



European Association of Urology



Review – Prostate Cancer

EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent

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Abstract

Objective: To present a summary of the 2020 version of the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Geriatric Oncology (SIOG) guidelines on screening, diagnosis, and local treatment of clinically localised prostate cancer (PCa).

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Evidence acquisition: The panel performed a literature review of new data, covering the time frame between 2016 and 2020. The guidelines were updated and a strength rating for each recommendation was added based on a systematic review of the evidence.

Evidence synthesis: A risk-adapted strategy for identifying men who may develop PCa is advised, generally commencing at 50 yr of age and based on individualised life expectancy. Risk-adapted screening should be offered to men at increased risk from the age of 45 yr and to breast cancer susceptibility gene (*BRCA*) mutation carriers, who have been confirmed to be at risk of early and aggressive disease (mainly *BRCA2*), from around 40 yr of age. The use of multiparametric magnetic resonance imaging in order to avoid unnecessary biopsies is recommended. When a biopsy is performed, a combination of targeted and systematic biopsies must be offered. There is currently no place for the routine use of tissue-based biomarkers. Whilst prostate-specific membrane antigen positron emission tomography computed tomography is the most sensitive staging procedure, the lack of outcome benefit remains a major limitation. Active surveillance (AS) should always be discussed with low-risk patients, as well as with selected intermediate-risk patients with favourable International Society of Urological Pathology (ISUP) 2 lesions. Local therapies are addressed, as well as the AS journey and the management of persistent prostate-specific antigen after surgery. A strong recommendation to consider moderate hypofractionation in intermediate-risk patients is provided. Patients with cN1 PCa should be offered a local treatment combined with long-term hormonal treatment.

Conclusions: The evidence in the field of diagnosis, staging, and treatment of localised PCa is evolving rapidly. The 2020 EAU-EANM-ESTRO-ESUR-SIOG guidelines on PCa summarise the most recent findings and advice for their use in clinical practice. These PCa guidelines reflect the multidisciplinary nature of PCa management.

Patient summary: Updated prostate cancer guidelines are presented, addressing screening, diagnosis, and local treatment with curative intent. These guidelines rely on the available scientific evidence, and new insights will need to be considered and included on a regular basis. In some cases, the supporting evidence for new treatment options is not yet strong enough to provide a recommendation, which is why continuous updating is important. Patients must be fully informed of all relevant options and, together with their treating physicians, decide on the most optimal management for them.

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1. Epidemiology and risk factors

The most recent summary of the European Association of Urology (EAU)-European Society for Radiotherapy and Oncology (ESTRO)-International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer (PCa) was published in 2017 [1]. In view of the volume of new data, there was a need for an updated summary. The present summary is based on the latest guidelines published in April 2020 [2]. This update is based on structured annual literature reviews and systematic reviews, as a continuous process. A strength rating has been provided for each recommendation according to EAU Guideline Office methodology (modified from the Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodology) [3].

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 per year) [4]. This is suggested to be a consequence of exogenous factors such as diet, chronic inflammation, sexual behaviour, and low exposure to ultraviolet radiation [5].

Metabolic syndrome has been linked to an increased risk of PCa [6], but there is still insufficient evidence to

recommend lifestyle changes or a modified diet to lower this risk though potentially beneficial for other diseases. Hypogonadal men have a below average risk of PCa [7], whilst testosterone therapy is not associated with an increased PCa risk [8]. No drugs or food supplements have been approved for PCa prevention. Age, African origin, and a family history of PCa (both paternal and maternal [9]) are well-established risk factors. With one first-degree relative diagnosed with PCa, the increased relative risk (RR) of developing PCa is 1.8. This increases in a man with the father and a brother (RR: 5.5) or two brothers (RR: 7.7) diagnosed with PCa [10]. About 9% of men with PCa have truly hereditary disease, which is associated with an onset 6–7 yr earlier than nonhereditary cases, but does not differ in other ways, apart from African descent with a more aggressive course of disease [11] as well as for breast cancer predisposition gene 2 (*BRCA2*) carriers [12].

These germline mutations (*BRCA1/2*) are present in up to 6% of unselected PCa patients [13]. Other mutations such as *HOXB13* or *ATM* among others might identify families at high risk [14]. Prospective studies confirmed the association between *BRCA2* mutations and aggressive PCa [15] with worse outcome compared with noncarriers after local therapy [12]. The prospective IMPACT targeted screening study confirmed a higher incidence of PCa, at a younger age and with more clinically significant tumours only in *BRCA2* mutation carriers compared with noncarriers [16].

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

Definition			
Low risk	Intermediate risk		High risk
PSA < 10 ng/mL and ISUP grade 1 (GS < 7) and cT1-2a	PSA 10–20 ng/ml or ISUP grade 2/3 (GS 7) or cT2b	PSA > 20 ng/mL or ISUP grade 4/5 (GS > 7) or cT2c	Any PSA, any GS (any ISUP grade), cT3–4, or cN+
Localised			Locally advanced
GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.			

2. Classification and staging

The 2017 TNM classification of the American Joint Committee on Cancer (AJCC) for staging of PCa should be used [17], where the cT stage is based on digital rectal examination (DRE) only. Compared with the 2009 version, the main difference is the lack of pT2 substage differentiation. The EAU risk group classification (Table 1) is based on grouping patients with a similar risk of biochemical recurrence after local treatment. However, emerging clinical data support this distinction between favourable- and unfavourable-risk patient categories within the intermediate-risk group [18,19]. The introduction of new imaging techniques such as magnetic resonance imaging (MRI; and targeted biopsy [TBx]) and prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) may impact the risk group distribution and its predictive value, and should be taken into account when making treatment decisions.

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 of 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 [20].

The 2014 ISUP Gleason Grading Conference on Gleason Grading of PCa [21] adopted the concept of grade groups of PCa to align PCa grading with the grading of other carcinomas, eliminating the anomaly that the least aggressive PCa has a GS of 6 and to highlight the clinical differences between GS 7 = 3 + 4 and 7 = 4 + 3 (Table 2).

Several tissue-based biomarkers have emerged recently, and five commercially available tests (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS, and ProMark) have been included in an American Society of Clinical Oncology

(ASCO)-EAU-American Urological Association (AUA) recommendation for localised PCa [22]. All these tests significantly improved the prognostic accuracy of clinical multivariable models for identifying men who would benefit from active surveillance (AS) and those with clinically significant PCa (csPCa) requiring curative treatment, as well as for guiding patient management after RP. Some studies showed that tissue biomarker tests and MRI findings independently improved the detection of clinically significant cancer in an AS setting, but it remains unclear which men would benefit from which tests. Since these assays have not been tested prospectively or shown to improve long-term outcomes (eg, quality of life [QoL], need for treatment, or survival), these should be offered only in subsets of patients in whom their result provides clinically actionable information.

3. Screening and early detection

Population or mass screening is defined as the “systematic examination of asymptomatic men (at risk)” and is usually initiated by health authorities. The coprimary objectives are a reduction in disease-specific mortality and a maintained QoL. Screening for PCa remains one of the most controversial topics in the urologic literature, and it is currently not recommended in most countries worldwide. A Cochrane review suggested that prostate-specific antigen (PSA) screening is associated with an increased diagnosis rate (relative risk [RR]: 1.3; 95% confidence interval [CI], 1.02–1.65), and 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) [23]. However, neither overall survival (OS; RR: 1.00; 95% CI, 0.96–1.03) nor cancer-specific survival (CSS) benefits were observed (RR: 1.00; 95% CI, 0.86–1.17). Moreover, screening was associated with overdiagnosis and overtreatment. The population-based European Randomised Study of Screening for Prostate Cancer (ERSPC) showed a reduction in PCa mortality in the screening arm (RR: 0.79; 95% CI, 0.69–0.91) after a median follow-up of 13 yr [24]. From the ongoing follow-up of the ERSPC trial (up to 16 yr in an ERSPC subgroup [25]), although the cancer-specific mortality difference remains unchanged, the number needed to invite and diagnose to avoid one death from PCa continues to fall and is now below the number needed to screen in breast cancer trials (Table 3) [26]. An OS benefit is still lacking, despite additional evidence suggesting a long-term benefit of PSA-based screening in terms of reducing cancer-specific mortality [27].

Table 2 – International Society of Urological Pathology 2014 grade.

Gleason score	ISUP grade
2–6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4 or 3 + 5 or 5 + 3)	4
9–10	5
ISUP = International Society for Urological Pathology.	

Table 3 – Follow-up data from the European Randomised Study of Screening for Prostate Cancer (ERSPC) study [24].

Years of follow-up	Number needed to invite ^a	Number needed to diagnose ^a
9	1410	48
11	979	35
13	781	27
16 ^b	570	18

^a The number of men to invite or diagnose to avoid the death of disease of one man.
^b ERSPC subcohort from the study of Hugosson et al [25] only.

The 2012 US Preventive Services Task Force (USPSTF) recommendation discouraging PSA-based screening (grade D) has led to a reduction in the use of PSA testing. This was associated with higher rates of advanced disease at diagnosis [28] and possibly cancer-related mortality [29]. In 2017, the USPSTF issued an updated statement suggesting that men aged 55–69 yr should be informed about the benefits and harms of PSA-based screening as this might be associated with a small survival benefit, leading to a grade C recommendation [30]. This represents a major change from discouraging PSA-based screening (grade D) to offering testing to selected men depending on individual circumstances (grade C). However, the grade D recommendation remains in place for men over 70 yr. Finally, a comparison of systematic and opportunistic screening suggested a reduction in overdiagnosis and cancer-specific mortality by systematic screening, whilst opportunistic screening resulted in a higher overdiagnosis rate with a marginal survival benefit at best [31].

The use of DRE alone in the primary care setting has sensitivity and specificity below 60%, and therefore cannot be recommended to exclude PCa [32]. However, informed men requesting an early diagnosis should be given a PSA test and should undergo a DRE. A risk-adapted strategy targeting men at a higher risk of PCa might reduce the number of unnecessary further tests. These higher risks include men aged >50 yr (>45 yr in men of African descent) or with a family history of PCa [9]. In men harbouring a *BRCA* mutation (mainly *BRCA2*), screening might be offered at the age of 40 yr [16]. Men with PSA values >1 ng/mL at the age of 40 yr and >2 ng/mL at 60 yr [33,34] are at an increased risk of PCa metastasis or death several decades later.

If screening is considered, the CAP trial in men aged 50–69 yr suggested that a single PSA test did not improve PCa-specific mortality. The single PSA screening detected more low-risk PCa cases but had no significant effect on PCa mortality after a median follow-up of 10 yr [35]. Optimal intervals for PSA testing and DRE follow-up are unknown. The proposal is a 2-yr interval for men at increased risk, whilst 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 [36]. Men who have <15 yr of life expectancy are unlikely to benefit from any form of early diagnosis.

Table 4 – Guidelines for screening and early detection.

Recommendations	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man with life-expectancy of at least 10–15 yr	Weak
Offer early PSA testing to well-informed men at an elevated risk of having PCa: 1 Men >50 yr of age 2 Men >45 yr of age with a family history of PCa 3 men of African descent >45 yr of age 4 Men carrying <i>BRCA2</i> mutations >40 yr of age	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 yr for those initially at risk: 1 Men with a PSA level of >1 ng/mL at 40 yr of age 2 Men with a PSA level of >2 ng/mL at 60 yr of age	Weak
Postpone follow-up to 8 yr in those not at risk Stop early diagnosis of PCa based on life expectancy and performance status; men who have life expectancy of <15 yr are unlikely to benefit	Strong

BRCA2 = breast cancer predisposition gene 2; PCa = prostate cancer; PSA = prostate-specific antigen.

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

4. Diagnosis

Definitive diagnosis depends on histopathological verification. In order to avoid unnecessary biopsies, a further risk assessment should be offered (Table 5).

An 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). PSA is a continuous parameter, with higher levels indicating a greater likelihood of PCa, precluding an optimal PSA threshold for detecting nonpalpable but cSPCa. A limited PSA elevation alone should be confirmed after a few weeks under standardised conditions (ie, no ejaculation, manipulations, or urinary tract infections) in the same laboratory before considering further testing. The empiric use of

Table 5 – Risk assessment for asymptomatic men.

Recommendations	Strength rating
To avoid unnecessary biopsies, offer further risk assessment to asymptomatic men with a normal digital rectal examination and a prostate-specific antigen level between 2 and 10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: 1 Risk calculator 2 Imaging 3 An additional serum or urine-based test	Strong
	Weak

Table 6 – Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 cancer detection^a.

ISUP grade		ISUP ≥ 2			ISUP ≥ 3		
		Cochrane meta-analysis [40]	MRI-FIRST trial [41]	4M trial [42]	Cochrane meta-analysis [40]	MRI-FIRST trial [41]	4M trial [42]
Biopsy naïve	Added value of MRI-TBx	6.3% (4.8–8.2)	7.6% (4.6–11.6)	7.0% (ND)	4.7% (3.5–6.3)	6.0% (3.4–9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6–6.9)	5.2% (2.8–8.7)	5.0% (ND)	2.8% (1.7–4.8)	1.2% (0.2–3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7–32.6)	37.5% (31.4–43.8)	30% (ND)	15.5% (12.6–19.5)	21.1% (16.2–26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7–11.8)	–	–	6.3% (5.2–7.7)	–	–
	Added value of systematic biopsy	2.3% (1.2–4.5)	–	–	1.1% (0.5–2.6)	–	–
	Overall prevalence	22.8% (20.0–26.2)	–	–	12.6% (10.5–15.6)	–	–

ISUP = International Society for Urological Pathology (grade); MRI-TBx = magnetic resonance imaging targeted biopsies; ND = not defined.

^aThe absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique. If a given biopsy technique is added (or omitted) to compute the percentage of cancers diagnosed in excess (or missed), it is necessary to take into account the cancer prevalence in the population.

antibiotics in an asymptomatic man should not be undertaken [37].

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. It is outperformed by some biomarkers that could help in discriminating between aggressive and nonaggressive tumours [38]. However, at this time, data are too limited to implement these markers into routine screening programmes. Risk calculators developed from cohort studies may also be useful in reducing further testing. None has clearly shown superiority over the others or can be considered optimal [39].

Multiparametric magnetic resonance imaging (mpMRI) is a major tool for biopsy optimisation with pooled sensitivity and specificity of 0.91 (95% CI: 0.83–0.95) and 0.37 (95% CI: 0.29–0.46) for ISUP grade ≥ 2 cancers, and 0.95 (95% CI: 0.87–0.99) and 0.35 (95% CI: 0.26–0.46) for ISUP grade ≥ 3 cancers, respectively [40]. MRI-TBx significantly outperforms systematic biopsy (SBx) for the detection of ISUP grade ≥ 2 cancers in the repeat-biopsy setting. In biopsy-naïve patients, the difference appears to be less marked and was not significant in the MRI-FIRST and 4M trials [41,42], whilst it was significant in the PRECISION trial [43]. However, it remains in favour of MRI-TBx in all three studies. In biopsy-naïve patients, addition of TBx increases the number of detected ISUP grade ≥ 2 and grade ≥ 3 PCa by 20–23% and 21–30%, respectively, whilst omission of SBx would miss 14–16% of ISUP grade ≥ 2 PCa and 6–27% of ISUP grade ≥ 3 PCa. In the repeat-biopsy setting, addition of TBx increases the number of detected ISUP grade ≥ 2 and grade ≥ 3 PCa by 40% and 50%, respectively; omission of SBx would miss 10% of ISUP grade ≥ 2 and 9% grade ≥ 3 PCa (Table 6). Biopsying only patients with a Likert/Prostate Imaging Reporting and Data System (PI-RADS) threshold of ≥ 3 may avoid around 30% (95% CI: 23–38) of all biopsy procedures, whilst missing 11% (95% CI: 6–18) of all detected ISUP grade ≥ 2 cancers [40]. Combining prostate-specific antigen

density (PSAD) with the PI-RADS score may help define patients who need biopsy. In patients with negative mpMRI findings (PI-RADS 1–2), the risk of finding csPCa at subsequent SBx is usually $\leq 10\%$ if the PSAD is < 0.15 ng/mL/cc. In contrast, it is 27–40% if the PSAD is > 0.15 –0.20 ng/mL/cc [44–46].

Despite the use of the PI-RADS version 2 scoring system [47], mpMRI inter-reader reproducibility remains moderate at best [48], which currently limits its broad use by nondedicated radiologists. However, significant improvement in the accuracy of mpMRI can be observed over time, especially after implementation of PI-RADS version 2 scoring and multidisciplinary meetings using pathological correlation and feedback [49].

It must be emphasised that mpMRI has been evaluated only in patients in whom the risk of csPCa was judged high enough to deserve biopsy. Therefore, prebiopsy mpMRI must not be used as an initial screening tool. Based on its low specificity, mpMRI in very low-risk patients would result in an increase in false-positive findings and subsequent unnecessary biopsies (Table 7).

5. Prostate biopsy

TRUS-guided or transperineal ultrasound-guided biopsy using an 18 G biopsy needle and a periprostatic block is the standard of care. When the same numbers of cores are taken, both transrectal and transperineal approaches, when performed without prior imaging with MRI, have comparable detection rates [50]; however, some evidence suggests a reduced risk of infection with the transperineal route [51]. Where mpMRI has shown a suspicious lesion, MR-TBx can be obtained through cognitive guidance, ultrasound/magnetic resonance fusion software, or direct in-bore guidance. Current literature does not show clear superiority of one technique over another [52]. At least four TBx samples should be taken from each suspicious lesions

Table 7 – Multiparametric MRI and biopsy: when and practical impact of result.

Introductory statement	LE
Systematic biopsy is an acceptable approach if mpMRI is unavailable.	3
Recommendations	Strength rating
<i>Recommendations for all men</i>	
Do not use mpMRI as an initial screening tool	Strong
Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback	Strong
<i>Recommendations in biopsy-naïve men</i>	
Perform mpMRI before prostate biopsy	Strong
When mpMRI is positive (ie, PI-RADS ≥ 3), combine targeted and systematic biopsy	Strong
When mpMRI is negative (ie, PI-RADS ≤ 2) and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient	Weak
<i>Recommendations in men with prior negative biopsy</i>	
Perform mpMRI before prostate biopsy	Strong
When mpMRI is positive (ie, PI-RADS ≥ 3), perform targeted biopsy only	Weak
When mpMRI is negative (ie, PI-RADS ≤ 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared decision making with the patient	Strong
LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System.	

[53,54]. On baseline biopsies, where no prior mpMRI has been performed or where mpMRI has not shown any suspicious lesion, the sample sites should be bilateral from the apex to base, as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from DRE/TRUS suspect areas.

Oral or intravenous antibiotics are recommended. For transrectal biopsy, quinolones were the drugs of choice, with ciprofloxacin being superior to ofloxacin [55]. A 3-d antibiotic prophylaxis regimen provided no benefit over single-dose prophylaxis [56]. Increased quinolone resistance is associated with a rise in severe postbiopsy infection [57]. Risk factors for quinolone resistance include previous TRUS biopsy, a current indwelling catheter, a urogenital infection, an international travel, or hospital admission within the previous 6 mo. Patients with any of these risk factors should be offered TRUS biopsy with prior rectal swab culture, targeted antibiotic prophylaxis, or a transperineal approach [58]. Rectal disinfection with povidone-iodine may also be considered in TRUS biopsy [58]. For transperineal biopsy, which avoids rectal flora, only a single dose of intravenous cephazolin is sufficient [59].

Table 8 – Guidelines for staging of prostate cancer.

	Strength rating
<i>Any risk group staging</i>	
Use prebiopsy mpMRI for local staging information	Weak
<i>Low-risk localised disease</i>	
Do not use additional imaging for staging purposes	Strong
<i>Intermediate-risk disease</i>	
In ISUP grade = 3, include at least cross-sectional abdominopelvic imaging and a bone scan for metastatic screening	Weak
<i>High-risk localised disease/locally advanced disease</i>	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone scan	Strong
ISUP = International Society for Urological Pathology; mpMRI = multiparametric magnetic resonance imaging.	

Each biopsy site should be reported individually, including its location, the ISUP 2005 GS, and extent. ISUP 2014 grade should be provided as a global grade, taking into account the Gleason grades of cancer foci in all biopsy sites [20]. If identified, lymphovascular invasion, perineural invasion, and extraprostatic extension (EPE) must each be reported, as well as intraductal carcinoma or cribriform pattern, as these represent independent factors for metastasis [60] and CSS [61].

6. Staging of PCa

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 8. The field of noninvasive nodal and metastatic staging of PCa is evolving very rapidly.

6.1. N category

Abdominal CT and MRI indirectly assess nodal invasion by using lymph node (LN) diameter and morphology. Usually, LNs with a short axis of >8 mm in the pelvis and >10 mm outside the pelvis are suspicious for malignancy, with sensitivity below 40% [62]. Pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases are 62% (95% CI: 51–66%) and 92% (95% CI: 89–94%), respectively [63]. Comparisons between choline PET/CT and diffusion-weighted MRI yielded contradictory results, with PET/CT sensitivity found to be superior [64], similar [65], or inferior [66]. From a meta-analysis, the pooled sensitivity and specificity of PSMA PET/CT for nodal staging on a per-node analysis are 75% and 99%, respectively [67]. A prospective, multicentre validation of ^{68}Ga -PSMA PET/CT in patients with newly diagnosed PCa and negative bone scan findings resulted in per-patient-based sensitivity and specificity of 41.5% (95% CI: 26.7–57.8) and 91% (95% CI: 79.3–96.6), respectively. A treatment change occurred in

12.6% of patients [68]. Based on a systematic review, ^{68}Ga -PSMA PET/CT was found to have higher sensitivity (0.65 [95% CI: 0.49–0.79], compared with 0.41 [95% CI: 0.26–0.57]) to mpMRI and a comparable specificity (0.94 [95% CI: 0.88–0.97], compared with 0.92 [95% CI: 0.86–0.95]) for preoperative nodal staging in intermediate- and high-risk PCa [69].

6.2. M category

Bone scintigraphy has been the most widely used method for evaluating bone metastases of PCa, with combined sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%), respectively, at patient level [70]. Diffusion-weighted whole-body and axial MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa [71]. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography, and abdominopelvic CT [72]. As compared with choline PET/CT, whole-body MRI is more sensitive whilst choline PET/CT shows higher specificity [70].

A recent systematic review on ^{68}Ga -PSMA PET reported high variation in sensitivity (median sensitivity on per-lesion analysis of 33–92% and on per-patient analysis of 66–91%) with good specificity (per lesion 82–100% and per patient 67–99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [73]. One prospective multicentre study evaluated changes in planned management before and after ^{68}Ga -PSMA PET/CT in 108 intermediate- and high-risk patients referred for primary staging. As compared with conventional staging, additional LN and bone/visceral metastases were detected in 25% and 6% of patients, respectively [74]. Management changes occurred in 21% of patients.

Evidence shows that choline PET/CT, PSMA PET/CT, and MRI provide a more sensitive detection of LN and bone metastases than the classical work-up. This has been confirmed in a prospective randomised trial including 302 newly diagnosed high-risk PCa. ^{68}Ga -PSMA PET/CT had a 27% greater accuracy for nodal and metastases staging than bone scan and CT scan (92% vs 65%; $p < 0.0001$), as well as a better sensitivity (85% vs 38%) and specificity (98% vs 91%) [75]. Yet, the clinical benefit of detecting metastases at an earlier time point and the resulting stage shift remain unclear [67]. In addition, the prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests are unknown. In particular, it is unclear whether patients with metastases, detectable only with PSMA PET/CT or whole-body MRI, should be managed using systemic therapies, or whether they should be subjected to aggressive local and metastases-directed therapies [76]. Results from randomised controlled trials (RCTs) evaluating the management and outcome of patients with (and without) metastases detected by more sensitive imaging are awaited before evidence-based decisions can be made to treat patients based on the results of these tests.

7. Evaluating life expectancy and health status

Older men with a high incidence of PCa may be undertreated. In the USA, only 41% of patients aged >75 yr with intermediate- and high-risk disease receive curative treatment compared with 88% of patients aged 65–74 yr [77].

Evaluation of life expectancy and health status is important in clinical decision making on screening, diagnosis, and treatment of PCa. In localised disease, >10 yr life expectancy is considered mandatory for any survival benefit from local treatment. Country-specific life tables are available; however, survival must be individualised [78] based, for example, on gait speed [79] or using tools such as the Cumulative Illness Score Rating–Geriatrics (CISR-G) [80], the Charlson Comorbidity Index (CCI) [81], or the clinical frailty score [82].

The International SIOG PCa Working Group recommends that treatment for senior adults should be based on a systematic evaluation of health status using the G8 screening tool [36] as well as the Mini-COG [83]. This is summarised in Fig. 1.

8. 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.

8.1. AS and watchful waiting

AS aims to reduce overtreatment in men with 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 (Table 9).

Mortality from untreated screen-detected PCa in patients with ISUP grade 1–3 can be as low as 7% at 15-yr follow-up [84]. An RCT was unable to show any survival difference at 10 yr between RP and WW in 731 men with screen-detected clinically organ-confined PCa [85]. Only patients with intermediate-risk PCa or with a PSA value of >10 ng/mL had a significant OS benefit from RP (hazard ratio: 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 without any curative treatment found that in men having a CCI score of ≥ 2 , tumour aggressiveness had little impact on OS at 10 yr [86]. These data highlight the role of WW in some patients with individual life expectancy of <10 yr.

A systematic review summarised the available data on AS [87]. There is considerable variation between studies regarding patient selection, follow-up policies, and criteria to switch to an active treatment. Selection criteria for AS are limited by a lack of prospective RCTs and led to a consensus meeting [88]. The most often published criteria include ISUP

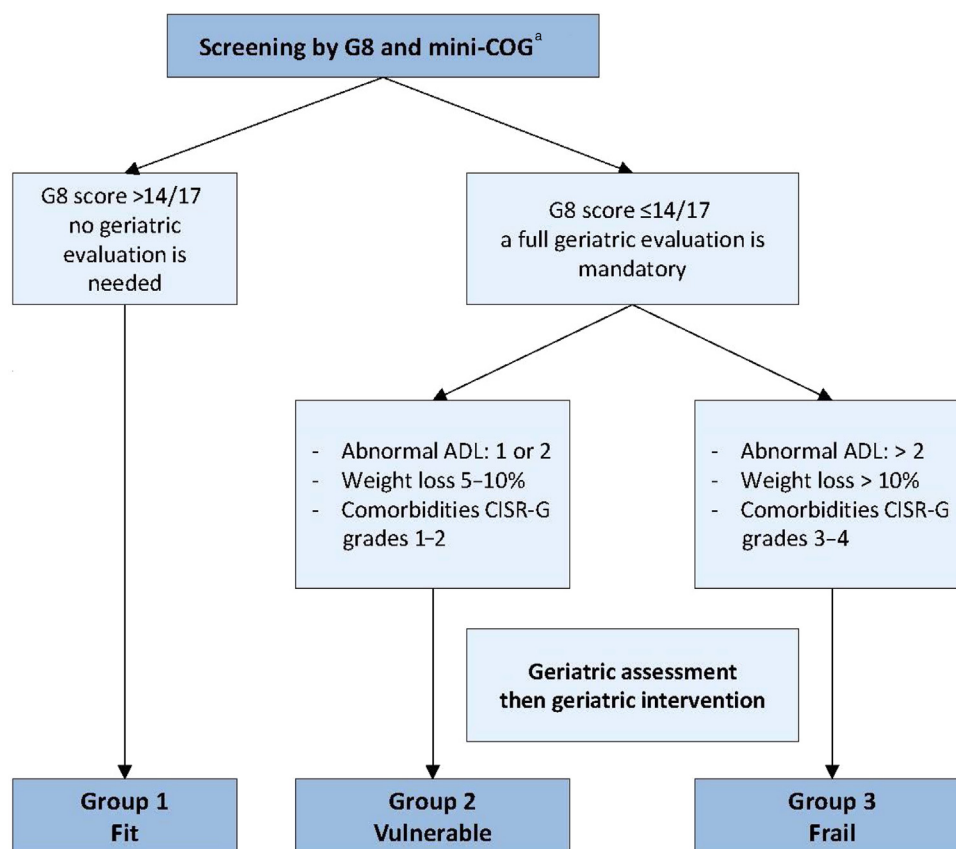


Fig. 1 – Workflow for stratifying senior adults. ADL = activities of daily living; CISR-G = Cumulative Illness Score Rating–Geriatrics. ^a For Mini-COG, a cut-off point of $\leq 3/5$ indicates a need to refer the patient for full evaluation of potential dementia. Reproduced with permission of Elsevier, from the study of Boyle et al [36].

grade 1, cT1c or cT2a, PSA < 10 ng/mL, no upfront mpMRI, and PSAD < 0.15 ng/mL/cc [89]. The latter threshold remains controversial [90]. In addition, where available, upfront mpMRI should be performed systematically [88]. There was no agreement regarding the maximum number of involved cores or the maximum percentage of core involvement, although there was recognition that cT2c disease and extensive disease on mpMRI should exclude men from AS [88]. A systematic review and meta-analysis found three clinicopathological variables that were significantly associated with reclassification: PSA density, more than two positive cores, and African-American descent [91].

There was an agreement that men with favourable ISUP 2 cancer (PSA < 10 ng/mL, < cT2b, and a small number of positive cores) could also be considered for deferred

treatment, especially following TBx [88]. However, it is clear that the presence of any grade 4 pattern on SBx is associated with a three-fold increased risk of metastases compared with ISUP grade 1, whilst a PSA value of up to 20 ng/mL might be an acceptable threshold [92,93]. Therefore, care must be taken when explaining this treatment strategy in selected intermediate-risk situations, especially in patients with the longest life expectancy.

Men with ISUP 3 disease should not be considered for AS [88], as well as those harbouring ductal or cribriform adenocarcinoma [94], sarcomatoid carcinoma, small cell carcinoma, EPE or lymphovascular invasion in needle biopsy, and perineural invasion.

Confirmatory rebiopsy within 6–12 mo to exclude sampling error was mandatory [92]. This might be

Table 9 – 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, repeat biopsy, mpMRI	Not predefined
Life expectancy	>10yr	<10 yr
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Disease stage	Mainly for low-risk patients	Can apply to patients at all stages

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

reconsidered following upfront mpMRI and a combination of TBx and SBx [88,95]. Whilst routine prebiopsy mpMRI is recommended, in men eligible for AS based upon SBx alone, mpMRI can detect suspicious lesions inducing reclassification at confirmatory biopsy [96]. However, SBx retains substantial added value at confirmatory biopsy [97]. The added value of the mpMRI targeted confirmatory biopsies has been confirmed in a prospective trial after 2 yr of follow-up [98].

The follow-up strategy is based on serial DRE (at least once yearly), PSA (at least once every 6 mo), and repeated biopsy. Several authors have reported data on sequential mpMRI evaluation, summarised in a review [99], with an overall upgrading from ISUP 1 to ISUP > 2 PCa of 30% following combined TBx and standard biopsies. Upgrading occurred in 39% of patients with MRI showing progression and in 21% of patients with MRI showing stable findings or regression. However, data suggesting avoidance of repeat biopsy or limiting them to MRI change or PSA progression only are too limited to be considered in routine clinical practice.

Men may remain on AS whilst they continue to consent and have life expectancy of >10 yr, and the disease remains indolent. Patient anxiety about continuing AS is recognised as a valid reason for switching to an active treatment [88]. More common is the development of other comorbidities, which may result in a decision to transfer to a WW strategy. A PSA change alone (especially a PSA doubling time of <3 yr) has a weak link with grade progression [100]. Similar to MRI change, this should trigger further investigation, including rebiopsy before considering active treatment [88].

8.2. Radical prostatectomy

The goal of RP is eradication of PCa whilst 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 in an RCT [101]. Patients should not be denied this procedure on the grounds of age alone [36] provided that they have at least 10 yr of life expectancy and are aware that increasing age is linked to an increased incontinence risk. Nerve-sparing RP can be performed safely in most men with localised PCa and, whilst preserving parasympathetic nerve branches of the pelvic plexus, might spare erectile function [102]. A high risk of EPE, such as any cT2c or cT3 or any ISUP > 3, is an usual contraindication for nerve sparing. An externally validated nomogram predicting side-specific EPE can help guide decision making [103]. Multiparametric MRI 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 pT3a stages [104]. Again the experience of the radiologist remains of paramount importance.

Outcome after RP has been shown to be dependent on both surgeon [105] and hospital volume [106]. Although various volume criteria have been set worldwide, the level of evidence is insufficient to pinpoint a specific lower volume limit.

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 margin rate compared with laparoscopic prostatectomy, although there is considerable methodological uncertainty. No formal differences exist in cancer-related continence or erectile dysfunction (ED) outcomes [107]. After 24 mo of follow-up, a RCT including 326 men did not reveal any significant differences in functional outcomes between the open and the robotic approach [108].

8.2.1. Pelvic LN dissection

Despite novel imaging techniques, pelvic LN dissection (PLND) remains the gold standard for N staging. The individual risk of finding positive LNs can be estimated using externally validated preoperative nomograms [109]. Updated versions with a higher threshold, also including mpMRI findings and TBx results, have been developed [110]. Whilst one recently updated nomogram may present the clinically most effective tool to date as it may spare more patients from an unnecessary PLND (using a threshold of 7%), a full external validation is still outstanding [111].

A risk of nodal metastases of >7% is an indication to perform an extended PLND (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 a pathological analysis. With this template, 75% of all anatomic landing sites are cleared, resulting in improved pathological staging, but at the cost of higher complication rates (19.8% vs 8.2%), mainly related to significant lymphoceles [112]. A recent systematic review demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [112]. However, it is generally accepted that ePLND provides important information for staging and prognosis.

A sentinel nodal dissection has shown sensitivity of 95.2% and a negative predictive value of 98.0% in detecting nodal metastases at ePLND in a systematic review [113]. However, based on insufficient quality evidence, sentinel node biopsy is still considered an experimental nodal staging procedure.

In men with pN + PCa, early adjuvant androgen deprivation therapy (ADT) was shown to achieve a 10-yr CSS rate of 80% [114]. Pelvic radiation therapy (RT) combined with long-term ADT appeared to be beneficial in pN++ PCa patients treated with an ePLND, with at least a local control improvement and possibly survival. The optimal candidates remain unclear: number of positive nodes, ISUP score, and margin status [115–117]. No data are available regarding adjuvant external-beam radiation therapy (EBRT) alone.

8.2.2. Low-risk PCa

The decision to offer RP as an alternative to AS should be based only on the patient's preference, the risk of side effects, and the probability of clinical progression. No LN dissection is needed.

8.2.3. Intermediate-risk localised PCa

Data from SPCG-4 [101] and a preplanned subgroup analysis (PIVOT) [118] highlight the benefit of RP compared with WW. The risk of having positive nodes is 3.7–20.1% [109]. An ePLND should be performed if the estimated risk for pN + exceeds 5% [109]. Otherwise, a nodal dissection can be omitted whilst accepting a low risk of missing positive nodes.

8.2.4. High-risk and locally advanced 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% [109]. Regarding each individual high-risk factor in patients treated with a multimodal approach, an ISUP 4/5 prostate-confined adenocarcinoma has a good prognosis after RP. In addition, frequent downgrading exists between the biopsy and the specimen GS [119]. At 10-yr follow-up, the CSS is up to 88% [120,121]. A PSA value of >20 ng/mL is associated with CSS at 10 yr ranging between 83% and 91% [120–122]. RP for cT3N0 PCa is associated with an increased risk of positive margins and pN + and/or distant relapse. Retrospective case series demonstrated CSS at 10 yr between 85% and 92% [123]. 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 [123]. At 10 yr, overall 91.3% CSS was observed: 95% for those having only one risk factor (ie, ISUP > 3, cT category higher than cT2, or PSA > 20 ng/mL), 88% for those having a cT3–4 and PSA > 20 ng/mL, and 79% if all three risk factors were present.

8.2.5. Adjuvant treatment after RP

Adjuvant use of bicalutamide 150 mg daily did not improve progression-free survival (PFS) in localised disease, whilst it improved PFS for locally advanced disease after RT. However, this never translated to an OS benefit [124]. A systematic review showed a possible benefit for PFS, but not for OS, with adjuvant androgen ablation [125].

EPE and positive surgical margins are associated with an increased risk of recurrence. Adjuvant RT (ART) was associated with improved biochemical PFS in three RCTs [126–128], although only SWOG 8794 suggested improved OS [128]. Preliminary data from RAVES and RADICALS, as well as a meta-analysis combining all findings, have been reported, suggesting that ART and early salvage radiotherapy (SRT) offer similar outcomes for event-free survival [129–131]. Full publications are needed before any further conclusions can be drawn. Thus, for patients with undetectable postoperative PSA and combined high-risk features such as pT3/R1/ISUP grades 4 and 5, two options can be offered in the framework of informed consent: either

immediate adjuvant EBRT to the surgical bed after recovery of urinary function or monitoring followed by early SRT before the PSA exceeds 0.5 ng/mL [132]. A recent phase 3 RCT comparing adjuvant docetaxel against surveillance after RP for locally advanced PCa failed to show any oncological benefit [133].

8.2.6. Persistent PSA after RP

Between 5% and 20% of men continue to have detectable PSA after RP (most often defined as post-RP PSA \geq 0.1 ng/mL within 4–8 wk of surgery) [134,135]. It is often associated with poor prognosis: 74% experience further PSA progression [134], and have an increased risk of metastases [136] and death [137]. However, not all patients with persistent PSA experience clinical recurrence [138]. As for PSA relapse, PSMA PET/CT is the most sensitive imaging modality to detect metastases [139].

The benefit of SRT in patients with persistent PSA remains unclear due to a lack of RCTs. Positive results have been suggested by Preisser et al [137] after a 1:1 propensity score matching between SRT and no RT; OS rate after RP was 86.6% versus 72.6% in the entire cohort ($p < 0.01$ at 10 yr). Poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade ≥ 4 in the specimen, and pT3b status [135,140,141]. The addition of ADT may improve PFS [140]. The available data suggest that patients with PSA persistence after RP may benefit from early aggressive multimodality treatment; however, the lack of prospective RCTs makes firm recommendations difficult.

8.2.7. Side effects of RP

Postoperative incontinence and ED are common problems following RP. There is no major difference based on the surgical approach, with an overall continence rate of 89–100% when a robotic procedure was conducted compared with 80–97% for a retropubic approach [142].

In a prospective controlled nonrandomised trial of patients treated in 14 centres, the incontinence rate was 21.3% after robotic and 20.2% after open surgery at 12 mo. The adjusted odds ratio (OR) was 1.08 (95% CI, 0.87–1.34). ED was observed in 70.4% after robotic and 74.7% after open surgery. The adjusted OR was 0.81 (95% CI, 0.66–0.98) [143]. In a RCT, no functional outcome difference was observed between open and robotic surgery after 2 yr [108].

8.3. Definitive RT

Dose-escalated intensity-modulated radiation therapy (IMRT) with image-guided RT (IGRT) is the gold standard for EBRT because it is associated with less toxicity than three-dimensional conformal radiation therapy (3D-CRT) techniques [144]. 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 of 74–80 Gy leads to a significant improvement in 10-yr biochemical recurrence-free survival [145–149]. In men with intermediate- and high-risk PCa, there is also evidence to support an OS benefit from a nonrandomised but well-

Table 10 – Major phase 3 randomised trials of moderate hypofractionation for primary treatment.

Study/author	n	Risk, ISUP grade, or NCCN	ADT	RT regimen	Median FU (mo)	Outcome
Lee et al, J Clin Oncol, 2016 [184]	550	Low risk	None	70 Gy/28 fx	70	5 yr DFS 86.3% (NS)
	542			73.8 Gy/41 fx		5 yr DFS 85.3%
Dearnaley et al, Lancet Oncol, 2016 [185]	1077/19 fx	15% low	3–6 mo before	57 Gy/19 fx	62	5 yr BCDF
	1074/20 fx	73% intermediate	and during EBRT	60 Gy/20 fx		85.9% (19 fx)
	1065/37 fx	12% high		74 Gy/37 fx		90.6% (20 fx)
						88.3% (37 fx)
Incrocci et al, Lancet Oncol, 2016 [186]	403	30% ISUP grade 1	None	64.6 Gy/19 fx	60	5 yr RFS 80.5% (NS)
	392	45% ISUP grade 2–3		78 Gy/39 fx		5 yr RFS 77.1%
		25% ISUP grade 4–5				
Catton et al, Clin Oncol, 2017 [187]	608	Intermediate risk	None	60 Gy/20 fx	72	5 yr BCDF both arms 85%
		53% T1c				HR: 0.96 (NS)
		46% T2a–c				
	598	9% ISUP grade 1		78 Gy/39 fx		
		63% ISUP grade 2				
		28% ISUP grade 3				

ADT=androgen deprivation therapy; BCDF=biochemical or clinical disease failure; DFS=disease-free survival; EBRT=external-beam radiation therapy; fx=fractions; FU=follow-up; HR=hazard ratio; ISUP=International Society for Urological Pathology; NCCN=National Comprehensive Cancer Network; NS=not significant; RFS=recurrence-free survival; RT=radiotherapy.

conducted propensity-matched retrospective analysis covering a total of 42 481 patients [150].

Biological modelling was the rationale to investigate hypofractionation (HFX): increased dose per fraction delivered in fewer fractions resulting in the investigation in RCTs in localised disease.

Moderate HFX is defined as RT with 2.5–4 Gy per fraction. Several studies report on moderate HFX applied in various techniques and, in part, also including hormone therapy (Table 10). A systematic review concludes that studies on moderate HFX delivered with 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking [151]. Moderate HFX should be performed only by experienced teams using high-quality EBRT using IMRT and IGRT in selected patients and adhering to published phase 3 protocols (see Table 10). HFX requires meticulous quality assurance, excellent image guidance, and close attention to organ-at-risk dose constraints to minimise the acute and long-term toxicity risk.

Ultra-HFX has been defined as RT with >4 Gy per fraction [152]. It requires IGRT and stereotactic body radiotherapy. Short-term biochemical control is comparable with conventional fractionation. However, there are concerns about high-grade genitourinary and rectal toxicity, and long-term

side effects remain unclear [151,153]. A systematic review included 38 studies with 6116 patients who received RT with <10 fractions and ≥5 Gy per fraction. Five- and 7-yr biological relapse-free survival rates were 95.3% and 93.7%, respectively, and estimated late grade ≥3 genitourinary and gastrointestinal toxicity rates were 2.0% and 1.1%, respectively [154]. Therefore, it seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome (Table 11).

8.3.1. Low-risk PCa

Offer moderate HFX, dose-escalated IMRT (74–78 Gy), or low-dose-rate brachytherapy (LDR BT) as an alternative to AS. This should be based only on the patient's preference, probabilities of clinical progression, and possible side effects.

8.3.2. Intermediate-risk PCa

Patients suitable for ADT should be given combined dose-escalated IMRT (76–78 Gy) or moderate hypofractionated RT with short-term ADT (4–6 mo) [155]. For patients unsuitable for (eg, due to comorbidities) or unwilling to accept (eg, to preserve their sexual health) ADT, the recommended treatment is IMRT at a dose of 76–80 Gy or a combination of IMRT and BT.

Table 11 – Selected trials on ultrahypofractionation.

Reference	n	Median FU (mo)	Risk group	Regimen (TD/fx)	Outcome
Widmark et al, Lancet, 2019 [188]	1200	60	89% intermediate 11% high	78 Gy/39 fx, 8 wk 42.7 Gy/7 fx, 2.5 wk No SBRT	FFS at 5 yr 84% in both arms Grade ≥2 acute GU toxicity 23% vs 28% (p=0.057) No difference in long-term toxicity
Brand et al, Lancet Oncol, 2019 [189]	847	Variable	8% low 92% intermediate	78 Gy/39 fx, 8 wk 36.25 Gy/5 fx, 1–2 wk SBRT	Grade ≥2 acute GI toxicity 12% vs 10% (p=0.38) Grade ≥2 acute GU toxicity 27% vs 23% (p=0.16)

FFS = failure-free survival; fx = fractions; FU = follow-up; GI = gastrointestinal; GU = genitourinary; n = number of patients; SBRT = stereotactic body radiotherapy; TD = total dose.

8.3.3. Localised high-risk PCa

The standard of care should be dose-escalated IMRT, possibly including the pelvic lymphatics [156]. A BT boost is an option as well [157]. Long-term ADT, generally for 2–3 yr, is always mandatory. The duration of ADT has to take into account performance status, comorbidities, and the number of poor prognostic factors.

8.3.4. Locally advanced PCa: T3–4 N0, M0

The standard of care for patients with T3–4 N0, M0 locally advanced PCa is IMRT combined with long-term ADT for at least 2–3 yr, as it results in better OS [158–160]. The combination is significantly better than EBRT or ADT monotherapy [161]. In both high-risk localised and locally advanced PCa, an upfront combination with docetaxel improves only relapse-free survival, with no clear survival benefit [162,163].

8.3.5. LN irradiation (cN0)

In men with cN0 PCa, RCTs failed to show a benefit from prophylactic pelvic nodal irradiation (46–50 Gy) in high-risk cases [164].

8.3.6. Side effects of definitive RT

Zelevsky et al [144] 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 and 81 Gy, with a median follow-up of 10 yr. The use of IMRT significantly reduced the risk of late grade ≥ 2 gastrointestinal toxicity to 5% compared with 13% with 3D-CRT. The incidence of grade ≥ 2 late genitourinary toxicity was 20% with 81 Gy IMRT versus 12% with lower doses. The overall incidences of late grade 3 toxicity were 1% and 3% for gastrointestinal and genitourinary toxicity, respectively.

A systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to RT 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 [165].

8.3.7. Treatment of cN1 PCa

The treatment of cN1 M0 PCa was evaluated in a systematic review including five studies [166] as well as in the STAMPEDE trial [167]. The findings suggest an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT, as compared with ADT alone, but none of the included studies were RCTs and neither of the two local treatment approaches proved superior in this setting.

8.4. Brachytherapy

LDR BT uses permanent radioactive seeds implanted into the prostate, and is an option for those with low-risk and favourable intermediate-risk disease (low-volume GS 3 + 4), prostate volume $< 50 \text{ cm}^3$, and an International Prostate Symptom Score of ≤ 12 [168]. Up to 85% relapse-free survival

at 10 yr is demonstrated [169]. LDR as a boost with EBRT can be used as dose escalation 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%) [170]. Careful selection of patients using uroflowmetry can avoid these significant side effects [171]. Previous TURP for benign prostatic hyperplasia increases the risk of postimplantation incontinence and urinary morbidity, and should be considered a relative contraindication. ED develops in about 40% of the patients after 3–5 yr.

High-dose rate (HDR) BT uses a radioactive source temporarily introduced into the prostate to deliver radiation. The use of published guidelines is strongly recommended [172]. HDR BT can be delivered in a single fraction or in 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. QoL changes are similar to high-dose EBRT alone [173]. HDR BT 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 [174].

9. Comparing various local therapies

The ProtecT trial is the only available RCT comparing three treatment modalities. A total of 1643 patients were randomised between active treatment (RP or EBRT + 6 mo of ADT) and active monitoring (AM) [175]. In this AM schedule, only patients with a PSA rise of $> 50\%$ in 12 mo underwent a repeat biopsy. Of the patients, 56% had low-risk disease, with 90% having a PSA level of $< 10 \text{ ng/mL}$, 77% having ISUP grade 1 (20% ISUP grade 2–3), and 76% having T1c, whilst the other patients were mainly of intermediate risk. After 10 yr of follow-up, the CSS was not statistically different between those actively treated and those on AM (99.3% and 98.2%, respectively, $p = 0.08$), as was the OS. Only metastatic progression differed (5.6% in the AM group as compared with 2.6% in the treated group). No significant difference in outcome was observed between the two active

Table 12 – Guidelines for quality of life in men undergoing local treatments.

Recommendations	Strength rating
Advise patients eligible for active surveillance that global quality of life is equivalent, for up to 5 yr, to radical prostatectomy or external beam radiotherapy	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients	Strong
Advise patients treated with brachytherapy about the negative impact on irritative urinary symptomatology at 1 yr but not after 5 yr	Weak

Table 13 – Summary of guidelines for local treatment of prostate cancer with curative intent.

		Strength rating
General recommendations		
Inform patients that no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall and prostate cancer-specific survival for clinically localised disease		Strong
Offer a WW policy to asymptomatic patients with life expectancy of <10 yr (based on comorbidities)		Strong
Active therapeutic options outside surgery and radiotherapy		
Offer only cryotherapy and high-intensity focused ultrasound within a clinical trial setting or a well-designed prospective cohort study		Strong
Offer only focal therapy within a clinical trial setting or a well-designed prospective cohort study		Strong
Guideline recommendations for the various disease stages		
<i>Low-risk disease</i>		
Active surveillance	Offer AS to patients with life expectancy of >10 yr and low-risk disease	Strong
	Patients with intraductal and cribriform histology on biopsy should be excluded from AS	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if confirmatory biopsy is performed	Strong
	Counsel patients about the possibility of needing further treatment in the future	Strong
Active treatment	Offer surgery and RT as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression	Weak
<i>Intermediate-risk disease</i>		
Active surveillance	Offer AS to highly selected patients (<10% Gleason pattern 4) accepting the potential increased risk of further metastases	Weak
Radical prostatectomy	Offer RP to patients with intermediate-risk disease and life expectancy of >10 yr	Strong
Extended pelvic lymph node dissection	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease	Strong
	Perform an ePLND in intermediate-risk patients if the estimated risk for positive lymph nodes exceeds 5%	Strong
Radiotherapeutic treatment	Offer LDR brachytherapy to selected patients: patients without a previous TURP, with a good IPSS, and with a prostate volume of <50 ml	Strong
	For EBRT, use a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 wk or 70 Gy/28 fx in 6 wk), in combination with short-term neoadjuvant plus concomitant ADT (4–6 mo)	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76–80 Gy) or a combination with brachytherapy	Weak
Other therapeutic options	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment	Weak
<i>High-risk localised disease</i>		
Radical prostatectomy	Offer RP to selected patients with high-risk localised PCa, as part of potential multimodal therapy	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa patients	Strong
Radiotherapeutic treatments	In patients with high-risk localised disease, use EBRT (76–78 Gy) in combination with long-term ADT (2–3 yr)	Strong
	In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2–3 yr)	Weak
Therapeutic options outside surgery and radiotherapy	Do not use ADT monotherapy in asymptomatic patients	Strong
<i>Locally-advanced disease</i>		
Radical prostatectomy	Offer RP to highly selected patients with cT3b–T4 N0 or any cN1 only as part of multimodal therapy	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa patients	Strong
Radiotherapeutic treatments	In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT	Strong
Radiotherapeutic treatment combined with surgery	Offer patients with cN1 disease a local treatment (either RP or EBRT) plus long-term ADT	Weak
Therapeutic options outside surgery and radiotherapy	Offer ADT monotherapy only to those patients unwilling or unable to receive any form of local treatment if they have a PSA doubling time of <12 mo and a PSA value of >50 ng/mL, a poorly differentiated tumour, or troublesome local disease-related symptoms	Strong
Adjuvant treatment after radical prostatectomy		
	Do not prescribe adjuvant ADT in pN0 patients	Strong
	Offer adjuvant EBRT to the surgical field for highly selected patients	Strong
	Discuss three management options with patients with pN + disease after an ePLND, based on nodal involvement characteristics:	Weak
	1 Offer adjuvant ADT	
	2 Offer adjuvant ADT with additional RT	
	3 Offer observation (expectant management) to a patient after ePLND and ≤ 2 nodes with microscopic involvement, and a PSA value of <0.1 ng/mL and absence of extranodal extension	
Noncurative or palliative treatments in a first-line setting		
<i>Localised disease</i>		
Watchful waiting	Offer WW to asymptomatic patients not eligible for local curative treatment and those with short life expectancy	Strong

ADT = androgen deprivation therapy; AS = active surveillance; EBRT = external-beam radiation therapy; ePLND = extended pelvic lymph node dissection; fx = fractions; HDR = high dose rate; IPSS = International Prostate Symptom Score; LDR = low dose rate; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; TURP = transurethral resection of the prostate; WW = watchful waiting.

treatment groups. With up to 5 yr, no difference in the overall QoL was reported. However, urinary as well as sexual scores were worse in the RP group than in the AM and RT groups. For men receiving RT with 6 mo of ADT, EPIC bowel scores were poorer than in men receiving AM and RP in all domains [176]. The findings regarding RP and RT are supported by other observational studies [177,178].

Regarding high-risk disease, a formal systematic review was unable to claim for any form of local treatment superiority comparing RP used as part of a multimodal treatment or RT combined with long-term ADT [156].

These data and a synthesis of 18 randomised and nonrandomised studies in a systematic review involving 13 604 patients are the foundation of the following recommendations (Table 12) [179].

10. Alternative local treatment options

Besides RP, EBRT, and BT, other modalities have emerged as possible therapeutic options in patients with clinically localised PCa. However, patients with life expectancy of >10 yr should be informed fully that there are limited data on the long-term outcome for cancer control beyond 10 yr [180].

A systematic review compared cryotherapy versus RP and EBRT [181]. 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 with RP and EBRT in a systematic review [181] as the primary treatment for localised PCa. Data from 4000 patients across 21 studies were included. HIFU had significantly worse disease-free survival at 1 yr compared with EBRT. The differences were no longer significant at 3 yr. The quality of the evidence was poor due to high risks of bias across studies precluding any clear conclusion.

Recently, focal therapy has been developed, with the aim of ablating tumours selectively whilst sparing the neuro-vascular bundles, sphincter, and urethra. Available data from 3230 patients across 37 studies were analysed in a systematic review [182]. The overall quality of the evidence was low as the majority of studies were single centre, noncomparative, and retrospective in design, with heterogeneity in the definitions of outcomes plus variation in the strategy and duration of follow-up. Although the review suggested that focal therapy has a favourable toxicity profile in the short to medium term, its oncological effectiveness remains unproven due to lack of reliable comparative data against standard interventions such as RP and EBRT. The only available RCT compared padeliporfin-based vascular-targeted photodynamic therapy versus AS in men with very-low-risk PCa [183]. Given the lack of robust comparative data on medium- to long-term oncological outcomes,

significant uncertainties remain in regard to focal therapy as a proven alternative to either AS or radical therapy. For now, focal therapy should be performed only within the context of a clinical trial setting or a well-designed prospective cohort study.

11. Conclusions

The present text represents a summary of the 2020 EAU-EANM-ESTRO-ESUR-SIOG PCa guidelines. A summary of recommendations is presented in Table 13. For more detailed information and a full list of references, refer to the full-text version available at the EAU web site (<http://uroweb.org/guideline/prostate-cancer/>).

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