



SPECIAL ARTICLE

EAU guidelines on prostate cancer. Part I: screening, diagnosis, and treatment of clinically localised disease^{☆,☆☆}

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Abstract

Objective: Our aim was to present a summary of the 2010 version of the European Association of Urology (EAU) guidelines on the screening, diagnosis, and treatment of clinically localised cancer of the prostate (PCa).

Methods: The working panel performed a literature review of the new data emerging from 2007 to 2010. The guidelines were updated, and level of evidence and grade of recommendation were 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 Web site (www.uroweb.org). Current evidence is insufficient to warrant widespread population-based screening by prostate-specific antigen (PSA) for PCa. A systematic prostate biopsy under ultrasound guidance and local anaesthesia is the preferred diagnostic method. Active surveillance represents a viable option in men with low-risk PCa and a long life expectancy. PSA doubling time in <3 years or a biopsy progression indicates the need for active intervention. In men with locally advanced PCa in

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PALABRAS CLAVE

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whom local therapy is not mandatory, watchful waiting (WW) is a treatment alternative to androgen-deprivation therapy (ADT) with equivalent oncologic efficacy. Active treatment is mostly recommended for patients with localised disease and a long life expectancy with radical prostatectomy (RP) shown to be superior to WW in a prospective randomised trial. Nerve-sparing RP 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 74 Gy and 78 Gy in low-risk and intermediate/high-risk PCa, respectively. For locally advanced disease, adjuvant ADT for 3 years results in superior disease-specific and overall survival rates and represents the treatment of choice. Follow-up after local therapy is largely based on PSA, and a disease-specific history with imaging is indicated only when symptoms occur.

Conclusions: The knowledge in the field of PCa is rapidly changing. These EAU guidelines on PCa summarise the most recent findings and put them into clinical practice.

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Guía de la EAU sobre el cáncer de próstata. Parte I: cribado, diagnóstico y tratamiento del cáncer clínicamente localizado

Resumen

Objetivo: Nuestro objetivo era presentar un resumen de la versión de 2010 de la guía de la Asociación Europea de Urología (EAU) para el cribado, diagnóstico y tratamiento del cáncer de próstata (CP) clínicamente localizado.

Métodos: El grupo de trabajo realizó una revisión de los nuevos datos aparecidos desde 2007 hasta 2010 en la literatura. Las guías se actualizaron y el nivel de evidencia y grado de recomendación se incorporaron al texto basándose en una revisión sistemática de la literatura, que incluía una búsqueda en las bases de datos en línea y revisiones bibliográficas.

Resultados: Existe una versión completa disponible en las oficinas o el sitio web de la EAU (www.uroweb.org). Los indicios actuales son insuficientes para garantizar un cribado extendido del conjunto de la población mediante el antígeno prostático específico (APE) para el CP. El método diagnóstico de elección es la biopsia sistematizada de la próstata bajo control ecográfico con anestesia local. El seguimiento activo representa una opción viable en varones con CP de bajo riesgo y una larga esperanza de vida. Un tiempo de duplicación del APE < 3 años, o una progresión en la biopsia, indicaría la necesidad de intervención activa. En varones con CP localmente avanzado en los que la terapia local no sea obligatoria, la espera en observación (*watchful waiting* [WW]) es un tratamiento alternativo a la terapia de bloqueo hormonal o de privación androgénica (TPA), con una eficacia oncológica equivalente. El tratamiento activo se recomienda en la mayoría de los pacientes con enfermedad localizada y una larga esperanza de vida, siendo la prostatectomía radical (PR) superior a la WW en un ensayo aleatorio prospectivo. La PR con conservación nerviosa es la técnica de elección en la enfermedad limitada al órgano; el bloqueo hormonal neoadyuvante no ha demostrado una mejoría en las variables de resultados. La radioterapia debe realizarse con al menos 74 Gy en el CP de bajo riesgo y con 78 Gy en el que presenta un riesgo intermedio/alto. Para casos en los que la enfermedad esté localmente avanzada la TPA adyuvante durante tres años logra tasas de supervivencia superiores a nivel general y específico de la enfermedad, y supone el tratamiento preferido. El seguimiento tras terapia local se basa principalmente en los niveles de APE, estando la anamnesis específica de la enfermedad con diagnóstico por imagen sólo indicada cuando aparecen los síntomas.

Conclusiones: Lo que se conoce acerca del campo del CP está cambiando rápidamente. Esta guía de la EAU para el CP resume los hallazgos más recientes y los aplica a la práctica clínica.

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Introduction

The most recent summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2008.¹ The long version of these guidelines has been continuously updated because many important changes affecting the clinical management of PCa have occurred. This paper summarises the 2010 update of the EAU guidelines on PCa. To facilitate evaluating the quality of the

information provided, level of evidence (LE) and grade of recommendation (GR) have been inserted according to the general principles of evidence-based medicine.²

Epidemiology

In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering

lung and colorectal cancers.³ PCa affects elderly men more often and therefore is a bigger health concern in developed countries. Thus about 15% of male cancers are PCa in developed countries compared with 4% of male cancers in developing countries.⁴ There are large regional differences in incidence rates of PCa with a range from 68.8 in Malta to 182 in Belgium.⁴

Risk factors

The factors that determine the risk of developing clinical PCa are not well known, although three well-established risk factors have been identified: increasing age, ethnicity, and 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 About 9% of individuals with PCa have true hereditary PCa, defined as three or more relatives affected or at least two who have developed early onset disease (i.e., <55 years of age).

Classifications

The Union Internationale Contre le Cancer 2009 TNM classification is used throughout the guidelines.⁶ The Gleason score is recommended for grading PCa. According to current international convention, the (modified) Gleason score of cancers detected in a prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component *plus* the highest grade, regardless of its extent (no 5% rule).⁷ In radical prostatectomy (RP) specimens, both the primary and the secondary Gleason grade should be reported. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported.

Prostate cancer screening

There is currently no evidence for introducing widespread population-based screening programmes for early PCa detection in all men⁸ (LE: 2). To evaluate the efficacy of PCa screening, two large randomised trials have been published: the Prostate, Lung, Colorectal, and Ovary (PLCO) trial in the United States and the European Randomised Study of Screening for Prostate Cancer (ERSPC) in Europe^{9,10} (LE: 1b).

The PLCO cancer screening trial randomly assigned 76,693 men to receive either annual screening with prostate-specific antigen (PSA) and digital rectal examination (DRE) or standard care as the control.⁹ After a follow-up of 7 years, the incidence of PCa per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio: 1.22).⁹ The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio: 1.13). The PLCO project team concluded that PCa-related mortality in screen-detected individuals was very low and not significantly different between the two study groups (LE: 1b).

The ERSPC trial included a total of 162,243 men between 55 and 69 years of age.¹⁰ The men were randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years, the cumulative incidence of PCa was 8.2% in the screened group and 4.8% in the control group.¹⁰ The absolute risk difference was 0.71 deaths per 1000 men. This means that 1410 men would need to be screened and 48 additional cases of PCa would need to be treated to prevent 1 death from PCa. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from PCa by 20% but was associated with a high risk of overtreatment (LE: 1b).

Both trials have received considerable attention and comments. In the PLCO trial, the rate of compliance in the screening arm was 85% for PSA testing and 86% for DRE. However, the rate of contamination in the control arm was as high as 40% in the first year and increased to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40–52% vs 86% in the ERSPC. Thus the PLCO trial will probably never be able to answer whether or not screening can influence PCa mortality.

In a recent retrospective analysis of PCa incidence, PCa metastasis and cause of death were evaluated for a group of 11,970 men who were included in the intervention arm of the ERSPC trial and a control population of 133,287 unscreened men during an 8-year observation period.¹¹ The relative risk (RR) of PCa metastasis in the screened population compared with the control population was 0.47 ($p < 0.001$). The RR of PCa-specific mortality was also significantly lower in the screening arm (RR: 0.63; $p = 0.008$). The absolute mortality reduction was 1.8 deaths per 1000 men. Based on these data, the real benefit of the ERSPC trial will only be evident after 10–15 years of follow-up, especially because the 41% reduction of metastasis in the screening arm will have an impact. Furthermore, we have to wait for the results of the economic burden and the side effects resulting from more intensive screening.

Based on the results of these two large randomised trials, most if not all of the major urologic societies have concluded that at present widespread mass screening for PCa is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man (see “Diagnosis and staging of prostate cancer” section). Two key questions remain open and empirical:

- At what age should early detection start?
- What is the interval for PSA and DRE?

The decision to undergo early PSA testing should be a shared decision between the patient and his physician based on information balancing its advantages and disadvantages. A baseline PSA determination at 40 years of age has been suggested on which the subsequent screening interval may then be based^{10–12} (GR: B). A screening interval of 8 years might be enough in men with initial PSA levels ≤ 1 ng/ml.¹⁰ Further PSA testing is not necessary in men >75 years and a baseline PSA ≤ 3 ng/ml because of their very low risk of dying from PCa.¹³

Table 1 Risk of prostate cancer in relation to low prostate-specific antigen values.

PSA level (ng/ml)	Risk of PCa (%)
0–0.5	6.6
0.6–1	10.1
1.1–2	17.0
2.1–3	23.9
3.1–4	26.9

PCa = prostate cancer; PSA = prostate-specific antigen.

Diagnosis and staging of prostate cancer

The main diagnostic tools to diagnose PCa include DRE, serum concentration of PSA, and transrectal ultrasound (TRUS)-guided biopsies. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level¹⁴ (LE: 2a). A suspect DRE in patients with a PSA level of up to 2 ng/ml has a positive predictive value of 5–30%¹⁵ (LE: 2a).

A threshold level of PSA that indicates the highest risk of PCa needs to be defined (Table 1). When analysing PSA serum levels, it has to be anticipated that not all PSA assays will result in the same serum concentration.¹⁶ Therefore, the situation for the clinical interpretation of PSA or percent free PSA (%fPSA) results is complicated. Method comparisons between the traditionally calibrated Hybritech PSA and free PSA (fPSA) assays and the new "standardised" World Health Organisation (WHO) calibrated Access assays yielded results that are approximately 25% lower for PSA and fPSA. A PSA cut-off of 3 or 3.1 µg/l should be considered for WHO-calibrated assays to achieve the same sensitivity/specificity profile as with a cut-off of 4 µg/l in traditionally calibrated assays. The %fPSA cut-offs can be retained.

The level of PSA is a continuous parameter: the higher the value, the more likely the existence of PCa. The finding that many men may harbour PCa, despite low levels of serum PSA, has been underscored by recent results from a US prevention study¹⁷ (LE: 2a). Table 1 gives the rate of PCa in relation to serum PSA for 2950 men in the placebo arm and with normal PSA values.

Several modifications of serum PSA value have been described that may improve the specificity of PSA in the early detection of PCa. They include PSA density, PSA density of the transition zone, age-specific reference ranges, and PSA molecular forms.

In a prospective multicentre trial, PCa was found on biopsy in 56% of men with a free/total (f/t) PSA < 0.10 but in only 8% of men with a f/t PSA > 0.25⁸ (LE: 2a). These data were confirmed in a recent screening test including 27,730 men with a serum PSA concentration between 2.1 and 10 ng/ml.¹⁸ Using f/t PSA, the number of unnecessary biopsies decreased significantly and the detection rate of PCa increased significantly. Nevertheless, the concept must be used with caution because several preanalytical and clinical factors may influence the f/t PSA. For example, free PSA is unstable at both 4 °C and at room temperature. The two concepts of PSA velocity (PSAV) and PSA doubling time (PSA DT) have limited use in the diagnosis of PCa because

of several unresolved issues, including background noise (total volume of prostate, benign prostatic hyperplasia), the interval between PSA determinations, and acceleration/deceleration of PSAV and PSA DT over time. Prospective studies have not shown that these measurements can provide additional information compared with PSA alone.^{19,20}

In contrast to the serum markers discussed previously, the new biomarker prostate cancer antigen 3 (PCA3) is measured in urine sediment obtained after prostatic massage.²¹ Determination of this PCa-specific RNA is experimental. At a population level it appears to be helpful, but its impact at a single-patient level remains highly questionable. So far, none of the biomarkers just mentioned can be used to counsel an individual patient on the need to perform a prostate biopsy to rule out PCa. The molecular marker might help in the decision-making process with regard to a repeat biopsy in men with a negative first biopsy but a persisting suspicion of PCa.^{22,23} Men with a positive follow-up biopsy had significantly higher PCA3 scores compared with men with a negative second biopsy (69.5 vs 37.7; $p < 0.001$). In men with a f/t PSA < 10%, PCA3 score was identified as a significant predictor of PCa. However, in men with a f/t PSA of 10–20% and >20%, the percentage of positive biopsies rose from 17.8% to 30.6% and from 23.9% to 37%, respectively, if a PCA3 score >30 was used.

TRUS or a transperineal laterally directed 18-gauge core biopsy has become the standard way to obtain material for histopathologic examination.^{24,25} The need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious DRE. The patient's biologic age, potential comorbidities, and the therapeutic consequences should also be considered. The first elevated PSA level should not prompt an immediate biopsy, but it should be verified after a few weeks by the same assay under standardised conditions except for high PSA values >20 ng/ml once prostatitis has been excluded.

At a glandular volume of 30–40 ml, at least eight cores should be sampled. More than 12 cores are not significantly more conclusive²⁶ (LE: 1a). Oral or intravenous quinolones are state-of-the-art preventive antibiotics with ciprofloxacin superior to ofloxacin²⁷ (LE: 1b). Ultrasound-guided periprostatic block is state of the art²⁸ (LE: 1b). On baseline biopsies, the sample sites should be as far posterior and lateral in the peripheral gland as possible. Additional cores should be obtained from suspect areas by DRE/TRUS.

Indications for repeat biopsies are rising and/or persistent PSA, suspicious DRE, and atypical small acinar proliferation of prostate. The optimal timing is still uncertain. The later the repeat biopsy is done, the higher the detection rate.²⁹ High-grade prostatic intraepithelial neoplasia (PIN) is only considered an indication for rebiopsy if it occurs multifocally²⁹ (LE: 2a). If clinical suspicion for PCa persists in spite of negative prostate biopsies, magnetic resonance imaging (MRI) may be used to investigate the possibility of an anterior located PCa, followed by TRUS or MRI-guided biopsies of the suspicious area.

Diagnosis of PCa is based on histologic examination.³⁰ Ancillary staining techniques (e.g., basal cell staining) and additional (deeper) sections should be considered if a suspect glandular lesion is identified.³⁰

Table 2 Guidelines and recommendations for (a) radical prostatectomy and (b) definitive radiation therapy.

(a)	
Indications	LE
<i>In patients with low- and intermediate-risk localised PCa (cT1a–T2b, Gleason score 2–7, and PSA ≤ 20) and a life expectancy >10 years</i>	1b
<i>Optional</i>	
Patients with stage T1a disease and a life expectancy >15 years or Gleason score 7	3
Selected patients with low-volume high-risk localised PCa (cT3a or Gleason score 8–10 or PSA > 20)	3
Highly selected patients with very high-risk localised PCa (cT3b–T4 N0 or any T N1) in the context of multimodality treatment	3
<i>Recommendations</i>	
Short-term (3-months) or long-term (9-months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is not recommended in the treatment of stage T1–T2 disease	1a
Nerve-sparing surgery should be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score <7, and PSA < 10 ng/ml)	3
Unilateral nerve-sparing procedures are an option in clinical stage T2a–c disease	4
(b)	
Indications	LE
In localised PCa T1c–T2c N0 M0, 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention. There is fairly strong evidence that low-, intermediate-, and high-risk patients benefit from dose escalation	2
For patients in the high-risk group, short-term ADT before and during radiotherapy results in increased OS	2a
Transperineal interstitial brachytherapy with permanent implants is an option for patients with cT1–T2a, Gleason score <7, PSA ≤ 10 ng/ml, prostate volume ≤ 50 ml, without a previous TURP and with a good IPSS	2b
Immediate postoperative external irradiation after RP for patients with pathologic tumour stage T3 N0 M0 improves biochemical and clinical disease-free survival	1
Immediate postoperative external irradiation after RP for patients with positive surgical margins improves biochemical and clinical disease-free survival	
An alternative option is to give radiation at the time of biochemical failure but before PSA rises above 0.5 ng/ml	3
In locally advanced PCa T3–4 N0 M0 and in high-risk disease, OS is improved by concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external irradiation for patients with a WHO 0–2 performance status	1
For a subset of patients with T2c–T3 N0-x and a Gleason score of 6, short-term ADT before and during radiotherapy may favourably influence OS	1b

ADT = androgen-deprivation treatment; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; IPSS = International Prostatic Symptom Score; LE = level of evidence; OS = overall survival; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; TURP = transurethral resection of the prostate; WHO = World Health Organisation.

For each biopsy site, the proportion of biopsies positive for carcinoma and the Gleason score, using the system adopted in 2005,³¹ should be reported. A diagnosis of Gleason score ≤ 4 should not be given on prostate biopsies.³¹ The proportion (percentage) or length (in millimetres) of tumour

involvement per biopsy^{30,31} and extraprostatic extension, if present, should be recorded. The presence of high-grade PIN and perineural invasion is usually reported.

The extent of a single small focus of adenocarcinoma, which is located in only one of the biopsies, should be

Table 3 Guidelines for the diagnosis of prostate cancer.

		GR
1	An abnormal DRE result or elevated serum PSA measurement could indicate PCa. The exact cut-off level of what is considered a normal PSA value has not been determined, but values of approximately <2–3 ng/ml are often used for younger men	C
2	The diagnosis of PCa depends on histopathologic (or cytologic) confirmation	B
	Biopsy and further staging investigations are only indicated if they affect the management of the patient	C
3	TRUS-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 10 systemic laterally directed cores are recommended, with perhaps more cores in prostates with a volume >40 ml	B
	Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates	C
	One set of repeat biopsies is warranted in cases with persistent indication (abnormal DRE, elevated PSA, or histopathologic findings suggestive of malignancy at the initial biopsy) for prostate biopsy	B
	Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient	C
4	Transrectal periprostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies	A

DRE = digital rectal examination; GR = grade of recommendation; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

clearly stated (e.g., <1 mm or <1%) because this might be an indication for a further diagnostic workup of the specimen or a rebiopsy before selecting therapy.^{32,33}

The decision to proceed with further diagnostic or staging workup is guided by which treatment options are available to the patient, taking the patient's preference, age, and comorbidity into consideration.^{34–41} Procedures that will not affect the treatment decision can usually be avoided. **Tables 3 and 4** summarise the guidelines on diagnosis and staging.

Primary local treatment of prostate cancer

Therapeutic management of PCa, even in clinically localised disease, has become more and more complex because of the various stage-specific therapeutic options available. It is advisable (1) to counsel patients with low-risk PCa (PSA < 10 ng/ml and biopsy Gleason score 6 and cT1c–cT2a) or intermediate-risk PCa (PSA 10.1–20 ng/ml or biopsy Gleason score 7 or cT2b–c) in an interdisciplinary setting with an urologist and a radiation oncologist, (2) to discuss

neoadjuvant and adjuvant treatment options in patients with high-risk PCa (PSA < 20 ng/ml or biopsy Gleason score 8–10 or \geq cT3a) with members of a multidisciplinary tumour board, and (3) to thoroughly document which guidelines were used for the decision-making process if no multidisciplinary approach was possible.

It is usually impossible to state that one therapy is clearly superior over another because of the lack of randomised controlled trials in this field. However, based on the available literature, some recommendations can be made. **Table 3** presents a summary, subdivided by stage at diagnosis; a few suggestions follow regarding the different treatment options available.

Active surveillance

Active surveillance (AS) must be differentiated from WW. The latter is based on a delayed symptomatic noncurative treatment in patients who are not candidates for an aggressive local therapy, whereas the former must be seen as suitable therapy for those who might also be offered a

Table 4 Guidelines for staging of prostate cancer.

		GR
1	Local staging (T staging) of PCa is based on findings from DRE and possibly MRI. Further information is provided by the number and sites of positive prostate biopsies, the tumour grade, and the level of serum PSA Despite its high specificity in the evaluation of ECE and SVI, TRUS is limited by poor contrast resolution, resulting in low sensitivity and the tendency to understage PCa. Even with the advent of colour and power Doppler to assist in identifying tumour vascularity, the accuracy of TRUS in local staging remains inadequate. In comparison with DRE, TRUS, and CT, MRI demonstrates higher accuracy for the assessment of uni- or bilobar disease (T2), ECE and SVI (T3), as well as the invasion of adjacent structures (T4). However, the literature shows a wide range in the accuracy of T staging by MRI, from 50% to 92%. The addition of DCE-MRI can be helpful in equivocal cases. The addition of MRSI to MRI also increases accuracy and decreases interobserver variability in the evaluation of ECE. ^{33,34}	C C
2	Lymph node status (N staging) is only important when potentially curative treatment is planned. Patients with stage T2 or less, PSA < 10 ng/ml, a Gleason score ≤6, and <50% positive biopsy cores have <10% likelihood of having node metastases and can be spared nodal evaluation Given the significant limitations of preoperative imaging in the detection of small metastases (<5 mm), pelvic lymph node dissection remains the only reliable staging method in clinically localised PCa Currently, it seems that only methods of histologic detection of lymph node metastases with high sensitivity, such as sentinel lymph node dissection or extended pelvic lymph node dissection, are suitable for lymph node staging in PCa	B C
3	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-differentiated or moderately differentiated tumours In equivocal cases, 18F-fluorodeoxyglucose-PET or PET/CT could be of value, especially to differentiate active metastases and healing bones	B C

CT = computed tomography; DCE-MRI = dynamic contrast-enhanced MRI; DRE = digital rectal examination; ECE = extracapsular extension; GR = grade of recommendation; MRI = magnetic resonance imaging; MRSI = magnetic resonance spectroscopic imaging; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; SVI = seminal vesicle invasion; TRUS = transrectal ultrasound.

curative approach. Such patients with very low-risk PCa are initially not treated but are followed and treated with a curative intent if progression or the threat of progression occurs during follow-up.

AS was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined low-risk PCa based on early data^{42,43} demonstrating that men with well-differentiated PCa have a 20-year PCa-specific survival rate of 80–90%. Only data from non-mature randomised clinical trials of AS with follow-up <10 years are currently available to use as evidence for this approach.

According to recent data, men with low-risk PCa and a life expectancy >10 years are good candidates for AS, and only about 30% of men will require delayed radical intervention.⁴⁴ Men with a life expectancy >15 years are at a higher risk of dying from PCa (LE: 3).

Different series have identified several eligibility criteria for potential AS patients⁴⁵:

- Clinically confined PCa (T1–T2)
- Gleason score ≤6
- Three or fewer biopsies involved with cancer

- $\leq 50\%$ of each biopsy involved with cancer
- PSA < 10 ng/ml

Moreover, different criteria were applied to define cancer progression,^{45,46} although all groups used these criteria:

- A PSA DT with a cut-off ranging between ≤ 2 and ≤ 4 years
- Gleason score progression to ≥ 7 at rebiopsy, at intervals ranging from 1 to 4 years
- PSA progression > 10 ng/ml

However, the role of PSA DT to identify the need for intervention was recently challenged.⁴⁷ In a cohort of 290 men who underwent AS for low-risk PCa, 35% developed biopsy progression (Gleason score ≥ 7 , more than two positive cores, or $> 50\%$ core involvement). PSA DT was not significantly associated with biopsy progression ($p = 0.83$); nor was PSAV ($p = 0.06$). In another study, 36% of men under AS demonstrated disease progression on rebiopsy.⁴⁸ The 5-year progression-free probability was 82% for patients with a negative first repeat biopsy compared with 50% for patients with a positive rebiopsy. Both trials underline the need for annual surveillance rebiopsies to monitor men adequately under AS independent of the results of PSA DT.

Conservative management in locally advanced prostate cancer

The literature reporting on deferred treatment for locally advanced PCa is sparse. In a recent prospective randomised clinical phase 3 trial (EORTC 30981), 985 patients with T0–4 N0–2 M0 PCa not eligible for local treatment with curative intent were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic disease progression or occurrence of serious complications.⁴⁹ After a median follow-up of 7.8 years, immediate ADT resulted in a modest but statistically significant increase in overall survival (OS) but no significant difference in PCa mortality or symptom-free survival. The time from randomisation to progression of hormone-refractory disease did not differ significantly. The median time to the start of deferred treatment after study entry was 7 years. In this group, 126 patients (25.6%) died without ever receiving treatment (44% of the deaths in this arm). Furthermore, the authors identified significant risk factors associated with a significantly worse outcome⁵⁰: In both arms, patients with a baseline PSA > 50 ng/ml were at a > 3.5 -fold higher risk of dying of PCa than patients with a baseline PSA ≤ 8 ng/ml. If the baseline PSA was between 8 ng/ml and 50 ng/ml, the risk of PCa death was approximately 7.5-fold higher in patients with a PSA DT < 12 months than in patients with a PSA DT > 12 months. The time to PSA relapse following a response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA may also reflect disease aggressiveness.

Radical prostatectomy

RP is the only treatment for localised PCa that has shown a cancer-specific survival benefit when compared with WW in a prospective randomised trial.^{51,52} Most of the patients recruited were of intermediate risk and did not harbour screen-detected PCa, so these data cannot be automatically transferred into daily routine practice. Nerve-sparing RP represents the approach of choice in all men with a normal erectile function and organ-confined disease. The need for and the extent of pelvic lymphadenectomy is controversial. The risk of lymph node involvement is low in men with low-risk PCa and $< 50\%$ positive biopsy cores.⁵³ In men with intermediate- and high-risk PCa, an extended pelvic lymphadenectomy should always be performed.⁵⁴

Management of cT3 PCa primarily has to be a multimodal-ity approach due to the high likelihood of positive lymph nodes and/or positive resection margins.^{55–60} Overstaging of cT3 PCa is relatively frequent and occurs in 13–27% of cases.^{55,56} The problem remains the selection of patients before surgery who have neither lymph node involvement nor seminal vesicle invasion (SVI). Nomograms including PSA level, stage, and Gleason score can be useful in predicting the pathologic stage of disease.⁵⁸ RP for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable and to improve oncologic outcome with excellent 5-, 10- and 15-year cancer-specific survival rates of 95%, 90%, and 79%, respectively.^{59,60}

Neoadjuvant androgen deprivation does not provide a significant advantage in OS and progression-free survival and therefore has no role in the surgical treatment of PCa.⁶¹

Adjuvant ADT following RP has always been controversial.⁶² Although the only prospective randomised trial demonstrated a significant survival advantage for immediate ADT in node-positive disease,⁶³ it has to be acknowledged that most patients had gross nodal disease and that 70% also had positive margins and/or SVI. It is not known if adjuvant ADT in patients with minimal nodal involvement will result in the same positive results. The most recent update on the Early Prostate Cancer trial has shown no benefit to OS by adding bicalutamide 150 mg/day to standard care.⁶⁴ In a recent retrospective analysis of the Surveillance Epidemiology and End Results databank, 731 men who underwent RP between 1991 and 1999 were identified with positive lymph nodes; 209 of them received adjuvant ADT.⁶⁵ There was no statistically significant difference in OS between the adjuvant ADT and non-ADT group, and there was no statistically significant survival difference with 90, 150, 180, and 365 days as the adjuvant ADT definition.

In patients with microscopic lymph node involvement only, no final recommendations can be made.

Adjuvant external-beam radiation therapy for pT3 or pTxR1 prostate cancer

Three prospective randomised trials have assessed the role of immediate postoperative radiotherapy. Although different in inclusion criteria, all trials concluded that immediate

postoperative radiotherapy significantly improves 5-year clinical or biologic survival by about 20% ($p < 0.0001$).^{66–68} Immediate postoperative radiotherapy proved to be well tolerated with a risk of grades 3–4 urinary toxicity in $\leq 3.5\%$.

The updated results of the Southwest Oncology Group 8794 trial⁶⁹ with a median follow-up of 11.5 years showed that adjuvant radiation significantly improved 15-year metastasis-free survival (46% vs 38%; $p = 0.036$) and OS (47% vs 37%; $p = 0.053$) compared with delayed radiotherapy. Table 2a summarises the guidelines on radical prostatectomy.

Thus for patients classified as T1–2 N0 (or T3 N0 with selected prognostic factors), pT3 pN0 with a high risk of local failure after RP due to positive margins, and/or SVI and negative PSA, two options can be offered within the frame of an informed consent:

- *Either* an immediate radiotherapy with 60–64 Gy to the surgical bed^{66–68} upon recovery of urinary function
- *Or* clinical and biologic monitoring followed by salvage radiotherapy with at least 66 Gy ideally when the PSA rises but does not exceed 0.5 ng/ml.

Radiation therapy

Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard, and intensity-modulated radiotherapy (IMRT), an optimised form of 3D-CRT, is becoming more widely used as is image-guided radiotherapy. Table 2b summarises the guidelines on radiation therapy in prostate cancer.

For external radiotherapy, a dose of at least 74 Gy is recommended for the management of low-risk PCa because biochemical disease-free survival is significantly higher when compared with a dose < 72 Gy (69% vs 63%; $p = 0.046$).⁷¹

For intermediate-risk PCa, many series have shown a significant impact of dose escalation on 5-year progression-free survival in cT1c–T3 PCa, with a dose ranging from 76 to 81 Gy.⁷²

In patients with high-risk disease, external irradiation with dose escalation improves 5-year biochemical disease-free survival⁷³ but seems insufficient to cover the risk of systemic relapse. For intermediate and highly localised PCa, a combination of external irradiation with 6 months of ADT resulted in a 13% improvement in the 8-year OS rate ($p < 0.001$).^{70,73} For locally advanced PCa, the data of the EORTC-22961 trial demonstrated a 4.7% benefit in OS after a median follow-up of 5.2 year in favour of 3-year ADT when compared with short-term ADT.⁷⁰

Therefore, concomitant (with or without neoadjuvant) and adjuvant ADT for 3 years is mandatory and represents the current standard in the radiotherapeutic management of high-risk PCa.

Various prospective randomised trials have evaluated the oncologic efficacy of ADT with or without external-beam radiation therapy (EBRT).^{74–76} The Scandinavian Prostate Cancer Group-7 trials included 875 men with locally advanced PCa who were randomly assigned to endocrine treatment or to ADT with EBRT at a dose of at least 70 Gy.⁷⁴

After a median follow-up of 7.6 years, the cancer-specific mortality was significantly higher in the ADT arm (23.9 vs 11.9%) as was the overall mortality (39.4% vs 29.6%) and the PSA failure rate (74.7% vs 25.5%; $p < 0.0001$). Two prospective randomised clinical trials with regard to the same issue were recently presented as abstracts.^{75,76} A Canadian study randomised 1205 men with locally advanced PCa to receive ADT or ADT with EBRT at a dose of 65–69 Gy.⁷⁵ After a median follow-up of 6 years, the addition of EBRT significantly reduced the risk of death (hazard ratio: 0.77; $p = 0.033$) with a 10-year cumulative disease-specific death rate of 15% vs 23%. A French study randomised 263 patients with locally advanced PCa to receive ADT or ADT and EBRT.⁷⁶ At a minimum follow-up of 5 years, the combined treatment achieved significantly superior results with regard to progression-free survival (60.9% vs 8.5%; $p = 0.001$), locoregional progression (9.7% vs 29%; $p = 0.0002$), and metastatic progression (3% vs 10.8%; $p = 0.018$).

Transperineal low-dose rate brachytherapy

Transperineal brachytherapy is a safe and effective technique for low-risk PCa. There is consensus on the following eligibility criteria⁷⁷:

- Stage cT1c–T2a N0, M0
- A Gleason score ≤ 6 assessed on a sufficient number of random biopsies
- An initial PSA level of ≤ 10 ng/ml
- $\leq 50\%$ of biopsy cores involved with cancer
- A prostate volume of < 50 ml
- A good International Prostate Symptom Score

Results of permanent implants have been reported from different institutions with a median follow-up ranging between 36 and 120 months.^{78,79} Recurrence-free survival after 5 and 10 years was reported to range from 71% to 93% and from 65% to 85%, respectively. There is no benefit in adding neoadjuvant or adjuvant ADT to low-dose rate brachytherapy.³⁷

Irradiation to the pelvic lymph nodes

With regard to the potential benefit of irradiation of the pelvic lymph nodes in men with high-risk localised PCa, the Groupe d'Etude des Tumeurs Uro-Génitales trial randomly assigned 444 patients to receive EBRT to the prostate (66–70 Gy) or to the prostatic bed and the pelvic lymph nodes (46 Gy).⁷⁹ The 5-year progression-free survival and OS were similar in both arms, so there is no general indication for irradiation to the pelvic lymph nodes.

Innovative techniques

Intensity-modulated radiotherapy enables radiation oncologists to increase radiation doses homogeneously, up to as much as 86 Gy within the target volume, while respecting the tolerance doses in organs at risk.

The Memorial Sloan-Kettering Cancer Centre has the largest experience with this technique, and its results have now been updated, reporting on disease control and toxicity in two cohorts of patients.^{80,81}

In the first cohort, 561 patients with organ-confined disease were treated with a dose of 81 Gy. The 8-year actuarial PSA relapse-free survival rates for patients in favourable-, intermediate-, and unfavourable-risk groups were 85%, 76%, and 72%, respectively, according to the then-current American Society for Radiation Oncology definition.

In the second cohort, 478 patients with organ-confined disease were treated with a dose of 86.4 Gy. The 5-year actuarial PSA relapse-free survival according to the nadir plus 2 ng/ml definition was 98%, 85%, and 70% for the low-, intermediate-, and high-risk groups, respectively.

Proton beam and carbon ion beam therapy

In theory, proton beams are an attractive alternative to photon beam radiotherapy for PCa because they deposit almost all of the radiation dose at the end of the particle's path in tissue (the Bragg peak) in contrast to photons that deposit radiation along their path. Additionally, there is a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

Only one randomised trial that incorporated proton therapy in one arm has recently reported long-term results.^{82,83} The Proton Radiation Oncology Group 9509 trial randomly

assigned 393 men with clinically localised PCa to receive EBRT with 70.2 Gy vs 79.2 Gy of combined photon and proton radiation. At a median follow-up of 9.4 year, the estimated 10-year biochemical progression rate for patients receiving the standard dose was 32% compared with 17% for patients receiving the high dose ($p < 0.001$). PCa symptom indices did not differ significantly between both groups with regard to urinary obstruction/irritation (23.3 vs 24.6; $p = 0.36$), urinary incontinence (10.6 vs 9.7; $p = 0.99$), bowel problems (7.7 vs 7.9; $p = 0.70$), and sexual dysfunction (68.2 vs 65.9; $p = 0.65$). However, a prospectively randomised trial using equivalent doses of IMRT and photon radiation will be needed to evaluate the oncologic efficacy of photons.

Follow-up of prostate cancer patients

Patients diagnosed with PCa who underwent local treatment with curative intent are usually followed for at least 10 years or until advanced age makes follow-up superfluous (Table 5). Determination of serum PSA together with a disease-specific history can be supplemented by DRE if locally recurrent disease is suspected.

Alternative local treatment options of prostate cancer

In addition to RP, EBRT, and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focussed ultrasound (HIFU) have emerged as alternative

Table 5 Guidelines for follow-up after primary treatment with curative intent.

	GR
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	B
After radical prostatectomy, a serum PSA level >0.2 ng/ml can be associated with residual or recurrent disease	B
After radiation therapy, a rising PSA level >2 ng/ml above the nadir PSA, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease	B
Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence	B
Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases TRUS and biopsy are not necessary before second-line therapy	B
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	C
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	B

CT=computed tomography; DRE=digital rectal examination; GR=grade of recommendation; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; TRUS=transrectal ultrasound.

therapeutic options in patients with clinically localised PCa who are not suitable for RP.^{84,85} However, at the time of writing, data from HIFU were not extensive enough to be considered in treatment recommendations. Applying the Grading of Recommendations Assessment, Development and Evaluation approach, the available evidence on the efficacy and safety of HIFU in PCa is of very low quality, mainly because the study designs lack control groups. More research is needed to explore the use of HIFU in PCa. The following factors might be indications: low- or intermediate-risk PCa and prostate size <40 ml at the time of therapy.

Long-term results are lacking, and 5-year biochemical progression-free rates are inferior to those achieved by RP in low-risk patients. Patients must be informed accordingly. The results of a randomised trial of EBRT vs CSAP in patients with clinically localised PCa were published recently and were promising.⁸⁶ Two hundred and forty-four men with low- and intermediate-risk PCa were assigned to both treatment arms, and all men received neoadjuvant ADT. After a median follow-up of 100 months, there were no differences with regard to disease progression at 36 months, OS, and disease-specific survival. Positive results might be due to the fact that neoadjuvant ADT was delivered and that both arms and patient numbers were too small to draw significant clinical conclusions.

Summary

The present text represents a summary, and for more detailed information and a full list of references, we refer you to the full-text version. These EAU guidelines (ISBN 978-90-79754-70-0) are available at the EAU Web site (www.uroweb.org).

Author contributions: Axel Heidenreich had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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