease. Despite these encouraging results, the time-point at which to initiate a cytotoxic regime in patients with hormone-refractory PCa remains controversial, and currently there is no indication for chemotherapy in patients with a PSA rise only. The most appropriate indication for chemotherapy is the clinical scenario of asymptomatic but extensive metastases or symptomatic metastases.

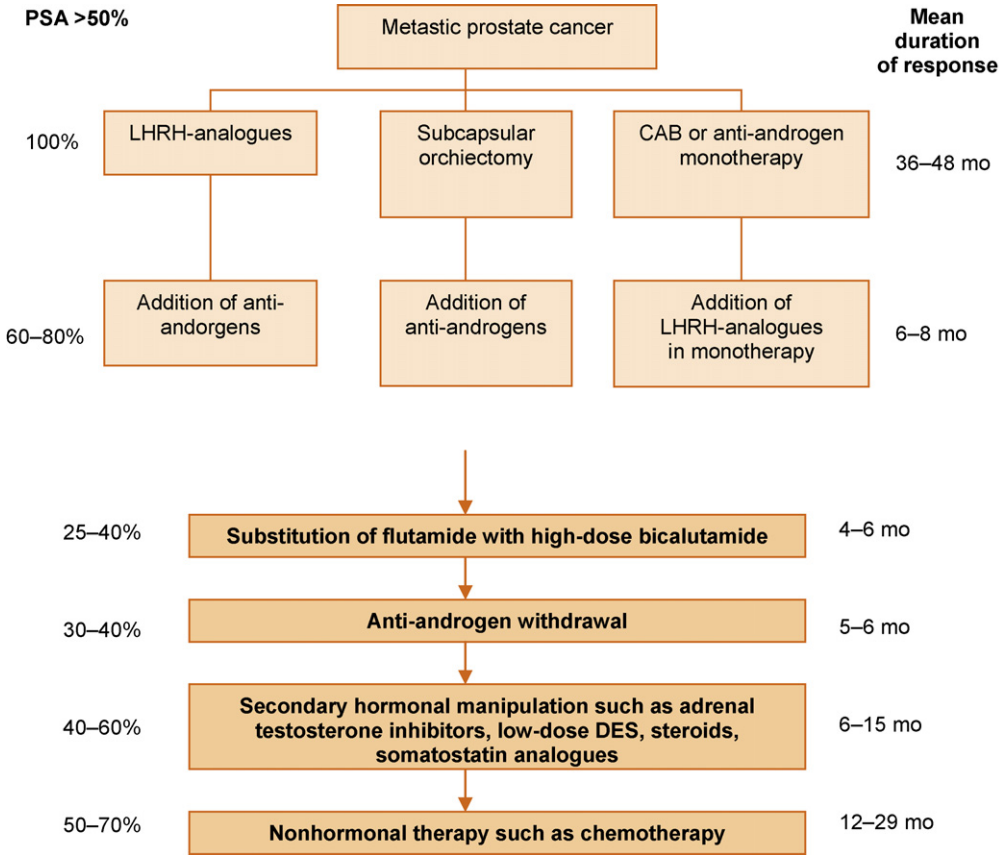

Fig. 1 – Flowchart of the potential therapeutic options after PSA progression following initial hormonal therapy.

12.3. *Palliative therapeutic options*

Many patients with hormone-refractory PCa have painful bone metastases and are not amenable to chemotherapy, making effective palliative treatment options (eg, palliative external beam radiation, cortisone, analgesics and anti-emetics) necessary. Hormone-refractory PCa is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses, and social workers. Critical issues of palliation must be addressed while considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue, and depression, which frequently occur.

Common complications due to skeletal metastases include bone pain, vertebral collapse or deformity pathological fractures, and spinal cord compression. The use of zoledronate has demonstrated a clinically significant effect in terms of prevention of skeletal complications and reduction of pain, or even total pain relief, in patients with hormone-refractory PCa [51]. Patients with hormone-refractory PCa metastatic to bone experience a significant reduction of skeletal-related events, a significant reduction of the frequency of pathological fractures, and a significant increase of time to first skeletal-related events, thereby significantly improving quality of life.

13. Summary

The present text represents a summary of the EAU guidelines on PCa; for more detailed information and a full list of references, we refer readers 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).

Conflicts of interest

Dr. Axel Heidenreich has financial relationships as a lecturer, consultant, and Advisory Board Member at Sanofi-Aventis, Novartis, Hoffmann-La Roche, Centocor.

During the EAU meeting in Berlin, 2007, Prof. Gunnar Aus has been taking part in a symposium related to High Intensity Focused Ultrasound (HIFU) for the treatment of prostate cancer. For chairing this symposium, he received financial compensation from EDAP, Lyon, France.

There are no financial disclosures to be made for Prof. M. Bolla, Dr. Steven Joniau, Prof. V.B. Matveev, Prof. Hans Peter Schmid, and Prof. Filliberto Zattoni.

References

[1] Aus G, Abbou CC, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2005;48:546–51.
[2] US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research 1992, p. 115–27. http://www.ahcpr.gov/.
[3] Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002;38:99–166.
[4] Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075–107.
[5] Gronberg H, Damber L, Damber JE. Familial prostate cancer in Sweden: a nationwide register cohort study. Cancer 1996;77:138–43.
[6] Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 1992;89:3367–71.
[7] Sobin LH, Wittekind C, editors. TNM classification of malignant tumours. ed. 6 New York: Wiley-Liss; 2002.
[8] Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974;111:58–64.
[9] De Koning HJ, Liem MK, Baan CA, Boer R, Schroder FH, Alexander FE. Prostate cancer mortality reduction by screening: power and time frame with complete enrolment in the European Randomized Screening for Prostate Cancer (ERSPC) trial. Int J Cancer 2002;98:268–73.
[10] Schmid H-P, Riesen W, Prikler L. Update on screening for prostate cancer with prostate specific antigen. Crit Rev Oncol Hematol 2004;50:71–8.
[11] Smith RA, Cokkinides V, Eyre HJ. Cancer screening in the United States 2007: a review of current guidelines, practices, and prospects. CA Cancer J Clin 2007;57:90–104.
[12] Aus G, Becker C, Franzén S, Lilja H, Lodding P, Hugosson J. Cumulative prostate cancer risk assessment with the aid of the free-to-total prostate specific antigen ratio. Eur Urol 2004;45:160–5.
[13] Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level $\leq$4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.
[14] Sun L, Moul JW, Hotaling JM, et al. Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged $<$50 years. BJU Int 2007;99:753–7.
[15] Guichard G, Larré S, Gallina A, et al. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. Eur Urol 2007;52:430–5.
[16] Morote J, Lopez M, Encabo G, de Torres I. Value of routine transition zone biopsies in patients undergoing ultrasound-guided sextant biopsies for the first time. Eur Urol 1999;35:294–7.

[17] Djavan B, Ravery V, Zlotta A, et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? J Urol 2001;166:1679–83.
[18] Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, Chisholm GD, Moskovitz B, Livne PM, Warner J. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994;330:242–8.
[19] Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998;280:975–80.
[20] Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005;23:8165–9.
[21] Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. J Urol 2006;176:1392–7.
[22] Bill-Axelson A, Holmberg L, Ruutu M, et al. Scandinavian Prostate Cancer Group study no. 4: radical prostatectomy versus watchful waiting in early prostate cancer. N Eng J Med 2005;352:1977–84.
[23] Walsh PC. The discovery of the cavernous nerves and development of nerve sparing radical retropubic prostatectomy. J Urol 2007;177:1632–5.
[24] Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007;52:29–37.
[25] Joniau S, Hsu C-Y, Lerut E, et al. A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral T3a prostate cancer. Eur Urol 2007;51:388–96.
[26] Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005;95:751–6.
[27] Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Cochrane Database Syst Rev 2006;CD006019.
[28] McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP, Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int 2006;97:247–54.
[29] Messing EM, Manola J, Yao J, et al. Eastern Cooperative Oncology Group study EST 3886: immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472–9.
[30] Kupelian P, Kuban D, Thames H, et al. Improved biochemical relapse-free survival with increased external radiation doses in patients with localized prostate cancer: the combined experience of nine institutions in patients treated in 1994 and 1995. Int J Radiat Oncol Biol Phys 2005;61:415–9.
[31] Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998;41:491–500.
[32] Pollack A, Zagars GK, Smith LG, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 2000;18:3904–11.
[33] Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002;360:103–6.
[34] Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.
[35] Ash D, Flynn A, Batterman J, de Reijke T, Lavagnini P, Blank L, ESTRA/EAU Urological Brachytherapy Group, EORTC Radiotherapy Group. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000;57:315–21.
[36] Machtens S, Baumann R, Hagemann J, et al. Long-term results of interstitial brachytherapy (LDR-brachytherapy) in the treatment of patients with prostate cancer. World J Urol 2006;24:289–95.
[37] Bottke D, Wiegel T. Adjuvant radiotherapy after radical prostatectomy: indications, results and outcome. Urol Int 2007;78:193–7.
[38] Aus G. Current status of HIFU and cryotherapy in prostate cancer – a review. Eur Urol 2006;50:927–34.
[39] Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med 2000;132:566–77.
[40] Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 2002;95:361–76.
[41] Iversen P, Tyrell CJ, Kaisary AV, et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology 1998;51:389–96.
[42] Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007;25:1596–605.
[43] Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer—data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984–90.
[44] Moul JW, Wu H, Sun L, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 2004;171:1141–7.
[45] Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological

Association Prostate Guidelines for localized prostate cancer update panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177:540–5.

[46] Roach III M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74.

[47] Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999;17:3461–7.

[48] Ryan CJ, Small EJ. Role of secondary hormonal therapy in the management of recurrent disease. Urology 2003; 62(Suppl 1):87–94.

[49] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513–20.

[50] Tannock IF, de Wit R, Berry WR, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

[51] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458–68.