European Association of Urology

Guidelines

EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent

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Article info

Abstract

Objective: To present a summary of the 2016 version of the European Association of Urology (EAU) - European Society for Radiotherapy & Oncology (ESTRO) - International Society of Geriatric Oncology (SIOG) Guidelines on screening, diagnosis, and local treatment with curative intent of clinically localised prostate cancer (PCa).
Evidence acquisition: The working panel performed a literature review of the new data (2013–2015). The guidelines were updated and the levels of evidence and/or grades of recommendation were added based on a systematic review of the evidence.
Evidence synthesis: *BRCA2* mutations have been added as risk factors for early and aggressive disease. In addition to the Gleason score, the five-tier 2014 International Society of Urological Pathology grading system should now be provided. Systematic screening is still not recommended. Instead, an individual risk-adapted strategy following a detailed discussion and taking into account the patient's wishes and life expectancy must be considered. An early prostate-specific antigen test, the use of a risk calculator, or one of the promising biomarker tools are being investigated and might be able to limit the overdetection of insignificant PCa. Breaking the link between diagnosis and treatment may lower the overtreatment risk. Multiparametric magnetic resonance imaging using standardised reporting cannot replace systematic biopsy, but robustly nested within the diagnostic work-up, it has a key role in local staging. Active surveillance always needs to be discussed with very low-risk patients. The place of surgery in high-risk disease and the role of lymph node dissection have been clarified, as well as the management of node-positive patients. Radiation therapy using dose-escalated inten-

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sity-modulated technology is a key treatment modality with recent improvement in the outcome based on increased doses as well as combination with hormonal treatment. Moderate hypofractionation is safe and effective, but longer-term data are still lacking. Brachytherapy represents an effective way to increase the delivered dose. Focal therapy remains experimental while cryosurgery and HIFU are still lacking long-term convincing results.

Conclusions: The knowledge in the field of diagnosis, staging, and treatment of localised PCa is evolving rapidly. The 2016 EAU-ESTRO-SIOG Guidelines on PCa summarise the most recent findings and advice for the use in clinical practice. These are the first PCa guidelines endorsed by the European Society for Radiotherapy and Oncology and the International Society of Geriatric Oncology and reflect the multidisciplinary nature of PCa management. A full version is available from the EAU office and online (http://uroweb.org/guideline/prostate-cancer/).

Patient summary: The 2016 EAU-STRO-IOG Prostate Cancer (PCa) Guidelines present updated information on the diagnosis, and treatment of clinically localised prostate cancer. In Northern and Western Europe, the number of men diagnosed with PCa has been on the rise. This may be due to an increase in opportunistic screening, but other factors may also be involved (eg, diet, sexual behaviour, low exposure to ultraviolet radiation). We propose that men who are potential candidates for screening should be engaged in a discussion with their clinician (also involving their families and caregivers) so that an informed decision may be made as part of an individualised risk-adapted approach.

1. Introduction

The most recent summary of the European Association of Urology (EAU) Guidelines on prostate cancer (PCa) was published in 2013 [1]. This update is based on structured yearly literature reviews and systematic review through an ongoing process. Evidence levels and grade of recommendation have been inserted according to the general principles of evidence-based medicine [2].

PCa remains the most common cancer in men in Europe (excluding skin cancer). Although the incidence of autopsy-detected cancers is roughly the same in different parts of the world, the incidence of clinically diagnosed PCa varies widely and is highest in Northern and Western Europe (>200 per 100 000 men/year) [3]. This is suggested to be a consequence of exogenous factors such as diet, chronic inflammation, sexual behaviour, and low exposure to ultraviolet radiation [4].

Metabolic syndrome has been linked with an increased risk of PCa [5], but there is insufficient evidence to recommend lifestyle changes or a modified diet to lower this risk. In hypogonadal men, testosterone therapy is not associated with an increased PCa risk [6]. No drugs or food supplements have been approved for PCa prevention.

Apart from age and African American origin, a family history of PCa (both paternal and maternal [7]) are well-established risk factors. If one first-degree relative has PCa, the risk is at least doubled. It increases by 5–11 times when two or more first-line relatives are affected [8]. About 9% of men with PCa have truly hereditary disease, which is associated with an onset 6–7 yr earlier than spontaneous cases, but does not differ in other ways. The only exception to this are carriers of the rare *BRCA2* germline abnormality, who seem to have an increased risk of early-onset PCa with aggressive behaviour [9–11].

2. Classification

The 2009 TNM classification for staging of PCa and the EAU risk group classification are used (Table 1). The latter classification is based on grouping patients with a similar risk of biochemical recurrence after local treatment.

The International Society of Urological Pathology (ISUP) 2005 modified Gleason score (GS) is the recommended PCa grading system. The biopsy GS consists of the Gleason grade of the most extensive pattern plus the highest pattern, regardless its extent. In radical prostatectomy (RP) specimens, the GS is determined differently: A pattern comprising ≤5% of the cancer volume is not incorporated in the GS, but its proportion should be reported separately if it is grade 4 or 5.

Table 1 – EAU risk groups for biochemical recurrence of localised and locally advanced prostate Cancer

Low-risk	Intermediate-risk	High-risk	
		Definition	
PSA < 10 ng/mL	PSA 10–20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7	or GS 7	or GS >7	any GS
and cT1-2a	or cT2b	or cT2c	cT3–4 or cN+
Localised	Localised	Localised	Locally advanced

GS = Gleason score; PSA = prostate-specific antigen.

Table 2 – International Society of Urological Pathology 2014 grade groups[*]

Gleason score	Grade group
≤6 (3+3 or 3+2 or 2+3 or 2+2)	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4+4 or 3+5 or 5+3)	4
9–10	5

[*] Grade groups can now be reported in addition to the overall or global Gleason score of a prostate biopsy or radical prostatectomy.

Table 3 – Follow-up data from the European Randomised Study of Screening for Prostate Cancer study [14]

Years of follow-up	Number needed to screen[*]	Number needed to treat[*]
9	1410	48
11	979	35
13	781	27

[*] Number of men needed to screen or treat to avoid the death of disease of one man.

The 2014 ISUP Gleason Grading Conference on Gleason Grading of Prostate Cancer [12] adopted the concept of grade groups of PCa to align PCa grading with the grading of other carcinomas, eliminate the anomaly that the most highly differentiated PCas have a GS 6 and highlight the clinical differences between GS 7 (3 + 4) and 7 (4 + 3) (Table 2).

3. Screening and early detection

Screening for PCa remains one of the most controversial topics in the urologic literature. A Cochrane review [13] suggests that PSA screening is associated with an increased diagnosis rate (relative risk [RR]: 1.3; 95% confidence interval [CI], 1.02–1.65), the detection of more localised (RR: 1.79; 95% CI, 1.19–2.70) and less advanced disease (T3–4, N1, M1) (RR: 0.80; 95% CI, 0.73–0.87). However, neither overall survival (OS; RR: 1.00; 95% CI, 0.96–1.03) nor cancer-specific survival (CSS) benefit were observed (RR: 1.00; 95% CI, 0.86–1.17). Moreover, screening was associated with overdiagnosis and overtreatment. All these considerations have led to a strong advice against systematic population-based screening in Europe and the United States. And yet the population-based European Randomised Study of Screening for Prostate Cancer (ERSPC) showed a reduction in PCa mortality in the screening arm (RR: 0.8; 95% CI, 0.65–0.98) after a median follow-up of 9 yr. Updated results from the ERSPC at 13 yr of follow-up showed an unchanged cancer-specific mortality reduction [14], but the number needed to screen and to treat to avoid one death from PCa decreased and is now below the number needed to screen in breast cancer trials [15] (Table 3). But an OS benefit is still lacking. The uptake of the current US Preventive Services Task Force recommendations has been associated with a substantial number of men with aggressive disease being missed [16]. Finally, a comparison of systematic and opportunistic screening suggested overdiagnosis and mortality reduction by systematic screening versus a higher overdiagnosis with at best a marginal survival benefit after opportunistic screening [17].

Targeting men at higher risk of PCa might reduce the number of unnecessary biopsies. These include men aged >50 yr (>45 yr in African American men) or with a family history of PCa. In addition men with a PSA >1 ng/ml at age 40 yr and >2 ng/ml at age 60 yr [18,19] are at increased risk of PCa metastasis or death several decades later. Risk calculators developed from cohort studies may also be useful in reducing the number of unnecessary biopsies. None has clearly shown superiority over each other or can be considered as optimal [20].

Optimal intervals for PSA testing and digital rectal examination (DRE) follow-up are unknown. A 2-yr interval for men at increased risk, while it could be expanded up to 8 yr for those not at risk. The age at which to stop early diagnosis should be based on individual's life expectancy, where comorbidity is at least as important as age [21]. Men who have <15 yr of life expectancy are unlikely to benefit.

All the available tools will still lead to some overdiagnosis. Breaking the link between diagnosis and active treatment is the only way to decrease the risk of overtreatment while maintaining the potential benefit of individual early diagnosis for men requesting it (Table 4).

4. Diagnosis

PCa is usually suspected on the basis of DRE and/or an elevated PSA. Definitive diagnosis depends on histopathologic verification. Abnormal DRE is an indication for biopsy, but as an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS).

Table 4 – Guidelines for screening and early detection

Recommendation	LE	GR
Do not subject men to PSA testing without counselling them about the potential risks and benefits.	3	B
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life expectancy of at least 10–15 yr.	3	B
Offer PSA testing in men at elevated risk of having PCa: • Men aged >50 yr • Men aged >45 yr and a family history of PCa • African American men aged >45 yr • Men with a PSA level >1 ng/ml at age 40 yr • Men with a PSA level >2 ng/ml at age 60 yr	2b	A
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 yr for those initially at risk: • Men with a PSA level >1 ng/ml at age 40 yr • Men with a PSA level >2 ng/ml at age 60 yr Postpone follow-up to 8 yr in those not at risk.	3	C
Decide on the age at which early diagnosis of PCa should be stopped based on life expectancy and performance status; men who have a life expectancy <15 yr are unlikely to benefit.	3	A

GR = grade of recommendation; LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen.

PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa, precluding an optimal PSA threshold for detecting nonpalpable but clinically significant PCa. A limited PSA elevation alone should be confirmed after a few weeks under standardised conditions (ie, no ejaculation, manipulations, and urinary tract infections) in the same laboratory before considering a biopsy. The empiric use of antibiotics in an asymptomatic patient should not be undertaken [22].

The free-to-total PSA ratio stratifies the risk of PCa in men with 4–10 ng/ml total PSA and a previous negative biopsy but may be affected by several preanalytical and clinical factors (eg, instability of free PSA at 4 °C and room temperature, variable assay characteristics, and large concomitant benign prostatic hyperplasia [BPH]). Novel assays for risk stratification measuring a panel of kallikreins including the Prostate Health Index test and the four-kallikrein score test are intended to reduce the number of unnecessary biopsies in men with a PSA between 2 and 10 ng/ml. Prospective multicentre studies demonstrated that both tests outperformed free-to-total PSA for PCa detection [23,24]. A formal comparison of these new tests is lacking.

5. Prostate biopsy

TRUS-guided biopsy using an 18G biopsy needle and a periprostatic block is the standard of care. When the same number of cores are taken, both transrectal and transperineal approaches have comparable detection rates [25,26].

Ten- to 12-core biopsies should be taken, bilateral from apex to base, as far posterior and lateral as possible from the peripheral gland. Additional cores should be obtained from DRE/TRUS suspect areas. Oral or intravenous quinolones are state-of-the-art preventive antibiotics, in spite of the increased resistance to quinolones, which is associated with a rise in severe infectious complications [27]. Other biopsy complications include haematospermia (37%), haematuria lasting >1 d (14.5%), and rectal bleeding lasting ≤2 d (2.2%). Each biopsy site should be reported individually, including its location, the ISUP 2005 GS, and extent. ISUP 2014 grade should be given as a global grade, taking into account the Gleason grades of cancer foci in all biopsy sites. If identified, intraductal carcinoma, lymphovascular invasion, perineural invasion, and extraprostatic extension must each be reported. Table 5 summarises the indications for repeat biopsy following an initial negative biopsy.

Many single-centre studies suggest that multiparametric magnetic resonance imaging (mpMRI) can reliably detect aggressive tumours with a negative predictive value (NPV) and positive predictive value ranging from 63% to 98% and from 34% to 68%, respectively [28]. The combination of systematic and targeted biopsies (MRI-Tbx) may also better predict the final GS [29]. As a result, some authors proposed performing systematic mpMRI before a prostate biopsy [30,31]. One meta-analysis suggested that MRI-Tbx had a higher detection rate of clinically significant PCa compared with TRUS biopsy (sensitivity 0.91 vs 0.76) and a lower rate

of detection of insignificant PCa (sensitivity 0.44 vs 0.83). However, this benefit was restricted to the repeated biopsy subgroup [32]. Two more recent randomised controlled trials (RCTs) restricted to the initial biopsy yielded contradictory results regarding the added value of MRI-Tbx combined with systematic biopsies [33,34]. Major limitations of mpMRI are its interobserver variability and the heterogeneity in the definitions of positive and negative examinations. The first version of the Prostate Imaging Reporting and Data System (PI-RADS) scoring system failed to improve interobserver variability as compared with subjective scoring [35]. An updated version (PI-RADS v2) needs to be evaluated further [36].

6. Staging of prostate cancer

The decision to proceed with a further staging work-up is guided by which treatment options are available, taking into account the patient's preference and comorbidity. A summary of the guidelines is presented in Table 6.

Table 5 – Indications for rebiopsy after a negative biopsy and the associated risk to find a prostate cancer

Indication	Associated PCa risk
Rising and/or persistently elevated PSA	–
Suspicious DRE	5–30%
Atypical small acinar proliferation (ie, atypical glands suspicious for cancer)	40%
Extensive (ie, ≥3 biopsy sites) high-grade PIN	~30%
Few atypical glands immediately adjacent to high-grade PIN	50%
Intraductal carcinoma as a solitary finding	>90% (mainly high-grade PCa)
Positive mpMRI	34–68%

DRE = digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PIN = prostatic intraepithelial neoplasia; PSA = prostate-specific antigen.

Table 6 – Guidelines for staging of prostate cancer

Risk group	LE	GR
Any risk group staging		
Do not use CT and TRUS for local staging	2a	A
Low-risk localised PCa		
Do not use additional imaging for staging purposes	2a	A
Intermediate-risk PCa		
In predominantly Gleason pattern 4, metastatic screening, include at least cross-sectional abdominopelvic imaging (s.a. CT/MRI) and a bone scan for staging purposes	2a	A*
In predominantly Gleason pattern 4, use prostate mpMRI for local staging	2b	A
High-risk localised PCa or high-risk locally advanced PCa		
Use prostate mpMRI for local staging	2b	A
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan	2a	A

CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PCa = prostate cancer; TRUS = transrectal ultrasound.

7.   Primary local treatment

Management decisions should be made after all options have been discussed with a multidisciplinary team (including urologists, radiation oncologists, medical oncologists, pathologists, and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered together with the patient.

8.   Active surveillance and watchful waiting

Active surveillance (AS) aims to reduce overtreatment in men with very low-risk PCa, without compromising opportunities for cure, whereas watchful waiting (WW) is a conservative management for frail patients until the possible development of clinical progression leading to symptomatic treatment. The major differences between these two modalities are detailed in Table 7.

Mortality from untreated screen-detected PCa in patients with GS 5–7 can be as low as 7% at 15 yr follow-up [37]. An RCT was unable to show an OS and CSS difference at 10 yr between RP and WW in 731 men with screen-detected clinically organ-confined PCa [38]. Only patients with intermediate risk or with a PSA >10 ng/ml had a significant OS benefit from RP (hazard ratio [HR]: 0.69 [0.49–0.98] and 0.67 [0.48–0.94], respectively). A population-based analysis in 19 639 patients aged ≥65 yr who were not given curative treatment found that in men having a Charlson Comorbidity Index score ≥2, tumour aggressiveness had little impact on OS at 10 yr [39]. These data highlight the potential role of WW in some patients with an individual life expectancy <10 yr.

A systematic review summarised the available data on AS [40]. There is considerable variation between studies regarding patient selection, follow-up policies, and when active treatment should be instigated. Selection criteria for AS include clinical T1c or T2a, PSA <10 ng/ml, and PSA density <0.15 ng/ml per ml (even if still controversial [41]), fewer than two to three positive cores with <50% cancer involvement of every positive core, GS 6. Extraprostatic extension or lymphovascular invasion should not be considered for AS [42]. Rebiopsy to exclude Gleason sampling error is considered important [41], and mpMRI has a major role based on its high NPV value for lesion upgrading and to exclude anterior prostate lesions [43]. Follow-up in AS is based on repeat biopsy [41], serial PSA measurements, and DRE, the optimal schedule remaining

unclear. Strategies how to incorporate mpMRI within this follow-up are evolving but are not yet established. The decision to switch to an active treatment is based on a change in the inclusion criteria (T stage and biopsy results). The use of a PSA change (especially a PSA doubling time <3 yr) remains contentious based on its weak link with grade progression. Active treatment may also be triggered upon a patient's request [44].

9.   Radical prostatectomy

The goal of RP is eradication of PCa while preserving continence and, whenever possible, potency. It is the only treatment for localised PCa to show a benefit for OS and CSS, compared with WW. Patients should not be denied this procedure on the grounds of age alone [21] provided they have at least 10 yr of life expectancy and are aware that increasing age is linked to increased incontinence risk. Nerve-sparing RP can be performed safely in most men with localised PCa. High risk of extracapsular disease, such as any cT2c or cT3 or any GS >7, are usual contraindications. An externally validated nomogram predicting side-specific extracapsular extension can help guide decision making [45]. mpMRI may be helpful for selecting a nerve-sparing approach because it has good specificity (0.91; 95% CI, 0.88–0.93) but low sensitivity (0.57; 95% CI, 0.49–0.64) for detecting microscopic pT3a stages [46]. But the experience of the radiologist remains of paramount importance.

Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details can improve surgical cancer control [47] and lower the complication rate.

There is still no evidence that one surgical approach is better than another (open, laparoscopic, or robotic), as highlighted in a formal systematic review. Robot-assisted prostatectomy is associated with lower perioperative morbidity and a reduced positive margins rate compared with laparoscopic prostatectomy, although there is considerable methodological uncertainty. No formal differences exist in cancer-related continence or erectile dysfunction outcomes [48].

9.1.   Pelvic lymph node dissection

The individual risk of finding positive lymph nodes can be estimated using externally validated preoperative nomograms such as that described by Briganti [49]. A risk of nodal

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Table 7 – Definitions of active surveillance and watchful waiting

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient specific
Assessment/Markers used	DRE, PSA, rebiopsy, mpMRI	Not predefined
Life expectancy	>10 yr	<10 yr
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Only for low-risk patients	Can apply to patients at all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

metastases >5% is an indication to perform an extended nodal dissection (ePLND). This includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, the nodes medial and lateral to the internal iliac artery, and the nodes overlying the common iliac artery and vein up to the ureteral crossing. It is recommended that for each region the nodes should be sent separately for pathologic analysis. With this template, 75% of all anatomic landing sites are cleared, resulting in improved pathological staging compared with a limited pelvic lymph node dissection, but at the cost of three-fold higher complication rates (19.8% vs 8.2%), mainly related to significant lymphoceles [50].

In men with pN+ PCa, early adjuvant androgen-deprivation therapy (ADT) was shown to achieve a 10-yr CSS rate of 80% [51]. Improving local control with pelvic radiation therapy (RT) combined with ADT appeared to be beneficial in pN1 PCa patients treated with an ePLND. Men with minimal-volume nodal disease (fewer than three lymph nodes) and GS 7–10 and pT3–4 or R1 as well as men with three to four positive nodes were more likely to benefit from combined ADT and RT after surgery [52].

9.2. Low-risk prostate cancer

The decision to offer RP should be based on the probabilities of clinical progression, side effects, and potential survival benefit. No lymph node dissection is needed.

9.3. Intermediate-risk localised prostate cancer

Data from SPCG-4 [53] and a preplanned subgroup analysis (PIVOT) [36] highlight the benefit of RP compared to WW. The risk of having positive nodes is 3.7–20.1% [49]. An ePLND should be performed if the estimated risk for pN+ exceeds 5% [49]. In all other cases, nodal dissection can be omitted while accepting a low risk of missing positive nodes.

9.4. High-risk and locally advanced prostate cancer

Patients with high-risk and locally advanced PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression, and death from PCa. Provided that the tumour is not fixed and not invading the urethral sphincter, RP combined with an ePLND is a reasonable first step in a multimodal approach. The estimated risk for pN+ is 15–40% [49]. Regarding each individual high-risk factor in patients treated with a multimodal approach, a GS 8–10 prostate-confined lesion has a good prognosis after RP. In addition, frequent downgrading exists between the biopsy and the specimen GS [54]. At 10- and 15-yr follow-up, the CSS is up to 88% and 66%, respectively [55,56]. A PSA >20 ng/ml is associated with a CSS at 10 and 15 yr ranging between 83% and 91% and 71% and 85%, respectively [55–57]. Surgery has traditionally been discouraged for cT3N0 PCa, mainly because of the increased risk of positive margins and lymph node metastases and/or distant relapse.

Retrospective case series demonstrated a CSS at 10 and 15 yr between 85% and 92% and 62% and 84%, respectively; 10-yr OS ranged between 76% and 77% [58]. The overall heterogeneity of this high-risk group was highlighted by a large retrospective multicentre cohort of 1360 high-risk patients treated with RP in a multimodal approach [58]. At 10 yr, a 91.3% CSS was observed. CSS was 95% for those having only one risk factor (ie, GS >7, cT category higher than cT2, or PSA >20 ng/ml), 88% for those having a cT3–4 and a PSA >20 ng/ml, and reduced to 79% if all three risk factors were present.

9.5. Side effects of radical prostatectomy

Postoperative incontinence and erectile dysfunction (ED) are common problems following RP. There is no major difference based on the surgical approach with an overall continence rate between 89% and 100% when a robotic procedure was conducted compared to 80–97% for the retropubic approach [59].

A prospective controlled nonrandomised trial of patients treated in 14 centres was published recently. At 12 mo after robotic surgery, 21.3% were incontinent, as were 20.2% after open. The adjusted OR was 1.08 (95% CI, 0.87–1.34). ED was observed in 70.4% after robotic and 74.7% after open. The adjusted OR was 0.81 (95% CI, 0.66–0.98) [60].

10. Definitive radiation therapy

Dose-escalated intensity-modulated radiation therapy (IMRT), with or without image-guided RT, is the gold standard for external-beam radiation therapy (EBRT) because it is associated with less toxicity compared to three-dimensional conformal radiation therapy (3D-CRT) techniques [61]. However, whatever the technique and their degree of sophistication, quality assurance plays a major role in the planning and delivery of RT.

RCTs have shown that escalating the dose into the range 74–80 Gy leads to a significant improvement in 5-yr biochemical-free survival [62–65]. In men with intermediate- or high-risk PCa, there is also evidence to support an OS benefit from a nonrandomised but well-conducted propensity matched retrospective analysis covering a total of 42 481 patients [66].

Biological modelling suggests that PCa may be sensitive to an increased dose per fraction resulting in the investigation in RCTs of hypofractionation (HFX) in localised disease. The largest reported randomised trial, using IMRT in predominantly intermediate-risk localised PCa, (CHHiP trial) demonstrates 60 Gy in 20 fractions (3 Gy/fraction) is non-inferior to 74 Gy in 37 fractions with 5-yr recurrence free rates of 90%. A third arm using 57 Gy in 19 fractions (3 Gy/fraction) was not demonstrated to be non-inferior in terms of biochemical control. No significant differences in the proportion or cumulative incidence of 5-yr toxicity were found when using the 3 Gy per fraction schedules [67]. Other trials have demonstrated increased toxicity with HFX. In the RTOG 0415 study, 70 Gy in 28 fractions (2.5 Gy/fraction) was investigated in low risk

PCa patients. Late Grade 2 GI and GU toxicities of 18.2% and 26.2% were noted with HFX compared to 11.4% and 20.5% using conventional fractionation [68]. Patient reported toxicity outcomes are awaited. Another randomised trial, using a higher dose per fraction of 3.4 Gy delivered to a total dose of 64.6 Gy (HYPRO trial), has demonstrated increased G3 and higher late urinary toxicity particularly in patients with pre-existing urinary symptoms [69]. HFX delivered with fewer treatments can increase the convenience for the patient and lower costs for the health care system, but only evidence based fractionation schedules should be used outside of clinical trials.

HFX requires meticulous quality assurance, excellent image guidance, and close attention to organ-at-risk dose constraints to minimise the long-term toxicity risk. Extreme HFX (5–10 Gy per fraction) in which radiation is delivered in five to seven fractions should still be considered as investigational.

10.1. Low-risk prostate cancer

Offer dose-escalated IMRT (74–78 Gy) without ADT.

10.2. Intermediate-risk prostate cancer

Patients suitable for ADT should be given combined dose-escalated IMRT (76–78 Gy) with short-term ADT (4–6 mo) [70]. For patients unsuitable for ADT (eg, due to comorbidities) or unwilling to accept ADT (eg, to preserve their sexual health), the recommended treatment is IMRT at a dose of 76–80 Gy or a combination of IMRT and brachytherapy.

10.3. Localised high-risk prostate cancer

The high risk of relapse outside the irradiated volume makes it mandatory to use a combined modality approach, consisting of dose-escalated IMRT, possibly including the pelvic lymphatics and long-term ADT, generally for 2 to 3 yr. The duration of ADT has to take into account performance status, comorbidities, and the number of poor prognostic factors.

10.4. Locally advanced prostate cancer: T3–4 N0, M0

The standard of care for patients T3–4 N0, M0 locally advanced PCa is IMRT combined with long-term ADT for at least 2 to 3 yr as it results in better OS [71–73]. The combination is clearly better than EBRT or ADT mono-therapy [74]. In both high-risk localised and locally advanced PCa, an upfront combination with docetaxel only improves relapse-free survival, with no survival benefit at 9 yr [75].

10.5. Lymph node irradiation

In men with cN0 PCa, RCTs failed to show a benefit from prophylactic pelvic nodal irradiation (46–50 Gy) in high-risk cases [76]. In men with cN1 or pN1 the outcome of RT alone is poor, and these patients should receive RT plus long-term ADT, as shown by the STAMPEDE trial, in which the use of RT improved failure-free survival in men with N+ PCa [77].

10.6. Postoperative external-beam radiation therapy after radical prostatectomy

Extracapsular invasion and positive surgical margins are associated with a risk of local recurrence and progression. Adjuvant RT was associated with improved biochemical progression-free survival in three RCTs [78–80], although only SWOG 8794 [80] suggested improved OS. Thus for patients classified as pT3 pN0 with a high risk of local failure with positive margins (highest impact), pT3a and/or pT3b with a postoperative PSA <0.1 ng/ml, two options can be offered in the framework of informed consent. Either immediate EBRT to the surgical bed after recovery of urinary function or monitoring followed by early salvage RT before the PSA exceeds 0.5 ng/ml [81].

10.7. Side effects of definitive radiation therapy

The Memorial Sloan Kettering Cancer Center group reported data on late toxicity from their experience in 1571 patients with T1–T3 disease treated with either 3D-CRT or IMRT at doses between 66 Gy and 81 Gy, with a median follow-up of 10 yr [61]. The use of IMRT significantly reduced the risk of late grade 2 or higher gastrointestinal (GI) toxicity to 5% compared with 13% with 3D-CRT. The incidence of grade $\geq$2 late genitourinary (GU) toxicity was 20% in patients treated with 81 Gy IMRT versus 12% with lower doses. The overall incidences of late grade 3 toxicity were 1% and 3% for GI and GU toxicity, respectively.

Systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to radiotherapy in the course of treatment for PCa demonstrate an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68), and rectum (OR: 1.62) with similar risks over lag times of 5 and 10 yr. Absolute risks over 10 yr are small (1–4%) but should be discussed with younger men in particular [82].

11. Brachytherapy

Low-dose rate (LDR) brachytherapy uses permanent radioactive seeds implanted into the prostate and is an option for those with low-risk disease and selected cases with intermediate-risk disease (low-volume GS 3 + 4), prostate volume <50 cm^3, and an IPSS $\leq$12 [83]. Up to 85% relapse-free survival at 10 yr is demonstrated [84]. LDR as a boost with EBRT can be used to dose escalate radiation in intermediate- and high-risk patients. Although seen as a low-impact treatment modality, some patients experience significant urinary complications following implantation, such as urinary retention (1.5–22%), postimplantation transurethral resection of the prostate (TURP) (8.7% of cases), and incontinence (0–19%) [85]. Careful selection of patients using uroflowmetry can avoid these significant side effects [86]. Previous TURP for BPH increases the risk of

Table 8 – Summary of the main findings regarding treatment of nonmetastatic prostate cancer

Recommendation	LE	GR
Management decisions should be made after all treatments have been discussed in a multidisciplinary team	4	A[*]
Offer RP to patients with low- and intermediate-risk PCa and a life expectancy >10 yr	1b	A
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, GS <7, and PSA <10 ng/ml, or refer to Partin tables/nomograms)	2b	B
In intermediate- and high-risk disease, use mpMRI as a decision tool to select patients for nerve-sparing procedures	2b	B
Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy >10 yr	2a	A
Offer RP in a multimodality setting to selected patients with locally advanced (cT3a) PCa and a life expectancy >10 yr	2b	B
Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b–4 N0 or any T N1)	3	C
Do not offer NHT before RP	1a	A
Do not offer adjuvant HT for pN0	1a	A
Offer adjuvant ADT for node positive (pN+)	1b	A
Offer EBRT using IMRT to all risk groups	2a	A
In patients with low-risk PCa, without a previous TURP, with a good IPSS and a prostate volume <50 ml, offer LDR brachytherapy	2a	A
In low risk PCa, use a total dose of 74–78 Gy	1a	A
In intermediate- risk PCa use a total dose of 76–78 Gy, in combination with short-term ADT (4–6 mo)	1b	A
In patients with high-risk localised PCa, use a total dose of 76–78 Gy in combination with long-term ADT (2–3 yr)	1b	A
In patients with locally advanced cN0 PCa, offer radiation therapy in combination with long-term ADT (2–3 yr)	1a	A
In patients with cN1 PCa, offer pelvic external irradiation in combination with immediate long-term ADT	2b	B
Offer adjuvant ADT for pN1 after ePLND	1b	A
Discuss adjuvant ADT with additional radiation therapy for pN1 after ePLND	2b	A
Offer observation (expectant management) for pN1 after ePLND when two or fewer nodes show microscopic involvement with a PSA <0.1 ng/ml and absence of extranodal extension	2b	B
In patients with pT3N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it at least improves biochemical-free survival	1a	A
Inform patients with pT3N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases	2b	A
Only offer cryotherapy and HIFU within a clinical trial	3	B
Do not offer focal therapy of the prostate outside a clinical trial	3	A

ADT = androgen-deprivation therapy; EBRT = external beam radiation therapy; ePLND = extended pelvic lymph node dissection; GR = grade of recommendation; GS = Gleason score; HIFU = high-intensity focussed ultrasound; HT = hormone therapy; IMRT = intensity-modulated radiation therapy; IPSS = International Prostate Symptom Score; LDR = low-dose rate; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; NHT = neoadjuvant hormone therapy; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; TURP = transurethral resection of the prostate.
[*] Upgraded following Panel consensus.

postimplantation incontinence and urinary morbidity. ED develops in about 40% of the patients after 3–5 yr.

High-dose rate (HDR) brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. HDR brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy as a method of dose escalation in intermediate- or high-risk PCa. Quality-of-life changes are similar to high-dose EBRT alone [87]. HDR brachytherapy as monotherapy has been pioneered in a small number of centres with low published toxicity and high biochemical control rates but currently mature data are not available on the optimal treatment schedule [88].

12. Alternative local treatment options

Besides RP, EBRT, and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa. However patients with a life expectancy >10 yr should be fully informed that there are limited data on the long-term outcome for cancer control beyond 10 yr. Recently, focal therapy has been developed, with the aim to ablate tumours selectively while sparing the neurovascular bundles, sphincter, and urethra. Based on the available data [89], it should still be considered as fully experimental.

Cryosurgery might be considered for patients with an organ-confined PCa or minimal tumour extension beyond the prostate, prostate volumes <40 ml, PSA <20 ng/ml, and GS <7.

A systematic review compared cryotherapy versus RP and EBRT [89]. Data from 3995 patients across 19 studies were included. In the short term, there was conflicting evidence relating to cancer-specific outcomes. The 1-yr disease-free survival was worse for cryotherapy than for either EBRT or RP. None of the other cancer-specific outcomes including OS showed any significant differences. The high risk of bias across studies precludes any clear conclusions.

High-intensity focussed ultrasound (HIFU) of the prostate was compared in a systematic review [89] with RP and EBRT as primary treatment for localised PCa. Data from 4000 patients across 21 studies were included. HIFU had a significantly worse disease-free survival at 1 yr compared with EBRT. The differences were no longer significant at 3 yr. The biochemical result was in contrast to OS at 4 yr, which was higher when using HIFU. The quality of the evidence was poor, due to high risks of bias across studies precluding any clear conclusion. The overall PCa Guidelines are summarised in Table 8.

13.   Conclusions

The present text represents a summary of the 2016 EAU-ESTRO-SIOG PCa Guidelines. For more detailed information and a full list of references, refer to the full-text version (ISBN 978-90-79754-71-7), available at the EAU Web site (http://uroweb.org/guideline/prostate-cancer/).

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