Guidelines

EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent—Update 2013

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Abstract

Context: The most recent summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCA) was published in 2011.

Objective: To present a summary of the 2013 version of the EAU guidelines on screening, diagnosis, and local treatment with curative intent of clinically organ-confined PCA.

Evidence acquisition: A literature review of the new data emerging from 2011 to 2013 has been performed by the EAU PCa guideline group. The guidelines have been updated, and levels of evidence and grades of recommendation have been added to the text based on a systematic review of the literature, which included a search of online databases and bibliographic reviews.

Evidence synthesis: A full version of the guidelines is available at the EAU office or online (www.uroweb.org). Current evidence is insufficient to warrant widespread population-based screening by prostate-specific antigen (PSA) for PCA. Systematic prostate biopsies under ultrasound guidance and local anesthesia are the preferred diagnostic method. Active surveillance represents a viable option in men with low-risk PCA and a long life expectancy. A biopsy progression indicates the need for active intervention, whereas the role of PSA doubling time is controversial. In men with locally advanced PCA for 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 recommended mostly for patients with localized disease and a long life expectancy, with radical prostatectomy (RP) shown to be superior to WW in prospective randomized trials. Nerve-sparing RP is the approach of choice in organ-confined disease, while neoadjuvant ADT provides no improvement in outcome variables. Radiation therapy should be performed with >74 Gy in low-risk PCA and 78 Gy in intermediate- or high-risk PCA. For locally advanced disease, adjuvant ADT for 3 yr results in superior rates for disease-specific and overall survival and is the treatment of choice. Follow-up after local therapy is largely based on PSA and a disease-specific history, with imaging indicated only when symptoms occur.

Conclusions: 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.

Patient summary: A summary is presented of the 2013 EAU guidelines on screening, diagnosis, and local treatment with curative intent of clinically organ-confined prostate cancer (PCA). Screening continues to be done on an individual basis, in consultation with a physician. Diagnosis is by prostate biopsy. Active surveillance is an option in low-risk PCA and watchful waiting is an alternative to androgen-deprivation therapy in locally advanced PCA not requiring immediate local treatment. Radical prostatectomy is the only surgical option. Radiation therapy can be external or delivered by way of prostate implants. Treatment follow-up is based on the PSA level.

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1. **Introduction**

The most recent summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2011 [1]. The aim of this paper is to present a summary of the 2013 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].

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 cancer [3]. PCa affects elderly men more often and therefore is a bigger health concern in developed countries. Approximately 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 per 1000 in Malta to 182 per 1000 in Belgium [4].

3. **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, ethnic origin, 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 by 5–11 times [5]. Approximately 9% of individuals with PCa have true hereditary PCa, defined as three or more relatives affected or at least two relatives who have developed early-onset disease, that is, disease before 55 yr of age.

Exogenous factors, such as food consumption, pattern of sexual behavior, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation [6], and occupational exposure, might also be involved in the development of clinical PCa. None of the prospective randomized trials performed has produced level 1 evidence to justify recommending lifestyle changes. However, the prospective randomized Selenium and Vitamin E Cancer Prevention Trial (SELECT) included 35 533 men with prostate-specific antigen (PSA) ≤4 ng/ml and randomized the men in the four arms to be treated with either selenium, vitamin E, selenium plus vitamin E, or placebo, with a reduction in the development of PCa as the primary end point [7]. After a follow-up of 7 yr, a significantly elevated risk of PCa was observed in the vitamin E treatment arm (hazard ratio [HR]: 1.17; 95% confidence interval [CI], 1.004–1.136; \( p = 0.008 \)). Treatment with selenium was not found to prevent PCa, but there was no significant increase in the development of PCa.

4. **Classifications**

The Union Internationale Contre le Cancer 2010 TNM classification is used throughout these guidelines [8].

The Gleason score is the recommended methodology 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—there is no 5% rule [9]. In radical prostatectomy (RP) specimens, both the primary and secondary Gleason grades are to be reported. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported.

5. **Prostate cancer screening**

There is currently no evidence for introducing widespread population-based screening programs for early PCa detection in all men [10] (LE: 2). To evaluate the efficacy of PCa screening, two large randomized trials have been published: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the United States and the European Randomized Study of Screening for Prostate Cancer (ERSPC) in Europe [11,12] (LE: 1b).

The PLCO cancer-screening trial randomly assigned 76 693 men to receive either annual screening with PSA and digital rectal examination (DRE) or standard care as the control [11]. After 7 yr of follow-up, 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 yr of age [12]. The men were randomly assigned to a group offered PSA screening at an average of once every 4 yr or to an unscreened control group. During a median follow-up of 9 yr, 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 result 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 (LE: 1b). In an update of the ERSPC trial, after a mean follow-up of 11 yr, the number of men needing to be screened decreased to 1055, and the number needing treatment decreased to 37 [13]. In an update of the Göteborg section of the ERSPC trial, which included 20 000 men, the authors reported a relative risk (RR) reduction of 50% in PCa mortality after a median follow-up of 14 yr. However, this finding was accompanied by a substantial risk of overdiagnosis [14]. Based on these data, the real benefit of the ESRC trial will be evident only after 10–15 yr of follow-up, particularly because of the impact of the 41% reduction in metastasis in the screening arm.

In a recent retrospective analysis, the PCa incidence, PCa metastasis, and cause of death were compared between 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-yr observation period [11]. The RR of PCa metastasis in the screened 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 (0.63, \( p = 0.008 \)). The absolute mortality reduction was 1.8 deaths per 1000 men.

Both trials have received considerable attention and comments, which were addressed extensively in the previous edition of the EAU guidelines on PCa [1].

Based on the results of these two large randomized 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 also section 6). Two key questions remain open and empirical: (1) At what age should early detection start? (2) What is the interval for PSA and DRE?

The decision to undergo early PSA testing should be shared between the patient and his physician based on information balancing the test’s advantages and disadvantages. A position paper of the EAU recently suggested a baseline PSA determination at age 40, on which the subsequent screening interval may then be based [12] (GR: B). A screening interval of 8 yr might be enough in men with initial PSA levels \( \leq 1 \) ng/ml [12–14]. Further PSA testing is not necessary in men >75 yr and with a baseline PSA \( \leq 3 \) ng/ml because of their very low risk of dying from PCa [15]. This type of risk-adapted screening has been supported by a case–control study comprising 21 277 men (27–52 yr) who provided a baseline PSA in 1974–1984 and 4922 men who were invited to provide a second PSA 6 yr later [16].

There was an association between the risk of death from PCa and the baseline PSA: 44% (95% CI, 34–53) of deaths occurred in men with a PSA concentration in the highest 10th percentile of the distribution of concentrations at ages 45–49 (\( \geq 1.6 \) µg/l), with a similar proportion for the highest 10th percentile at ages 51–55 (\( \geq 2.4 \) µg/l: 44%; 95% CI, 32–56). Although a 25- to 30-yr risk of PCa metastasis could not be ruled out by concentrations below the median at ages 45–49 (0.68 µg/l) or 51–55 (0.85 µg/l), the 15-yr risk remained low at 0.09% (95% CI, 0.03–0.23) at 45–49 yr and 0.28% (95% CI, 0.11–0.66) at 51–55 yr, suggesting that longer intervals between screening would be appropriate in this group.

6. Diagnosis and staging of prostate cancer

The main tools to diagnose PCa include DRE, serum concentration of PSA, and transrectal ultrasound (TRUS)-guided biopsy. In approximately 18% of all patients, PCa is detected by a PCa-suggestive finding on DRE alone, regardless of the PSA level [17] (LE: 2a). A suspect DRE in patients with a PSA level of\( \leq 2 \) ng/ml has a positive predictive value of 5–30% [18] (LE: 2a). A PSA cut-off of 3 or 3.1 µg/l should be considered for World Health Organization–calibrated assays to achieve the same sensitivity and specificity profile found with a cut-off of 4 µg/l in traditionally calibrated assays [19]. The cut-offs for the ratio of free to total PSA (%fPSA) can be retained.

The level of PSA is a continuous parameter: The higher the value, the more likely is the existence of PCa. The finding that many men may harbor PCa despite low levels of serum PSA has been underscored by recent results from a US prevention study [20] (Table 1) (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, which may improve the specificity of PSA in the early detection of PCa. These modifications include PSA density, PSA density of the transition zone, age-specific reference ranges, and PSA molecular forms.

In a prospective multicenter trial, PCa was found on biopsy in 56% of men with %fPSA < 0.10 but in only 8% of men with %fPSA > 0.25 [10] (LE: 2a). These data have been confirmed in a recent screening test including 27 730 men with a serum PSA concentration between 2.1 and 10 ng/ml [21]. Using %fPSA, the number of unnecessary biopsies decreased significantly and the detection rate of PCa increased significantly, so %fPSA should be routinely considered in every patient with suspicious findings.

The concepts of PSA velocity (PSA-V) and PSA doubling time (PSA-DT) have limited use in the diagnosis of PCa because of several unresolved issues. Prospective studies have not shown that these measurements can provide additional information compared with PSA alone [22,23].

In contrast to the serum markers previously discussed, the biomarker PCA3 is measured in urine sediment obtained after prostatic massage [24]. Determination of this PCa-specific RNA is experimental. At a population level, this method appears to be helpful, but its impact at the level of the individual patient remains highly questionable. So far, none of the biomarkers can be used to counsel an individual patient on the need to perform a prostate biopsy to rule out PCa. The molecular marker may help in the decision-making process with regard to a repeat biopsy in men with a negative first biopsy but a persistent suspicion of PCa [25,26]. 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 %fPSA < 10%, the PCA3 score was identified as a significant predictor of PCa. However, in men with %fPSA 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.

Ultrasound-guided transrectal or transperineal laterally directed 18G core biopsy has become the standard way to obtain material for histopathologic examination [27,28]. The need for prostate biopsies should be determined on the basis of the PSA level, a suspicious DRE, the patient’s biologic age, potential comorbidities, and the therapeutic consequences. The first elevated PSA level should not

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

<table>
<thead>
<tr>
<th>PSA level, ng/ml</th>
<th>Risk of PCAs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.5</td>
<td>6.6</td>
</tr>
<tr>
<td>0.6–1</td>
<td>10.1</td>
</tr>
<tr>
<td>1.1–2</td>
<td>17.0</td>
</tr>
<tr>
<td>2.1–3</td>
<td>23.9</td>
</tr>
<tr>
<td>3.1–4</td>
<td>26.9</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; PCa = prostate cancer.
prompt an immediate biopsy. The level should be verified after a few weeks by the same assay under standardized conditions, except for high PSA values (>20 ng/ml), after prostatitis has been excluded.

At a glandular volume of 30–40 ml, at least 10–12 cores should be sampled [29] (LE: 2a). More than 12 cores are not significantly more conclusive [29] (LE: 1a). Oral or intravenous quinolones are state-of-the-art preventive antibiotics, although increasing frequencies of resistance have to be reported [31] and have been associated with ciprofloxacin superior to ofloxacin [30] (LE: 1b). In the last few years, increased resistance to antibiotics, with ciprofloxacin superior to ofloxacin [30] (LE: 1b). Transition zone biopsies are not recommended in the first set of biopsies because of low detection rates. One set of repeat biopsies is warranted in cases with persistent indication for prostate biopsy (abnormal DRE, elevated PSA, ASAP, multifocal PIN) [33]. Based on these findings, the need to obtain culture results of prebiopsy rectal swabs to identify the most appropriate antibiotic has been raised by recent studies. Oral or intravenous quinolones are state-of-the-art preventive antibiotics, although increasing frequencies of resistance have to be considered [31].

<table>
<thead>
<tr>
<th>Guideline</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. An abnormal DRE result or elevated serum PSA measurement could indicate PCa. The exact cut-off level for what is considered to be a normal PSA value has not been determined, but values of approximately &lt;2–3 ng/ml are often used for younger men.</td>
<td>C</td>
</tr>
<tr>
<td>2. The diagnosis of PCa depends on histopathologic confirmation.</td>
<td>B</td>
</tr>
<tr>
<td>3. Biopsy and further staging investigations are indicated only if they affect the management of the patient.</td>
<td>C</td>
</tr>
<tr>
<td>4. TRUS-guided systemic biopsy with ≥10 systemic, laterally directed cores is recommended, with perhaps more cores in prostates with a volume &gt;40 ml.</td>
<td>B</td>
</tr>
<tr>
<td>5. Recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on the individual patient.</td>
<td>C</td>
</tr>
<tr>
<td>6. Transrectal periprostatic injection with a local anesthetic agent is to be offered to patients as effective analgesia when undergoing prostate biopsies.</td>
<td>A</td>
</tr>
<tr>
<td>7. Oral or intravenous quinolones are state-of-the-art preventive antibiotics, although increasing frequencies of resistance have to be considered.</td>
<td>A</td>
</tr>
</tbody>
</table>

Table 2 – Guidelines for the diagnosis of prostate cancer

ASAP = atypical small acinar proliferation in the prostate; DRE = digital rectal examination; GR = grade of recommendation; PIN = prostatic intraepithelial neoplasia; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

adopted in 2005 [38,39] should be reported. A diagnosis of Gleason score ≤4 should not be given on prostate biopsies [31]. The proportion (percentage) or length (in millimeters) of tumor involvement per biopsy [37,38] and, if present, extraprostatic extension should be recorded. The presence of high-grade PIN and perineural invasion are usually reported.

The extent of a small, focus of adenocarcinoma that is located in only one of the biopsies should be clearly stated (eg, <1 mm or <1%), as it might be an indication for further diagnostic work-up of the specimen or a rebiopsy before selecting therapy [38].

The decision to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking the patient’s preference, age, and comorbidity into consideration [40–45]. Procedures that do not affect the treatment decision can usually be avoided. A short summary of the guidelines on diagnosis and staging of PCa is presented in Tables 2 and 3.

7. Primary local treatment of prostate cancer

The therapeutic management of PCa, even clinically localized disease, has become increasingly complex because of the various stage-specific therapeutic options available. It is therefore advisable to do the following:

- 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 a urologist and a radiation oncologist.
- Discuss neoadjuvant and adjuvant treatment options in patients with high-risk PCa (PSA <20 ng/ml or biopsy Gleason score 8–10 or ≥cT3a) in a multidisciplinary tumor board.
- Thoroughly document which guidelines have been used for the decision-making process if no multidisciplinary approach was possible.
Table 3 – Guidelines for staging of prostate cancer

<table>
<thead>
<tr>
<th>Guideline</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Local staging (T staging) of PCa is based on MRI. Further information is provided by the number and sites of positive prostate biopsies, the tumor grade, and the level of serum PSA.</td>
<td>C</td>
</tr>
<tr>
<td>2. Lymph node status (N staging) need be assessed only when potentially curative treatment is planned.</td>
<td>B</td>
</tr>
<tr>
<td>Patients with stage &lt;T2, PSA &lt;10 ng/ml, a Gleason score ≤6, and &lt;50% positive biopsy cores have a &lt;10% likelihood of having node metastases and can be spared nodal evaluation.</td>
<td>B</td>
</tr>
<tr>
<td>In clinically localized intermediate- and high-risk PCa, staging must be done by pelvic lymph node dissection, since it is the only reliable staging method, given the significant limitations of preoperative imaging in the detection of small (&lt;5-mm) metastases.</td>
<td>B</td>
</tr>
<tr>
<td>In equivocal cases, 18F-fluorodeoxyglucose PET or PET/CT could be of value, especially to differentiate active metastases and healing bones.</td>
<td>C</td>
</tr>
</tbody>
</table>

CT = computed tomography; GR = grade of recommendation; MRI = magnetic resonance imaging; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

7.1. Low-risk prostate cancer

7.1.1. Active surveillance

Active surveillance (AS) represents a suitable therapy for patients who might also be offered a 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 [46,47] demonstrating that men with well-differentiated PCa have a 20-yr PCa-specific survival rate of 80–90%.

The most advanced cohort to date, reported by Klotz et al. [48], included 450 patients with clinical stage T1c or T2a, PSA <10 ng/ml, and Gleason score ≤6 (PSA <15), with patients >70 yr of age having a Gleason score ≤7 (3 + 4). Initially, six biopsies were performed, followed by the usual extended 12-core protocol during the study. At a median follow-up of 6.8 yr, the 10-yr overall survival was 68%. At 10 yr, the disease-specific survival was 97.2%, with 62% of men still alive on AS. Subsequently, 30% of patients underwent a radical treatment for the following reasons: 48% for a PSA-DT <3 yr, 27% for Gleason score progression on repeat biopsies, and 10% because of patient preference. A variety of additional studies on AS in clinically organ-confined disease have now been published [49] and have confirmed a low rate of progression and cancer-specific death in well-selected patients with very-low-risk disease. However, an extended follow-up is necessary to obtain definitive results. Thus, AS might mean no treatment at all for patients >70 yr or patients with a life expectancy >10 yr, while AS in younger patients might mean a possible treatment delayed for years. The repeated biopsies that are part of AS might then become important for their potential adverse effect on nerve preservation if surgery is subsequently considered.

Different series have identified several eligibility criteria for potential AS patients [49]:

- Clinically confined PCa (T1–T2)
- Gleason score ≤6
- Three or fewer biopsies involved with cancer
- ≤50% of each biopsy involved with cancer
- PSA <10 ng/ml.

Different criteria were applied to define cancer progression [49], although most groups used the following criteria:

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

However, the role of PSA-DT in identifying the need for intervention has recently been challenged [50–52]. In a cohort of 290 men who underwent AS for low-risk PCa, 35% of the men developed biopsy progression (Gleason score ≥7, more than two positive cores, or >50% core involvement). The PSA-DT was not significantly associated with biopsy progression (p = 0.83), nor was the PSA-V (p = 0.06).

In another study, 36% of men under AS demonstrated disease progression on rebiopsy [51]. The 5-yr progression-free probability was 82% for patients with a negative first repeat biopsy, compared with 50% for patients with a positive rebiopsy [52]. Both trials underline the need for surveillance rebiopsies at 1 and 4yr to adequately monitor men under AS, independent of the results of PSA-DT [53].

7.1.2. Radical prostatectomy

RP is the only surgical treatment for localized PCa. The treatment has shown a cancer-specific survival benefit in a subset of patients compared with WW in two prospective randomized trials [54,55]. No such trials are available for the alternative treatment options. Most of the recruited patients had low- to intermediate-risk PCa and did not harbor screen-detected PCa, so these data cannot be automatically translated into daily routine clinical practice.

Between 1989 and 1999, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomized 695 patients with clinical stage T1–T2 to WW or RP [54]. This study began after PSA screening had been introduced into clinical practice, but was diagnosing only 5% of men with PCa. After a median follow-up of 12.8 yr, this study showed a significant decrease in cancer-specific mortality, overall
mortality, metastatic risk progression, and local progression in patients treated with RP compared with WW (LE: 1b).

Subgroup analysis showed that the difference was not modified by PSA level (<10 or >10 ng/ml) or by the Gleason score (≥7) at the time of diagnosis. However, the patient’s age at the time of randomization had a profound impact, with the benefit in overall survival and metastasis-free survival being seen only in men <65 yr of age. A further subgroup analysis by Vickers et al. [56] demonstrated a wide variation in individualized predictions of surgery benefit, depending on age and tumor characteristics. At 65 yr, the absolute 10-yr risk reduction in PCa mortality attributable to RP ranged from 4.5% to 17.2% for low-risk compared with high-risk patients, respectively. The use of surgery was associated with minimal benefit much beyond the age of 70 yr. These findings suggest that it is hard to justify surgery in patients with Gleason 6, T1 disease or in patients much older than 70 yr. Conversely, surgery seems to benefit patients with Gleason 8 or Gleason 7 stage T2.

These findings are limited by the fact that estimates from SPCG-4 have to be applied cautiously to contemporary patients.

The Prostate Cancer Intervention Versus Observation Trial recruited 731 men with clinically organ-confined PCa (cT1c–2N0M0, PSA <50 ng/ml, age <75 yr, life expectancy >10 yr) to treatment with either RP or WW [55]. Only 50% of men had a nonpalpable PCA, compared with 12% of patients in the SPCG-4 trial [20]. After a mean follow-up of 10 yr, there were no statistically significant differences between both treatment arms in mortality (47% vs 49.9%, respectively; p = 0.22) and PCa-specific survival (5.8% vs 8.4%, respectively; p = 0.09). There were also no statistically significant differences concerning overall survival between both treatment groups when considering patient age, Gleason score, performance status, and Charlson comorbidity score. Only patients with a pretreatment PSA serum concentration >10 ng/ml or high-risk PCA experienced a significant benefit in overall survival, with an RR reduction in mortality of 33% (p = 0.02) and 31% (p < 0.01), respectively. The pooled analysis identified an RR reduction and an absolute risk reduction of 31% and 10.5%, in patients with intermediate- or high-risk PCA, respectively (p < 0.01). Patients who underwent RP also experienced a statistically significant reduction in the development of bone metastases (4.7% vs 10.6%, p < 0.01).

In conclusion, a benefit of RP compared with WW was achieved only in patients with an intermediate or high risk of progression who were <65 yr, whereas RP in classic low-risk PCa patients did not demonstrate an advantage with regard to overall survival and metastasis-specific survival. The benefits of this trial are limited because survival estimates can be applied only cautiously to contemporary patients.

Nerve-sparing RP represents the approach of choice in all men with normal erectile function and organ-confined disease. Robot-assisted laparoscopic RP (RALP) is displacing RP as the gold standard surgical approach for clinically localized PCa in the United States and is also being increasingly used in Europe. This trend has occurred despite the lack of high-quality evidence to support its superiority over more established treatment modalities. Recent in-depth systematic reviews of the literature have compared the results of retropubic RP and RALP. Positive surgical margin rates are at least equivalent to robot-assisted RP (RARP), but firm conclusions about biochemical recurrence and other oncologic end points are difficult to draw because of the relatively short follow-up in the published literature and limited experience with RARP in locally advanced PCa. RARP may offer advantages in postoperative recovery for urinary continence and erectile function, although most published studies addressing these outcomes have methodological limitations [57–60].

The need for and the extent of pelvic lymphadenectomy are discussed controversially. The risk of lymph node involvement is low in men with low-risk PCa and <50% positive biopsy cores [61–63].

Guidelines and recommendations for RP are given in Table 4.

7.1.3. Radiation therapy and low-dose-rate brachytherapy

Three-dimensional conformal radiation therapy (3D-CRT) remains the gold standard in external-beam radiation therapy (EBRT) in many countries and institutions. However, image-guided intensity-modulated radiation therapy (IMRT), which is an optimized form of 3D-CRT using implanted fiducial markers in the prostate, should become the standard treatment of choice based on 11 published studies including 4559 patients with clinically localized PCA [64]. IMRT is being more widely used because of its ability to escalate dosage without increasing acute and/or late

### Table 4 – Guidelines and recommendations for radical prostatectomy

<table>
<thead>
<tr>
<th>Indications</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with low- and intermediate-risk localized PCa (cT1a–T2b and Gleason score 6–7 and PSA &lt;20) and a life expectancy &gt;10 yr</td>
<td>1b</td>
</tr>
<tr>
<td>Patients with stage T1a disease and a life expectancy &gt;15 yr or Gleason score 7</td>
<td>1b</td>
</tr>
<tr>
<td>Selected patients with low-volume, high-risk, localized PCa (cT3a or Gleason score 8–10 or PSA &gt;20 ng/ml)</td>
<td>3</td>
</tr>
<tr>
<td>Highly selected patients with very high-risk localized PCa (cT3b–T4N0 or any TN1) in the context of multimodality treatment</td>
<td>3</td>
</tr>
<tr>
<td>Short-term (3-mo) or long-term (9-mo) neoadjuvant therapy with gonadotrophin releasing-hormone analogs is not recommended in the treatment of clinically localized low-risk or high-risk PCa.</td>
<td>1a</td>
</tr>
<tr>
<td>Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c and Gleason score &lt;7 and PSA &lt;10 ng/ml).</td>
<td>3</td>
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<tr>
<td>Unilateral nerve-sparing procedures are an option in stage T2a–T3a disease.</td>
<td>4</td>
</tr>
</tbody>
</table>

LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen.
In localized PCa (T1c–T2aN0M0), 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention.

For high-risk patients, long-term ADT before and during RT is recommended, as it results in increased overall survival.

In patients with locally advanced PCa (T3–T4AN0M0) who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT. The use of ADT alone is inappropriate.

Transperineal brachytherapy with permanent implants is an option for patients with cT1–T2a, Gleason score ≤7a, PSA < 10 ng/ml, prostate volume < 50 ml, without a previous TURP and with a good IPSS.

Immediate postoperative external irradiation after RP for patients with pathologic tumor stage T3N0M0 improves biochemical and clinical disease-free survival.

In patients with pathologic tumor stage T3N0M0, immediate postoperative external irradiation after RP may improve biochemical and disease-free survival, with the highest impact in cases with positive surgical margins.

In patients with pathologic tumor stage T2–T3N0M0, salvage irradiation is indicated in cases of persisting PSA or biochemical failure with rising PSA levels < 0.5 ng/ml. Salvage RT might be initiated, even at low PSA levels of 0.1–0.2 ng/ml, if a continuous PSA increase has been documented.

In patients with locally advanced PCa, T3–T4AN0M0, concomitant and adjuvant hormonal therapy for a total duration of 3 yr, with external-beam radiation for patients with WHO 0–2 performance status, is recommended, as it improves overall survival.

In a subset of patients with T2–T3N0M0 and Gleason score 2–6, short-term ADT before and during RT can be recommended, as it may favorably influence overall survival.

In patients with very-high-risk PCa, c–pN1M0, and no severe comorbidities, the therapeutic role of pelvic external irradiation and immediate long-term ADT is unclear; the adjuvant treatment options have to be discussed on an individual basis, taking into consideration the age of the patient, comorbidities, and biology of the cancer.

Table 5 – Guidelines and recommendations for definitive radiation therapy

<table>
<thead>
<tr>
<th>Guideline/recommendation</th>
<th>LE</th>
<th>GR</th>
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<tbody>
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<td>2b</td>
<td>B</td>
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<tr>
<td>Immediate postoperative external irradiation after RP for patients with pathologic tumor stage T3N0M0 improves biochemical and clinical disease-free survival.</td>
<td>1</td>
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</table>

ADT = androgen deprivation therapy; 3D-CRT = three-dimensional conformal radiation therapy; EBRT = external-beam radiation therapy; GR = grade of recommendation; IMRT = intensity-modulated radiation therapy; IPSS = International Prostate Symptom Score; LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; TURP = transurethral resection of the prostate; WHO = World Health Organization.

Guidelines and recommendations for the use of definitive radiation therapy (RT) are listed in Table 5.

7.2. Intermediate- and high-risk prostate cancer

7.2.1. Radical prostatectomy

There is no consensus regarding the optimal treatment of men with high-risk, clinically localized PCa. Decisions on whether to select surgery as local therapy should be based on the best available clinical evidence, and RP is a reasonable first step in selected patients with a low tumor volume.

Management of high-risk localized PCa must be discussed in an interdisciplinary team, since a multimodal approach will probably be needed because of the high likelihood of positive surgical margins (33.5–66% of patients) and the presence of positive lymph nodes (7.9–49% of patients) [70–75]. Of patients primarily treated by surgery, 56–78% eventually require adjuvant or salvage RT or hormonal therapy [71,73].

Overstaging of cT3 PCa is relatively frequent and occurs in 13–27% of cases [73,74]. Patients with pT2 disease and those with specimen-confined pT3 disease have similarly good biochemical and clinical progression-free survival [71,73]. Nerve-sparing RP can be performed safely in clinically localized high-risk PCa, provided that intra-operative frozen sections are taken without compromising the oncologic and functional outcomes [76].

Biochemical progression-free survival varies between 38% and 51% at 10 yr if patients are treated with RP as monotherapy. However, in the total cohort of patients with high-risk, clinically localized PCa, excellent 5-, 10-, and...
15-yr cancer-specific survival rates of 95%, 90%, and 79%, respectively, have been published, including all patients who also underwent adjuvant and salvage procedures [77,78].

PCa with markedly elevated PSA serum concentrations is not a contraindication for RP. Spahn et al. published the largest multicenter surgical series to date, including 712 patients with PSA >20 ng/ml, and reported a cancer-specific survival rate of 90% and 85% at 10- and 15-yr follow-up, respectively [77]. In the same analysis, they demonstrated that the combination of PSA >20 ng/ml with cT3 stage and/or biopsy Gleason score 8–10 significantly lowered the cancer-specific survival rate. More recently, Gontero and coworkers described a subanalysis of the same patient cohort [78]. The 10-yr cancer-specific survival rate was 80%, 85%, and 91% in patients with PSA >100, 50.1–100, and 20.1–50 ng/ml, respectively. However, most patients with PSA levels >100 ng/ml are likely to be harboring occult metastatic disease and must be informed about the high likelihood of adjuvant or salvage therapy in a postoperative multimodality approach.

RP for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable and to improve the oncologic outcome [77,78]. In men with intermediate- and high-risk PCa, an extended pelvic lymph node dissection (ePLND) should always be performed [63] to obtain optimal information about the extent of lymph node involvement for use in counseling patients concerning the potential need for adjuvant treatment options. The true therapeutic benefit of ePLND, however, is still unclear.

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Nevertheless, the combination of RP and early androgen-deprivation therapy (ADT) in microscopic pN+ PCa has been shown to achieve a 10-yr cancer-specific survival rate of 80%. A retrospective observational study has shown a dramatic improvement in cancer-specific survival and overall survival in favor of completed RP compared with abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and that the abandonment of RP in N+ cases may not be justified [79]. These findings have been corroborated in a contemporary retrospective analysis [80]. RP resulted in superior survival of patients with N+ PCa after controlling for lymph node tumor burden. The findings from these studies support the role of RP as an important component of multimodal strategies for N+ PCa.

The incidence of tumor progression is lower in patients with fewer positive lymph nodes and in patients with microscopic invasion only [81]. In patients who prove to be pN+ after RP, early ADT has been shown to significantly improve cancer-specific survival and overall survival in a prospective randomized trial [82]. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumor characteristics. It is not known if adjuvant ADT in patients with minimal nodal involvement will result in the same positive results. The most recent retrospective analysis of the Surveillance Epidemiology and End Results data bank found no statistically significant difference in overall survival between the adjuvant ADT and non-ADT groups [83,84].

Follow-up of PSA and delayed start of ADT in patients with rising PSA level is therefore an acceptable option in selected cases. It is interesting to note that maximal local control with RT of the prostatic fossa appears to be beneficial in PCa patients with pN+ after RP who are treated adjuvantly with continuous ADT [85]. However, this finding is based on the data of one retrospective matched pair analysis; data are awaited from prospective trials such as Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS).

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

Three prospective randomized trials have assessed the role of immediate postoperative RT. Although different in inclusion criteria, all trials concluded that immediate postoperative RT significantly improved 5-yr clinical or biologic survival by approximately 20% (p < 0.0001) [86–88]. Immediate postoperative RT proved to be well tolerated, with a risk of grade 3–4 urinary toxicity in ≤3.5% of patients.

The updated results of the SWOG 8794 trial [88] with a median follow-up of 11.5 yr found that adjuvant RT significantly improved 15-yr metastasis-free survival compared with WW (46% vs 38%, p = 0.036) and overall survival (47% vs 37%, p = 0.053), which may be the result of uneven group compositions with different competing mortality risks [89]. However, long-term data from the European Organization for Research and Treatment of Cancer (EORTC) trial with a mean follow-up of 10.6 yr did not demonstrate a significant benefit concerning overall survival (80.7% vs 76.9%, respectively) and metastasis-free survival (11.3% vs 11.0%, respectively) [90]. Only progression-free survival (58.9% vs 39.4%, respectively) and local failure (16.5% vs 7.0%, respectively) were significantly improved. The frequency of severe (Radiation Therapy Oncology Group [RTOG] grade ≥3) RT-induced toxicity was higher in the group of adjuvant RT compared with WW (5.3% vs 2.5%, p = 0.052), but this rate was reduced to <1% with 3D-CRT [87]). Therefore, the indication for adjuvant RT should be made with caution and should be discussed in an interdisciplinary tumor board.

Thus, for patients with a high risk of local failure after RP because of positive margins and/or invasion of the seminal vesicles and negative PSA, two options can be offered within the framework of informed consent: (1) immediate RT with 66.6 Gy to the surgical bed [91,92] on recovery of urinary function or (2) clinical and biologic monitoring followed by salvage RT with ≥66 Gy, ideally when the PSA rises but does not exceed 0.5 ng/ml [91–93]. However, salvage RT might be initiated at lower PSA serum levels, even in the range of 0.1–0.3 ng/ml, once a continuous PSA progression has been documented.

7.2.3. Radiation therapy

For intermediate-risk PCa, there are three treatment options based on the patient’s age, comorbidities, and sexual health:
1. EBRT with dose escalation from 76 to 81 Gy, which in many series has shown a significant impact on 5-yr progression-free survival [94,95].

2. A combination of EBRT plus low- or high-dose brachytherapy.

3. Short-term (4–6-mo) ADT combined with a conventional dose (70 Gy) of EBRT.

For high-risk localized PCa, the combination of EBRT with ADT is highly recommended, as shown by phase 3 randomized trials [96,97], which display a significant improvement in overall survival. This recommendation holds true even if higher doses of EBRT are currently used to treat high-risk disease.

Nabid et al. [98] reported the results of a phase 3 trial in high-risk PCa comparing the effectiveness and safety of short-duration compared with longer-duration ADT followed by external irradiation. A total of 630 NO-X M0 patients were included: T1c–T2a–b with Gleason score >7 and/or baseline PSA >20 ng/ml, or T3–4 stages. Patients were randomly allocated to ADT treatment for 18 mo (320 patients) or 36 mo (310 patients). ADT consisted of a luteinizing hormone–releasing hormone agonist with 1 mo of antiandrogen, started 4 mo before 3D-CRT delivering 44 Gy to the pelvic lymph nodes and 70 Gy to the prostate. The median age was 71 yr (range: 65–74). With a 77-mo median follow-up, the 10-yr overall survival was 63.6% (36-mo treatment arm) compared with 63.2% (18-mo treatment arm) (p = 0.429), and the 10-yr specific survival was 87.2% in both treatment arms. In this trial, T1c–T2a–b stages represented 75.4%, and T3–4 stages represented only 24.6%, while in the EORTC trial 22863 (which was the reference of this study), the percentage of T3–4 was 89.6%. It would therefore be wise to restrict these results to high-risk localized PCa and to consider that 18 mo of ADT could represent a new treatment standard in combination with high-dose, high-precision external irradiation.

For locally advanced PCa, the data of the EORTC-22961 trial demonstrate a 4.7% benefit in overall survival after a median follow-up of 5.2 yr in favor of 3-yr ADT compared with short-term ADT [99]. The RTOG 92–02 study compared 4 mo of neoadjuvant ADT with 4 mo of neoadjuvant ADT plus an additional 24 mo of adjuvant ADT in 1554 men with T2c–T4 PCa and reported improvements in local progression, disease-free survival, biochemical survival, and metastasis-free survival in the adjuvant ADT group [100]. However, an overall survival benefit was restricted to men with a Gleason score of 8–10 in the subgroup analysis. Therefore, concomitant (with or without neoadjuvant) and adjuvant ADT for 3 yr is mandatory and represents the current standard in the radiotherapeutic management of high-risk PCa.

Various prospective randomized trials have evaluated the oncologic efficacy of ADT with or without EBRT [101–103]. The SPCG-7 trials included 875 men with locally advanced PCa who were randomly assigned to endocrine treatment or to ADT plus EBRT at a dose of ≥70 Gy [101]. After a median follow-up of 7.6 yr, the cancer-specific mortality was significantly higher in the ADT arm compared with the ADT plus EBRT arm (23.9% vs 11.9%), as was the mortality (39.4% vs 29.6%) and the PSA failure rate (74.7% vs 25.5%) (p < 0.0001). A Canadian study randomized 1205 men with locally advanced PCa to receive ADT or ADT with EBRT at a dose of 65–69 Gy [102]. After a median follow-up of 6 yr, the addition of EBRT significantly reduced the risk of death (HR: 0.77; p = 0.033), with a 10-yr cumulative disease-specific death rate of 15% compared with 23%. A French study randomized 263 patients with locally advanced PCa to receive ADT or ADT plus EBRT [103]. At a minimum follow-up of 5 yr, the combined treatment achieved significantly superior results with regard to progression-free survival (60.9% vs 8.5%, p = 0.001), loco-regional progression (9.7% vs 29%, p = 0.0002), and metastatic progression (3% vs 10.8%, p = 0.018).

Patients must be informed about potential late GU or GI toxicity and about the impact of irradiation on erectile function. Late toxicity was analyzed using a dose of 70 Gy in the prospective EORTC randomized trial 22863, graded according to a modified RTOG scale. Eighty-six patients (22.8%) had grade >2 urinary or intestinal complications or leg edema, 72 of whom had grade 2 (moderate) toxicity; 10 patients had grade 3 (severe) toxicity; and 4 patients died because of grade 4 (fatal) toxicity. Although there were four late treatment-related deaths (1%), the long-term toxicity was limited, with a grade 3 or 4 late complication rate of <5% being reported.

8. Irradiation to the pelvic lymph nodes

There is no firm evidence base for prophylactic whole-pelvic irradiation (46–50 Gy), since randomized trials have failed to show a benefit in high-risk cases [104–107]. The use of ePLND may be needed to improve the selection of patients who may be able to benefit from pelvic lymph node irradiation. The results of pelvic lymphadenectomy, particularly in young patients, will enable radiation oncologists to tailor both the planning target volume and the duration of ADT—specifically, no pelvic irradiation for pN0 patients, but pelvic irradiation for pN1 patients with long-term ADT. The benefits of high-dosage pelvic nodal irradiation using IMRT merit further investigation in a phase 2 trial. One such trial is currently recruiting through the RTOG study, while a second randomized phase 2 trial is ongoing in the United Kingdom.

9. Proton-beam and carbon ion–beam therapy

Proton-beam therapy is a promising but costly treatment for PCa. Although there are theoretical physical advantages, this therapy has so far been shown to be only comparably safe and effective when compared with the alternatives and not necessarily superior [108].

The Proton Radiation Oncology Group 9509 trial randomly assigned 393 men with clinically localized PCa to receive EBRT with 70.2 Gy compared with 79.2 Gy of combined photon and proton radiation [109] in a dose-escalation trial. At a median follow-up of 9.4 yr, the estimated 10-yr biochemical progression rate for patients
Mean follow-up was 42 included 803 patients with low-, intermediate-, and high-risk patients were 83–75%, the metastasis-free survival rate at 8 yr was 97%. The 5- and specific survival rates at 8 yr were 89% and 99%, respectively. The treatment-free survival rates were 84–79%, 68–61%, and 52–54%, respectively.

Besides RP, EBRT, and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) have emerged as alternative therapeutic options in patients with clinically localized PCa who are not suitable for RP [110–112].

Crouzet et al. [111] analyzed the oncologic and functional outcomes of the largest patient cohort, which included 803 patients with low-, intermediate-, and high-risk PCa in 40.2%, 46.3%, and 13.5% of patients, respectively. Mean follow-up was 42 ± 33 mo. The overall and cancer-specific survival rates at 8 yr were 89% and 99%, respectively. The metastasis-free survival rate at 8 yr was 97%. The 5- and 7-yr biochemical-free survival rates (Phoenix criteria) for low-, intermediate-, and high-risk patients were 83–75%, 72–63%, and 68–62%, respectively (p = 0.03); the additional treatment-free survival rates were 84–79%, 68–61%, and 52–54%, respectively (p < 0.001).

Currently, data from HIFU are not extensive enough to be considered in treatment recommendations. Applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the available evidence on the efficacy and safety of HIFU in PCs is very low quality, mainly because of study designs that lack control groups, and patients must be informed accordingly. Indications might be (1) low- or intermediate-risk PCs or (2) prostate volume <40 ml at the time of therapy.

The results of the only randomized trial of EBRT compared with CSAP in patients with clinically localized PCs were published recently, with promising results [113]. A total of 244 men with low- and intermediate-risk PCs were assigned to both treatment arms, and all men received neoadjuvant ADT. After a median follow-up of 100 mo, there were no differences with regard to disease progression at 36 mo, overall survival, or disease-specific survival. Positive results might be because of the fact that neoadjuvant ADT was delivered, and both arms and patient numbers are too small to draw significant clinical conclusions.

12. Summary
The present text represents a summary. For more detailed information and a full list of references, refer to the full-text version. These EAU guidelines (ISBN 978–90–79754–71–7) are available at the EAU Web site (http://www.uroweb.org/guidelines/online-guidelines/).

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.

Study concept and design: Heidenreich, Mottet.

Acquisition of data: Heidenreich, Bastian, Bellmunt, Bolla, Joniau, van der Kwast, Mason, Matveev, Wiegel, Zattoni, Mottet.

Analysis and interpretation of data: Heidenreich, Bastian, Bellmunt, Bolla, Joniau, van der Kwast, Mason, Matveev, Wiegel, Zattoni, Mottet.

Drafting of the manuscript: Heidenreich.

Critical revision of the manuscript for important intellectual content: Heidenreich, Bastian, Bellmunt, Bolla, Joniau, van der Kwast, Mason, Matveev, Wiegel, Zattoni, Mottet.

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References


