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Prostate Cancer – Editor's choice

EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer—2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent

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Abstract

Background and objective: 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 Urological Pathology (ISUP)-International Society of Geriatric Oncology

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(SIOG) guidelines provide recommendations for the management of clinically localised prostate cancer (PCa). This paper aims to present a summary of the 2024 version of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on the screening, diagnosis, and treatment of clinically localised PCa.

Methods: The panel performed a literature review of all new data published in English, covering the time frame between May 2020 and 2023. The guidelines were updated, and a strength rating for each recommendation was added based on a systematic review of the evidence.

Key findings and limitations: 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. The use of multiparametric magnetic resonance imaging in order to avoid unnecessary biopsies is recommended. When a biopsy is considered, a combination of targeted and regional biopsies should be performed. Prostate-specific membrane antigen positron emission tomography imaging is the most sensitive technique for identifying metastatic spread. Active surveillance is the appropriate management for men with low-risk PCa, as well as for selected favourable intermediate-risk patients with International Society of Urological Pathology grade group 2 lesions. Local therapies are addressed, as well as the management of persistent prostate-specific antigen after surgery. A recommendation to consider hypofractionation in intermediate-risk patients is provided. Patients with cN1 PCa should be offered a local treatment combined with long-term intensified hormonal treatment.

Conclusions and clinical implications: The evidence in the field of diagnosis, staging, and treatment of localised PCa is evolving rapidly. These PCa guidelines reflect the multidisciplinary nature of PCa management.

Patient summary: This article is the summary of the guidelines for "curable" prostate cancer. Prostate cancer is "found" through a multistep risk-based screening process. The objective is to find as many men as possible with a curable cancer. Prostate cancer is curable if it resides in the prostate; it is then classified into low-, intermediary-, and high-risk localised and locally advanced prostate cancer. These risk classes are the basis of the treatments. Low-risk prostate cancer is treated with "active surveillance", a treatment with excellent prognosis. For low-intermediary-risk active surveillance should also be discussed as an option. In other cases, active treatments, surgery, or radiation treatment should be discussed along with the potential side effects to allow shared decision-making.

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1. Introduction

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 Urological Pathology (ISUP)-International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer—2024, part I, provides a comprehensive update on the screening, diagnosis, and local treatment with curative intent for the management of clinically localised prostate cancer (PCa).

2. Methods

The most recent summary of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on PCa was published in 2021 based upon the 2020 update [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 2024 [2].

For the 2024 EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on PCa, new evidence was identified, collated, and appraised through a structured assessment of the literature. Databases searched included Medline, EMBASE, and the Cochrane Libraries. Detailed search strategies are available on the on the EAU website: www.uroweb.org/guidelines. Recommendations within the guidelines were developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. Strong recommendations are made when evidence quality is high and/or there is a favourable balance of benefits to harms and patient preferences. Weak recommendations are made when the evidence is of lower quality and/or benefits and patient preferences are less clear [3].

3. Guidelines

3.1. *Epidemiology and risk factors*

PCa remains the most common cancer in men in Europe (excluding skin cancer). Although the incidence of autopsy-detected cancers is generally the same in different parts of the world, the incidence of clinically diagnosed PCa varies widely and is high in Northern and Western Europe (age-standardised rates of 111.6 and 97.2 per 100 000 men per year) [4]. Age, African origin, and a family history

of PCa [5] 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 [6]. However, it appears that this is related to multiple single-nucleotide polymorphisms [7] rather than gene defects.

Nevertheless, carriers of gene alterations in *BRCA2* [8], *MSH2*, and *MSH6* (Lynch syndrome) [9] are at an increased risk and to a lesser degree those with *BRCA1* [10]. Only a small subpopulation of men have true hereditary disease (three or more cases in the same family, PCa in three successive generations, or two or more men <55 yr diagnosed with PCa), which is associated with an onset 6-7 yr earlier than nonhereditary cases but does not differ in other ways [6].

Germline mutations can drive the development of aggressive PCa. Therefore, the following men should be considered for germline testing:

1. Men with metastatic PCa who are candidates for targeted treatment.
2. Men with *BRCA* mutations on somatic testing.
3. Men with multiple family members diagnosed with clinically significant PCa (csPCa) at age <60 yr or a family member who died from PCa.
4. Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

A wide variety of exogenous/environmental factors have been discussed as being associated with the risk of developing PCa or as being aetiologically important for the progression from latent to clinical PCa. However, currently there are no known effective preventative dietary or pharmacological interventions. Hypogonadal men receiving testosterone supplements do not have an increased risk of developing PCa [11]. Furthermore, although the evidence is limited, men who are managed expectantly for PCa, or who received radical curative therapy, do not have worse outcomes when receiving testosterone supplementation, despite a theoretically higher risk of progression after correction of the hypogonadal situation [12].

3.2. Classification and staging

The 2017 tumour, node, metastasis (TNM) classification of the Union for International Cancer Control eighth edition for staging of PCa should be used [13]. The cT stage was based on digital rectal examination (DRE) only; however, changes in the diagnostic pathway, particularly the introduction of imaging techniques such as magnetic resonance imaging (MRI), prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging, and targeted biopsy, are causing a stage shift in the risk group distribution, and this should be taken into account when making treatment decisions. The EANM recently proposed a molecular imaging TNM (miTNM) classification, using PSMA PET/computed tomography (CT) findings [14]. The prognosis of the miT, miN, and miM substages is likely to be better than their T, N, and M counterparts because PSMA PET/CT is more sensitive than the usual work-up based on bone scan and abdominopelvic CT. The extent of this prognosis shift remains to be assessed as well as its practical interest and impact.

Table 1 – International Society of Urological Pathology 2014 grade (group) system

Gleason score	ISUP grade group
2-6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4, 3 + 5, or 5 + 3)	4
9-10 (4 + 5, 5 + 4, or 5 + 5)	5

ISUP = International Society of Urological Pathology.

The ISUP 2005 Gleason score (GS) together with its 2014 and 2019 modifications is the recommended PCa grading system [15,16]. The biopsy GS consists of the Gleason grade of the most extensive pattern plus the highest pattern, regardless of its extent. In addition to reporting of the carcinoma features for each biopsy side, an overall (or global) GS based on the carcinoma-positive biopsies should be provided. For targeted and regional biopsy cores of one lesion, this overall GS for the combined cores should be used. In radical prostatectomy (RP) specimens, 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 [16]. The 2019 ISUP Gleason Grading Conference on Gleason grading of PCa [16] supported the concept of grade groups, eliminating the anomaly that the least aggressive PCa has a GS of 6 and to highlight the clinical differences between GS 3 + 4 and 4 + 3 (Table 1).

The D'Amico risk group classification is based on grouping patients with a similar risk of biochemical recurrence (BCR) after local treatment. However, it is becoming clear that subdividing intermediate-risk disease into ISUP grade groups 3 is clinically helpful. Cambridge Prognostic Groups use a five-tier model based on ISUP grade group, prostate-specific antigen (PSA), and cT stage, and were shown to have significantly better discriminative performance than current three-tier risk groups for the more clinically relevant endpoint of PCa-specific mortality [17]. This model separates both intermediate- and high-risk groups in clinically relevant subgroups and has been validated in separate cohorts [17,18].

3.3. Screening and early detection

The diagnostic pathway for PCa (Fig. 1) aims for timely detection of significant PCa, whilst leaving insignificant PCa undetected, balancing diagnostic accuracy with the burden on an individual and health care provider. Patient-specific factors such as ethnicity, family history, age, and comorbidity should always be considered.

Localised PCa is usually asymptomatic. Individual requests for PSA testing may be considered following discussion of the rationale and risk of identifying insignificant cancer. Local progression may cause symptoms such as lower urinary tract symptoms, erectile dysfunction (ED), retention, pain, or haematuria. Bone metastases may cause pain or spinal cord compression. Definitive diagnosis normally depends on histopathological verification in prostate biopsy cores. However, men with a high suspicion of malig-

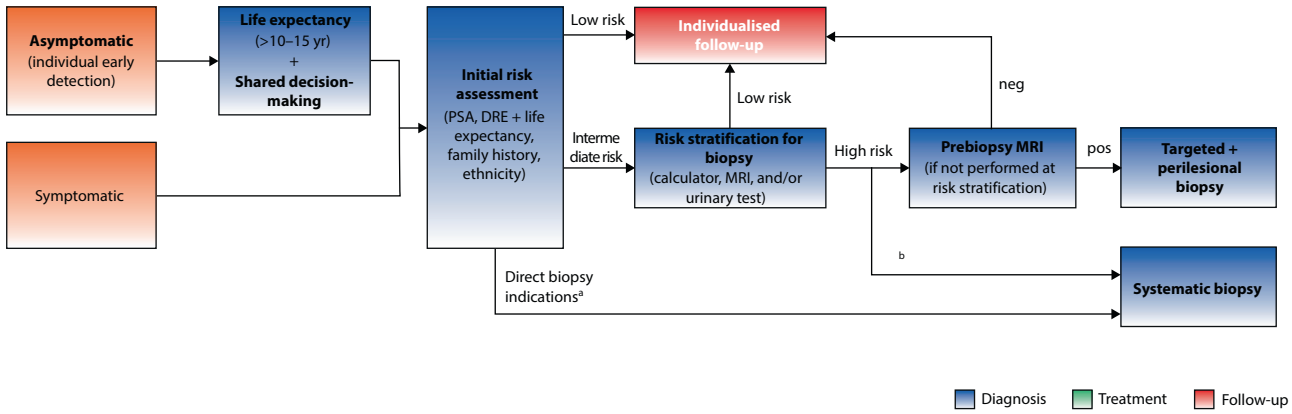

Fig. 1 – Flow diagram for early detection/suspicion prostate cancer biopsy indications. DRE = digital rectal examination; MRI = magnetic resonance imaging; neg = negative; pos = positive; PSA = prostate-specific antigen. [a] PSA >50, cT3-4. [b] If MRI not available/possible.

nancy (eg, malignant feeling prostate and PSA >100 ng/ml) and a positive bone scan might avoid a biopsy especially if pre-existing comorbidities would exclude second-line treatment.

Screening for PCa remains one of the most controversial topics in the urological literature. The coprimary objectives are a reduction in disease-specific mortality and maintained quality of life (QoL). A Cochrane review of randomised PCa screening trials with PCa mortality as an endpoint was updated in 2018 [19]. The main findings of the updated publication from the results of five randomised controlled trials (RCTs), randomising >721 718 men, are as follows:

1. Screening is associated with an increased diagnosis of PCa (incidence ratio [IR]: 1.23, 95% confidence interval [CI]: 1.03-1.48).
2. Screening is associated with the detection of more localised disease (RR: 1.39, [1.09-1.79]) and less advanced PCa (T3-4, N1, M1; RR: 0.85 [0.72-0.99]).
3. No PCa-specific survival benefit was observed (IR: 0.96 [0.85-1.08]). This was the main endpoint in all trials.

Nevertheless, the largest study—the population-based European Randomised Study of Screening for Prostate Cancer (ERSPC), which included >182 000 men, showed a significant reduction in PCa mortality in the screening arm (RR: 0.79; 95% CI: 0.69-0.91) [20]. In the Goteborg screening trial, with 18 yr of follow-up, the ratio of death from PCa for the screening group compared with the control group was 0.65 (95% CI: 0.49-0.87), and for men starting screening at age 55-59 yr, it was 0.47 (95% CI: 0.29-0.78) [21]. The number needed to invite was 231; the number needed to diagnose (NND) was 10. In the Rotterdam section of the ERSPC, with 21 yr of follow-up, the risk ratio of death due to PCa was 0.73 in the screening group, with the number needed to invite of 246 and the NND of 14 to prevent one death due to PCa [22]. To prevent one metastasised case, the number needed to screen was 121 and the NND was 7.

Optimal intervals for PSA testing are unknown. The proposal is a 2-yr interval for men at an increased risk (eg, PSA 2-3 ng/ml), whilst it could be expanded up to 8 yr for those not at risk (eg, PSA <1 ng/ml). 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 [23]. Men who have <15 yr of life expectancy are unlikely to benefit from any form of early diagnosis. Despite improvements, the diagnostic algorithm may still lead to 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.

3.4. *Diagnostic tools*

The different available diagnostic tools can be used separately, or in multiple-tier combinations, to indicate the need for a prostate biopsy. 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 clinically significant PCa. 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 [24].

Risk calculators developed from cohort studies may also be useful in reducing further testing. Prostate-specific antigen density (PSA-D; serum PSA divided by prostate volume) may also help predict the presence of csPCa especially in smaller prostates using a cut-off of 0.15 ng/ml/cc [25]. It is certainly one of the strongest predictors in risk calculators, and together this may allow men to avoid the need for biopsy.

Multiparametric magnetic resonance imaging (mpMRI) is increasingly important for biopsy optimisation. In a Cochrane meta-analysis, which compared MRI with template biopsies (≥20 cores) in biopsy-naïve and repeat-biopsy settings, MRI had 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 [26]. In biopsy-naïve men, an MRI-based indication for biopsy after referral leads to lower rates of biopsy, fewer men diagnosed with PCa labelled as insignificant, and more

men diagnosed with PCa labelled as csPCa [27,28] as compared with systematic biopsy alone. This is also true in men with prior negative biopsy [26,29]. Combining PSA-D and MRI may also be helpful. Based on a meta-analysis of >3000 biopsy-naive men, a risk-adapted data table of csPCa was developed, linking Prostate Imaging Reporting and Data System (PI-RADS) score (1-2, 3, and 4-5) to PSA-D categories (<0.10, 0.10-0.15, 0.15-0.20, and >0.20 ng/ml; Table 2) [30]. This risk-adapted matrix table may guide the decision to perform a biopsy.

The Stockholm3 test is a prediction model that is based on several clinical variables (age, first-degree family history of PCa, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free PSA to total PSA, human kallikrein 2, macrophage inhibitory cytokine 1, and *microseminoprotein-β* [MSMB]), and a polygenic risk score for predicting the risk of PCa with ISUP grade group ≥2, and was shown to reduce the percentage of clinically insignificant cancers when used in combination with MRI in a PSA screening population [31].

Table 2 – Risk data table of clinically significant prostate cancer, related to PI-RADS score and PSA-D categories in biopsy-naive men, clinically suspected of having significant disease[a]

Detection of clinically significant prostate cancer (ISUP grade group ≥2), % (*n*/*N*)					
		PSA-density risk groups			
PI-RADS risk categories	Prevalence ISUP grade group ≥2 PCa, % (*n*/*N*)	Low <0.10 31 (678/2199)	Intermediate-low 0.10–0.15 28 (612/2199)	Intermediate-high 0.15–0.20 16 (360/2199)	High ≥0.20 25 (553/2199)
Compiled totals of csPCa risk					
PI-RADS 1–2	6 (48/839)	3 (11/411)	7 (17/256)	8 (8/104)	18 (12/68)
PI-RADS 3	16 (41/254)	4 (3/74)	13 (11/88)	29 (12/41)	29 (15/51)
PI-RADS 4–5	62 (687/1106)	31 (59/189)	54 (144/286)	69 (148/215)	77 (336/434)
All PI-RADS	35 (776/2199)	11 (73/674)	28 (172/612)	47 (168/360)	66 (363/553)
Risk-adapted matrix table for biopsy decision management					
PI-RADS 1–2		No biopsy	No biopsy	No biopsy	Consider biopsy
PI-RADS 3		No biopsy	Consider biopsy	Highly consider biopsy	Perform biopsy
PI-RADS 4–5		Perform biopsy	Perform biopsy	Perform biopsy	Perform biopsy

csPCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSA-D = PSA density.

[a] Colour key:

Very low	0–5% csPCa (below population risk)
Low	5–10% csPCa (acceptable risk)
Intermediate low	10–20% csPCa
Intermediate high	20–30% csPCa
High	30–40% csPCa
Very high	>40% csPCa

It also has the potential to decrease the number of mpMRI scans required in PCa screening [32].

Though mainly used for staging purposes, PSMA PET/CT (or PSMA PET/MRI) prostate expression may be used to indicate and target biopsies. For csPCa detection, pooled sensitivity of 0.89 and pooled specificity of 0.56 have been reported [33]. In a prospective trial of 291 patients, combined PSMA + MRI improved the negative predicted value compared with MRI alone (91% vs 72%, test ratio = 1.27 [1.11-1.39], $p < 0.001$). Sensitivity was also improved (97% vs 83%, $p < 0.001$), but specificity was reduced (40% vs 53%, $p = 0.011$) [34].

3.5. Prostate biopsy

Ultrasound (US)-guided prostate biopsy is the standard of care under local anaesthesia [35]. For systematic biopsies, where no prior imaging is used for targeting, the sample sites should be bilateral from the apex to base, as far posterior and lateral as possible in the peripheral gland taking 12 cores [36]. Where MRI has shown a suspicious lesion, adding targeted biopsy to systematic biopsy in biopsy-naive patients increases the number of detected ISUP grade ≥2 and grade ≥3 PCa cases by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-targeted biopsy increases the detection of ISUP grade group ≥2 and grade group ≥3 PCa cases by approximately 40% and 50%, respectively [26,28,37].

MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software, or direct in-bore guidance, as in appropriately trained individuals, there appears to be no difference between the techniques in cancer detection [38]. It may also be possible to avoid systematic biopsies entirely by including perilesional/regional biopsies. A meta-analysis of eight studies [39] showed a nonsignificant difference in the detection of ISUP grade group ≥2 cancer in the MRI-directed targeted and regional biopsy approaches, compared with the recommended practice of MRI-directed targeted plus systematic biopsy approach (RR: 0.95, 95% CI: 0.90-1.01; $p = 0.09$). However, the MRI-directed targeted and regional biopsy approach detected significantly more ISUP grade group ≥2 cancers than MRI-targeted biopsy alone (RR: 1.18, 95% CI: 1.10-1.25; $p < 0.001$). This difference is small for PI-RADS 5 lesions. In addition, the MRI-targeted and regional biopsy approaches could avoid detecting 12-17% of the insignificant cancers (ISUP grade group 1) detected by the classical combined approach [40,41].

Prostate biopsy can be performed by either the transperineal or the transrectal approach. The only systematic review (SR) and meta-analysis comparing MRI-targeted transrectal biopsy with MRI-targeted transperineal biopsy, analysing eight studies, showed higher sensitivity for the detection of csPCa when the transperineal approach was used (86% vs 73%) [42]. This benefit was especially pronounced for anterior tumours. It is associated with increased discomfort for the patient [43], but evidence also suggests reduced infection risk with the transperineal route [44,45] such that antibiotic prophylaxis might not be required. This may be important after the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones, resulting in the suspension of the indication for perioperative antibiotic prophylaxis including prostate biopsy.

Each biopsy site should be reported individually, including its location, GS, ISUP grade group, and extent. If identified, lymphovascular invasion and extraprostatic extension (EPE) must each be reported, as well as intraductal carcinoma and invasive cribriform pattern, as these represent independent factors for metastasis [46] and cancer-specific survival (CSS) [47]. Clinicians and patients should note that MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer; as a consequence, ISUP grade group ≥2 cancers detected by MRI-targeted biopsy are, on average, of better prognosis than those detected by systematic biopsy alone [48]. When long-term follow-up of patients who underwent MRI-targeted biopsy is available, a revision of the risk-group definition will become necessary. In the meantime, results of MRI-targeted biopsy must be interpreted in the context of this potential grade shift.

3.6. 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 (Table 3).

3.7. T category

The cT category relies on DRE finding but increasing use of MRI, and in particular, T2-weighted imaging is driving stage migration. In 552 men treated by RP at seven different Dutch centres, MRI showed significantly higher sensitivity (51% vs 12%; $p < 0.001$) and lower specificity (82% vs 97%; $p < 0.001$) than DRE for non-organ confined disease. All risk groups redefined that using MRI findings rather than DRE findings showed better BCR-free survival due to improved discrimination and the associated stage shift [49].

3.8. N category

Abdominal CT and MRI indirectly assess nodal invasion by using lymph node (LN) diameter and morphology. Usually,

Table 3 – Recommendations for staging of prostate cancer

Recommendations	Strength rating
Any risk group staging	
Use prebiopsy magnetic resonance imaging for local staging information.	
Low-risk localised disease	
Do not use additional imaging for staging purposes.	
Intermediate-risk disease	
For patients with International Society of Urological Pathology grade group 3 disease, include at least cross-sectional abdominopelvic imaging and a bone scan for metastatic screening.	Weak
Perform PSMA PET/CT if available to increase accuracy.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening using PSMA PET/CT if available and at least cross-sectional abdominopelvic imaging and a bone scan.	Strong

CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

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% [50]. As CT and MRI lack sensitivity for direct detection of positive LNs, nomograms combining clinical and biopsy findings have been used to estimate the risk of patients harbouring positive LNs [51]. PSMA PET/CT has good specificity for LN involvement. In a review and meta-analysis including 37 articles, a subgroup analysis was performed in patients undergoing PSMA PET/CT for primary staging. On a per-patient based analysis, the sensitivity and specificity of 68Ga-PSMA PET were 77% and 97%, respectively, after extended LN dissection at the time of RP. On a per-lesion based analysis, sensitivity and specificity were 75% and 99%, respectively [52]. In summary, PSMA PET/CT is more sensitive in N staging than MRI, abdominal contrast-enhanced CT, or choline PET/CT. However, small LN metastases, under the spatial resolution of PET, may still be missed.

3.9. *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 [53]. 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 [54]. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography, and abdominopelvic CT [55]. However, PSMA PET/CT appears to be the most accurate form of staging metastatic spread. In a prospective multicentre study in patients with high-risk PCa before curative surgery or radiotherapy (RT; proPSMA trial), 302 patients were assigned randomly to conventional imaging or ^{68}Ga-PSMA-11 PET/CT [56]. The primary outcome focused on the accuracy of first-line imaging for the identification of pelvic LNs or distant metastases. Accuracy of ^{68}Ga-PSMA PET/CT was 27% (95% CI: 23-31) higher than that of CT and bone scintigraphy (92% [95% CI: 88-95] vs 65% [95% CI: 60-69]; $p < 0.0001$). Conventional imaging had lower sensitivity (38% [95% CI: 24-52] vs 85% [95% CI: 74-96]) and specificity (91% [95% CI: 85-97] vs 98% [95% CI: 95-100]) than PSMA PET/CT. Furthermore, ^{68}Ga-PSMA PET/CT scan prompted management change more frequently than conventional imaging (41 [28%] men [95% CI: 21-36] vs 23 [15%] men [95% CI: 10-22], $p = 0.08$), with fewer equivocal findings (7% [95% CI: 4-13] vs 23% [95% CI: 17-31]) and lower radiation exposure (8.4 vs 19.2 mSv; $p < 0.001$) [56]. As a consequence, replacing bone scan and abdominopelvic CT by more sensitive imaging modalities may be a consideration in patients with high-risk PCa undergoing initial staging. It remains unclear how adapted treatment will impact outcomes overall.

3.10. *Evaluating life expectancy and health status*

Evaluation of life expectancy and health status is important in clinical decision-making on screening, diagnosis, and treatment of PCa. Country-specific life tables are available; however, survival must be individualised [57] based, for example, on gait speed [58] or using tools such as the Cumulative Illness Score Rating—Geriatrics (CISR-G) [59], the Charlson Comorbidity Index (CCI) [60], or the clinical frailty score [61]. To assess senior adults' suitability for treatment, the panel suggests a systematic evaluation of health status using the G8 screening tool [23] as well as the Mini-COG [62]. This may identify reversible health issues, which after treatment would facilitate alternative treatment options.

In localised disease, >10 yr life expectancy is considered mandatory for any survival benefit from local treatment. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes. In an analysis of 19 639 patients aged >65 yr who were not given curative treatment, most men with a CCI score of $\geq$2 had died from competing causes at 10-yr follow-up regardless of their age at the time of diagnosis. Tumour aggressiveness had little impact on overall survival (OS), suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score of $\leq$1 had a low risk of death at 10 yr, especially for well or moderately differentiated lesions [63]. Patients with life expectancy of <10 yr should undergo monitoring with the initiation of androgen deprivation to palliate symptoms (watchful waiting). Estimation of competing benefits of active versus conservative treatment and death from any cause at 10 and 15 yr can be estimated using the PREDICT Prostate tool (available from https://prostate.predict.nhs.uk/).

3.11. *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 using a shared care approach to balance of benefits and side effects of each therapeutic modality together with the patients' views and preferences.

3.12. *Active surveillance*

Whilst all available radical treatment options are associated with significant unwanted side effects, mortality from untreated screen-detected PCa in patients with ISUP grade group 1-3 has been recorded as just 7% after 15-yr follow-up [64]. As a consequence, active surveillance (AS) strategies aim to reduce overtreatment in men with localised ISUP grade group 1 and possibly 2 PCa, without compromising opportunities for cure.

An SR summarised the available data on AS [65]. Protocols do not fully align regarding patient selection, follow-up policies, and criteria to switch to an active treatment, although there is a significant overlap. The most often published criteria based upon standard systematic biopsies include ISUP grade 1, cT1c or cT2a, PSA <10 ng/ml, low-risk disease, and PSA-D <0.15 ng/ml/cc. [66]. The addition of MRI and additional targeted biopsies, when indicated, results in fewer failures of surveillance (19% vs 35%, $p = 0.017$) and fewer patients progressing to ISUP grade group $\geq$2 cancer (9.9% vs 23%, $p = 0.048$) at 2-yr follow-up [67]. Therefore, men eligible for AS after combined systematic and MRI-targeted biopsies do not require confirmatory

biopsy [68]. It remains important to exclude sampling errors for men selected on the basis of a systematic or MRI-targeted biopsy alone [26,28,37].

There is increasing recognition that AS can be extended to other groups. In the ProtecT RCT, 1643 patients were randomised into one of three arms: active treatment with RP or external beam radiotherapy (EBRT) or active monitoring (AM) with outcomes now reported at 15 yr [69]. Follow-up involved PSA monitoring and DRE alone, with relaxed criteria to define progression and no role for MRI or scheduled repeat biopsy. Categorisation at study entry was inaccurate, as demonstrated by the fact that, in men undergoing RP within 12 mo of randomisation, histology showed that 50.5% had ISUP grade group $\geq$2, whilst 28.5% had pT3 or pT4 disease. Despite this, AM was as effective as active treatment at 15 yr (CSS = 96.9% in the AM group vs 97.8% in the RP group and 97.1% in the EBRT group, p = 0.53), but at a cost of an increased metastatic progression risk (9.4% vs 4.7% and 5.0%, respectively). It is, therefore, clear that men with favourable ISUP grade group 2 cancer (PSA <10 ng/ml, <cT2b, and a small number of positive cores) could also be considered for deferred treatment [70]. Men with harbouring intraductal or invasive cribriform adenocarcinoma [71], sarcomatoid carcinoma, small cell carcinoma, EPE, or lymphovascular invasion in needle biopsy [72] should not be considered.

The follow-up strategy is based on serial PSA (at least once every 6 mo), DRE, and MRI (at least once yearly), and includes standard repeat biopsy. However, several factors have been found to be associated with low reclassification rates and long progression-free survival (PFS): negative baseline or repeat MRI during AS [68,73], low PSA-D [68,74], low PSA velocity [75], or negative biopsy (ie, no cancer at all) at confirmatory or repeat biopsy during AS [76]. Patients with stable (PRECISE 3) disease on repeat MRI during AS and a low PSA-D (<0.15) have a very low rate of progression, and repeat biopsy may therefore be omitted [77].

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 best managed with psychological support [78] before considering switching to an active treatment. A PSA or MRI change should trigger further investigation, including rebiopsy before considering active treatment [70,78]. The development of other comorbidities resulting in life expectancy falling below 10 yr should merit a new discussion with the patient and may result in a decision to transfer to a watchful waiting (WW) strategy.

3.13. *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 [79]. Patients should not be denied this procedure on the grounds of age alone [23] provided that they have at least 10 yr of life expectancy and are aware that increasing age is linked to an increased incontinence risk. Data from SPCG-4 [79] and a preplanned subgroup analysis (PIVOT) [80] highlight the benefit of RP compared with WW in men with intermediate-risk disease.

Provided that the tumour is not fixed and not invading the urethral sphincter, RP combined with extended pelvic LN dissection (ePLND) is a reasonable first step in patients with high-risk and locally advanced PCa. Especially now, PSMA PET/CT imaging allows identification of many of the men with metastatic disease [56]. Amongst the individual elements that make up high-risk disease, 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 [81]. At 10-yr follow-up, the CSS is up to 88% [82]. A PSA value of >20 ng/ml is associated with CSS at 10 yr, ranging between 83% and 91% [82]. 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% [83]. 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 [83]. 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 cT3-4 and PSA >20 ng/ml, and 79% if all three risk factors were present.

Incontinence is a concern for all men undergoing surgery, and SRs and meta-analyses found that every extra millimetre of membranous urethral length seen on MRI preoperatively improves early return to continence after RP [84,85]. A greater membranous urethral length, as measured on preoperative MRI, was an independent prognostic factor for return to urinary continence within 1 mo after RP and remained prognostic at 12 mo [85]. Therefore, it is likely that preservation of as much urethral length as possible during RP will maximise the chance of early return to continence. It may also be useful to measure urethral length preoperatively on MRI to facilitate counselling of patients on their relative likelihood of early postoperative continence [86].

Nerve-sparing (NS) 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 [87]. An SR of 19 studies analysing the parameters used for the selection of NS found that individual clinical and radiological factors were poor at predicting EPE and, consequently, the appropriateness of NS. However, nomograms that incorporated mpMRI performed better [88]. Multiparametric MRI may be helpful for selecting an NS 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 [89].

There is still no evidence that one surgical approach is better than another (open, laparoscopic, or robotic), as highlighted in a formal SR. Robot-assisted prostatectomy is associated with lower perioperative morbidity and a reduced positive margin rate than laparoscopic prostatectomy, although there is considerable methodological uncertainty. No formal differences exist in cancer-related continence or ED outcomes [90]. After 24 mo of follow-up, an RCT including 326 men did not reveal any significant differences in functional outcomes between the open and robotic approaches [91].

3.14. Pelvic LN dissection

Extended pelvic LN dissection, which 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, and the nodes medial and lateral to the internal iliac artery, provides accurate staging information [92]. However, two RCTs have failed to show a benefit of an extended approach versus a limited pelvic LN dissection on early oncological outcomes [93,94], and it is associated with a nearly 20% risk of complication rates mainly related to significant lymphoceles [92].

In men with pN+ PCa, early adjuvant androgen deprivation therapy (ADT) was shown to achieve a 10-yr CSS rate of 80% [95]. Pelvic RT combined with long-term ADT appeared to be beneficial in pN+ PCa patients treated with ePLND, with at least a local control improvement and possibly survival. The optimal candidates remain unclear: number of positive nodes, ISUP grade group, and margin status [96,97].

3.15. Adjuvant treatment after RP

EPE and positive surgical margins are associated with an increased risk of recurrence. However, for patients with undetectable postoperative PSA, a meta-analysis suggests that adjuvant radiation treatment and early salvage radiotherapy (SRT; before PSA >0.5 ng/ml) offer similar outcomes for event-free survival [98]. For patients with adverse pathology, that is, ISUP grade group 4-5 and pT3/4 with or without positive margins [99], immediate adjuvant EBRT to the surgical bed after recovery of urinary function is still recommended.

3.16. Persistent PSA after RP

Between 5% and 20% of men continue to have detectable PSA after RP (most often defined as post-RP PSA 0.1 ng/ml within 4-8 wk of surgery) [100,101]. It is often associated with poor prognosis: 74% experience further PSA progression [100] and an increased risk of metastases [102] and death [103]. As for PSA relapse, PSMA PET/CT is the most sensitive imaging modality to detect metastases [104].

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 [103] after a 1:1 propensity score matching between SRT and no RT; the 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 [101,105,106]. The addition of ADT may improve PFS [105]. 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.

3.17. Definitive RT

Dose-escalated intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy are the gold standard for EBRT because it is associated with less toxicity than three-dimensional conformal radiation therapy techniques [107]. However, with such techniques, organ movement becomes a critical issue in terms of both tumour control and treatment toxicity. Therefore, these are performed with some form of image-guided RT (usually gold marker or cone-beam CT), in which organ movement can be visualised and corrected for in real time. Using this combination, rates of severe late side effects (grade >3) for the rectum are 2-4% and for the genitourinary (GU) tract 2-6% [108]. An SR and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrates an increased risk of developing second cancers for the bladder (odds ratio [OR]: 1.39), colorectal (OR: 1.68), and rectum (OR: 1.62), with similar risks over lag times of 5 yr and 10 yr. Absolute risks over 10 yr are small (1-4%) but should be discussed with younger men in particular [109].

RCTs have shown that escalating the dose into the range of 74-80 Gy leads to a significant improvement in 10-yr BCR-free survival [110,111] and PCa-specific survival [112]. In men with intermediate- and 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 [113].

The combination of ADT with various forms of RT has been studied extensively, with extremely strong evidence for the use of such combined modality therapy in several settings. An individual patient data meta-analysis included 12 trials with 10 853 patients. The median follow-up was over 11 yr. The use of ADT was clearly associated with significant improvements in BCR, metastatic recurrence, metastasis-free survival, and OS. The benefits of ADT were independent of RT dose, age, and risk groups [114]. For intermediate-risk disease, a short duration of 4-6 mo is optimal [115], whilst a longer one, 2-3 yr, is needed for high-risk patients [116].

Fractionated RT utilises difference in the DNA repair capacity of normal and tumour tissue. Slowly proliferating cells are more sensitive to an increased dose per fraction. As PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8-2 Gy. It is also more convenient for the patient and of low cost. Therefore, the UK CHHIP trial [117] recruited 3216 men with T1b-T3a disease, who were randomised to 74 Gy in 37 fractions, 57 Gy in 19 fractions, or 60 Gy in 30 fractions (moderate hypofractionated). At 5 yr of follow-up, the 60 Gy arm was shown to be noninferior to the 74 Gy arm and has therefore been recommended for practice. There were no differences in late toxicity between the three arms, and these finding were confirmed when the 10-yr data were presented [118]. In the PACE-B trial [119], extreme hypofractionation at 36.25 Gy in five-fraction stereotactic body radiotherapy was compared with conventional schedules of RT in patient with T1-2 disease ISUP grade group 1 (8%), ISUP grade group 2 (92%), and PSA <20 ng/ml. The 5-yr RTOG toxicity rates were similar, although with a slight increase in grade 2 or worse GU toxicity (3.2% vs 5.5%). More interestingly, 5-yr BCR-free rates were equivalent when presented recently [120]. This should be confirmed when the data are published as a standard of RT for patients with intermediate-risk disease. Androgen deprivation was

not permitted in this trial. Data are still missing for high-risk disease.

In patients with localised high-risk PCa, dose-escalated IMRT, possibly including the pelvic lymphatics [121], and/or a brachytherapy (BT) boost is an option [122]. Long-term ADT, generally for 2-3 yr, is always mandatory. The duration of ADT must take into account performance status, comorbidities, and the number of poor prognostic factors.

3.18. Brachytherapy

Low-dose rate (LDR) BT uses permanent radioactive seeds implanted into the prostate, and as a monotherapy, is an option for those with favourable intermediate-risk disease (low-volume GS 3 + 4) and good urinary function defined as an International Prostate Symptom Score of <12 and a maximum flow rate of >15 ml/min [123]. Up to 85% relapse-free survival at 10 yr is demonstrated [124]. Patients having had a previous transurethral resection of the prostate (TURP) can undergo BT without an increase in the risk of urinary toxicity, with due attention to dose distribution. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the posterolateral sides of the prostate, and there should be at least a 3-mo interval between TURP and BT to allow for adequate healing [125].

Although seen as a low-impact treatment modality, some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), postimplantation TURP (8.7% of cases), and incontinence (0-19%) [126]. ED develops in about 40% of the patients after 3-5 yr.

LDR as a boost with EBRT can be used as dose escalation in unfavourable intermediate- and high-risk patients, combined with 12 mo of ADT. PSA PFS improved from 70% to 85% at 10 yr, although there was no impact on metastasis-free survival or OS. It was associated with increased late grade 3+ GU toxicity (18% compared with 8%) and two treatment-related deaths [127,128]. Urinary toxicity was mainly in the development of urethral strictures and incontinence.

High-dose rate (HDR) BT uses a radioactive source temporarily introduced into the prostate to deliver radiation. 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 [129]. An SR of non-RCTs and data from population studies suggest that outcomes with EBRT plus HDR BT are superior to those with EBRT alone [130], but randomised evidence is still awaited.

3.19. Alternative local treatment options

New modalities have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity, and improved functional outcomes. Unfortunately, these have largely been evaluated in cohorts of patients who we now recognise to have little to gain from treatment in terms of oncological control.

3.20. Cryotherapy

Cryotherapy has been used for whole-gland treatment in PCa either as a primary or as a salvage treatment option. Freezing of the prostate is ensured by the placement of 17-gauge cryo-needles under TRUS guidance, placement of thermosensors at the level of the external sphincter and rectal wall, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the midgland and at the neurovascular bundle. There is a lack of prospective comparative data regarding oncological outcomes of whole-gland cryosurgery as a curative treatment option for men with localised PCa, with most studies being noncomparative single-arm case series with short follow-up [131]. The main adverse effects of whole-gland cryosurgery are ED (18%), urinary incontinence (2-20%), urethral sloughing (0-38%), rectal pain and bleeding (3%), and rectourethral fistula formation (0-6%) [131].

3.21. High-intensity focused ultrasound treatment

High-intensity focused ultrasound (HIFU) consists of focused US waves emitted from a transducer that cause tissue damage by mechanical and thermal effects as well as by cavitation. Data have shown poor long-term oncological outcomes for men undergoing whole-gland treatment for high-risk localised disease [132], which prevents it from being considered as a reasonable alternative to the established curative treatment options. In addition, the expected improvements in functional outcome failed to materialise, with 12% of patient developing incontinence and 61% developing ED [133].

Consequently, interest has switched to treating small low- or intermediate-risk unifocal tumours with focal therapy aiming to ablating tumours whilst sparing the neurovascular bundles, sphincter, and urethra. Prospective registry data confirm low treatment-related toxicity (a 4% decrease in pad-free continence and a reduction in the International Index of Erectile Function of 0.4 points) [134]. Oncological outcomes are less clear with no randomised comparative data. Case series suggest 88% failure-free survival at 5 yr defined as the need for salvage treatment or systemic therapy [135]. One repeated focal HIFU session was allowed and performed in 25% of all patients. It should also be noted that since the US energy is most often delivered from the rectal cavity, HIFU faces challenges in delivering energy to the anterior part in large prostates. For now, focal therapy should be performed only within the context of a clinical trial setting or a well-designed prospective registry. The question remains which, if any, of these small unifocal tumours need treatment.

3.22. Locally advanced PCa: T3-4 N0, M0

Data from retrospective case series of men undergoing RP for T3 disease using conventional imaging demonstrated over 60% CSS at 15 yr and over 75% OS at 10 yr [136–138]. For cT3b-T4 disease, PCa cohort studies showed 10-yr CSS of over 87% and OS of 65%. For patients treated with RT, OS and disease-free survival were significantly better

with additional adjuvant ADT for 3 yr [139]. Comparative data of surgery versus radiation strategies are still awaited.

3.23. *Treatment of cN1 PCa*

The treatment of cN1 M0 PCa was evaluated in an SR [140] including five studies. The findings suggest an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT, as compared with ADT alone. The intensification of systemic treatment with either abiraterone acetate or docetaxel, for very high-risk localised or cN1 disease, has also been assessed in analyses from the STAMPEDE multi-arm RCT. Two RCTs from the study reported on the addition of abiraterone acetate to the standard of care in men with de novo high-risk/locally advanced M0 disease, or relapse after primary curative therapy with high-risk features. Of the patients, 39% (n = 774) were N1 on conventional imaging. RT in addition to long-term ADT was administered in 71% of these patients. A meta-analysis involving 1974 patients [141] demonstrated an improvement in metastasis-free survival (82% vs 69% at 6 yr) and OS (hazard ratio 0.60, $p < 0.001$), suggesting that combined abiraterone (for 2 yr) and ADT (for 3 yr) should be a standard of care in cN1 patients in addition to prostate and whole-pelvic RT. A similar analysis assessing the role of docetaxel in this population failed to show a similar benefit.

4. Conclusions

The present text represents a summary of the 2024 EAU-EANM-ESTRO-ESUR-ISUP-SIOG PCa guidelines. A summary of recommendations is presented in Table 4. For more detailed information and a full list of references, refer to the full-text version available at the EAU website (http://uroweb.org/guideline/prostate-cancer/).

Table 4 – Recommendations for managing prostate cancer by stage

Recommendations	Strength rating
Watchful waiting	
Manage patients with life expectancy of <10 yr by watchful waiting.	Strong
Management of low-risk disease	
Active surveillance	
Manage patients with life expectancy of >10 yr and low-risk disease by AS.	Strong
Selection of patients	
Perform MRI before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
If a patient has had upfront MRI followed by systematic and targeted biopsies, there is no need for confirmatory biopsies.	Weak
Strategy of surveillance	
Repeat biopsies should be performed at least once every 3 yr for 10 yr.	Weak
In case of prostate-specific antigen progression or change in digital rectal examination or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
Management of intermediate-risk disease	
Active surveillance	
Offer AS to selected patients with ISUP grade group 2 disease (eg, <10% pattern 4, PSA <10 ng/ml, ≤cT2a, low disease extent on imaging, and low extent of tumour in biopsies, ≤ 3 positive cores with Gleason score 3 + 4, and ≤50% cancer involvement/core), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with cribriform or intraductal histology on biopsy should be excluded from AS.	Strong
Patients with ISUP grade group 3 disease should be excluded from AS protocols.	Strong
Reclassify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal >3 positive cores or maximum CI >50%/core of ISUP grade group 2 disease.	Weak
Radical prostatectomy	
Offer RP to patients with life expectancy of >10 yr.	Strong
Radical prostatectomy can safely be delayed for at least 3 mo.	Weak
Offer nerve-sparing surgery to patients with a low risk of extracapsular disease on that side.	Strong
Radiotherapeutic treatment	
Offer LDR brachytherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong
Offer IMRT/VMAT plus IGRT, with 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 ADT (4-6 mo).	Strong
Offer focal boosting to MRI-defined dominant intraprostatic tumour when using conventionally fractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that organ at risk constraints are not exceeded	Weak
Offer ultrahypofractionated IMRT/IGRT or SBRT, using either 36.25 Gy (40 Gy to the prostate) in 5 fx or 42.7 Gy in 7 fx delivered on alternate days.	Weak
Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (4-6 mo).	Weak
Offer HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (4-6 mo).	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy within clinical trials or registries.	Strong
Management of high-risk localised disease	
Radical prostatectomy	
Offer RP to selected patients as part of potential multimodal therapy.	Strong
Extended pelvic lymph node dissection	
In patients undergoing a lymph node dissection, you should perform an ePLND.	Strong

Table 4 (*continued*)

Recommendations	Strength rating
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatment	
Offer patients IMRT/ VMAT plus IGRT with 76-78 Gy in combination with long-term ADT (2-3 yr).	Strong
Offer focal boosting to MRI-defined dominant intraprostatic tumour when using normofractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that organ at risk constraints are not exceeded.	Weak
Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2-3 yr).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy.	Strong
Management of locally advanced disease	
Radical prostatectomy	
Offer RP to patients with cN0 disease as part of multimodal therapy.	Weak
In pN0 patients with ISUP grade group 4-5 and pT3 ± positive margins after RP, offer adjuvant IMRT/ VMAT plus IGRT.	Strong
Extended pelvic lymph node dissection	
In patients undergoing a lymph node dissection, you should perform an ePLND.	Strong
Radiotherapeutic treatments	
Offer patients with cN0 disease IMRT/VMAT plus IGRT in combination with long-term ADT.	Strong
Offer patients with cN0 disease and good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT.	Weak
Offer long-term ADT for at least 2 yr.	Strong
Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 yr of abiraterone to cN0M0 patients with ≥2 high-risk factors (cT3-4, Gleason ≥8, or PSA ≥40 ng/ml).	Strong
Offer IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and 2 yr of abiraterone to cN1M0 patients.	Strong
Management of persistent PSA after RP	
Offer a prostate-specific membrane antigen positron emission tomography/computed tomography scan to men with a persistent PSA value of >0.2 ng/ml if the results influence subsequent treatment decisions.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

ADT = androgen deprivation therapy; AS = active surveillance; CI = core involvement; ePLND = extended pelvic lymph node dissection; fx = fractions; HDR = high dose rate; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; ISUP = International Society of Urological Pathology; LDR = low dose rate; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; RP = radical prostatectomy; SBRT = stereotactic body radiotherapy; VMAT = volumetric modulated arc therapy.

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References

[1] Mottet N, van den Berg RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis and local treatment with curative intent. Eur Urol 2021;79:243–62.
[2] Cornford P, Tilki D, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology Guidelines Office; 2024.
[3] Guyatt GH et al. Going from evidence to recommendations. BMJ 2008;336:1049–51.
[4] Culp MB, Soerjomataram I, Efstathiou JA, Bray F. Recent global patterns in prostate cancer incidence and mortality rates. Eur Urol 2020;77:38–52.
[5] Albright F, Stephenson RA, Agarwal N, et al. Prostate cancer risk prediction based on complete prostate cancer family history. Prostate 2015;75:390–8.
[6] Hemminki K. Familial risk and familial survival in prostate cancer. World J Urol 2012;30:143–8.
[7] Huynh-Le M-P, Karunamuni R, Fan CC, et al. Common genetic and clinical risk factors: association with fatal prostate cancer in the cohort of Swedish men. Prostate Cancer Prostatic Dis 2021;24:845–51.
[8] Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRAC2 mutation carriers. Eur Urol 2019;76:831–42.
[9] Bancroft EK, Page EC, Brook MN, et al. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. Lancet Oncol 2021;22:1618–31.
[10] Nyberg T, Tischkowitz M, Antoniou AC. BRAC1 and BRAC2 pathogenic variants and prostate cancer risk: systematic review and meta-analysis. Br J Cancer 2022;126:1067–81.
[11] Haider A et al. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median follow-up of 3 registries. J Urol 2015;193:80–6.
[12] Golla V et al. Testosterone therapy on active surveillance and following definitive treatment for prostate cancer. Curr Urol Rep 2017;18:49.
[13] Brierley JD et al. TNM classification of malignant tumors. ed. 8. UICC International Union Against Cancer; 2017.
[14] Ceci F et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging 2021;48:1626–38.
[15] Epstein JI et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228–42.
[16] van Leenders G et al. The 2019 International Society of Urological Pathology (ISUP) consensus conference on grading of prostatic carcinoma. Am J Surg Pathol 2020;44:e87–99.
[17] Gnanapragasam VJ et al. Improving clinical risk stratification at diagnosis in primary prostate cancer: a prognostic modelling study. PLoS Med 2016;13:e1002063.
[18] Gnanapragasam VJ et al. The Cambridge Prognostic Groups for improved prediction of disease mortality at diagnosis in primary non-metastatic prostate cancer: a validation study. BMC Med 2018;16:31.
[19] Ilic D et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ 2018;362:k3519.
[20] Hugosson J et al. A 16-yr follow-up of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2019;76:43–51.
[21] Hugosson J et al. Eighteen-year follow-up of the Goteborg Randomized Population-based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. Scand J Urol 2018;52:27–37.
[22] de Vos II et al. A detailed evaluation of the effect of prostate-specific antigen-based screening on morbidity and mortality of prostate cancer: 21-year follow-up results of the Rotterdam Section of the European Randomised Study of Screening for Prostate Cancer. Eur Urol 2023;84:426–34.
[23] Boyle HJ, Alibhai S, Decoster L, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer 2019;116:116–36.
[24] Nordstrom T et al. Repeat prostate-specific antigen tests before prostate biopsy decisions. J Natl Cancer Inst 2016;108:dwj165.
[25] Grey ADR et al. Multiparametric ultrasound versus multiparametric MRI to diagnose prostate cancer (CADMUS): a prospective, multicentre, paired-cohort, confirmatory study. Lancet Oncol 2022;23:428–38.
[26] Drost FH et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev 2019;4:CD012663.
[27] Kasivisvanathan V et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.
[28] Rouviere O et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100–9.
[29] Exterkate L et al. Is there still a need for repeated systematic biopsies in patients with previous negative biopsies in the era of magnetic resonance imaging-targeted biopsies of the prostate? Eur Urol Oncol 2020;3:216–23.
[30] Schoots IG et al. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation. BJU Int 2021;127:175–8.
[31] Gronberg H et al. Prostate cancer diagnostics using a combination of the Stockholm3 blood test and multiparametric magnetic resonance imaging. Eur Urol 2018;74:722–8.
[32] Nordstrom T et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. Lancet Oncol 2021;22:1240–9.
[33] Kawada T et al. Diagnostic performance of prostate-specific membrane antigen positron emission tomography-targeted biopsy

for detection of clinically significant prostate cancer: a systematic review and meta-analysis. Eur Urol Oncol 2022;5:390–400.
[34] Emmett L et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682–9.
[35] Kanagarajah A et al. A systematic review on the outcomes of local anaesthetic transperineal prostate biopsy. BJU Int 2023;131:408–23.
[36] Eichler K et al. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol 2006;175:1605–12.
[37] van der Leest M, Cornel E, Israel B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naive men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570–8.
[38] Wegelin O et al. The FUTURE trial: a multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. Eur Urol 2019;75:582–90.
[39] Hagens MJ et al. Diagnostic performance of a magnetic resonance imaging-directed targeted plus regional biopsy approach in prostate cancer diagnosis: a systematic review and meta-analysis. Eur Urol Open Sci 2022;40:95–103.
[40] Brisbane WG et al. Targeted prostate biopsy: umbra, penumbra, and value of perilesional sampling. Eur Urol 2022;82:303–10.
[41] Noujeim JP et al. Optimizing multiparametric magnetic resonance imaging-targeted biopsy and detection of clinically significant prostate cancer: the role of perilesional sampling. Prostate Cancer Prostatic Dis 2023;26:575–80.
[42] Tu X et al. Transperineal magnetic resonance imaging-targeted biopsy may perform better than transrectal route in the detection of clinically significant prostate cancer: systematic review and meta-analysis. Clin Genitourin Cancer 2019;17:e860–70.
[43] Bass EJ et al. Magnetic resonance imaging targeted transperineal prostate biopsy: a local anaesthetic approach. Prostate Cancer Prostatic Dis 2017;20:311–7.
[44] Roberts MJ et al. Prostate biopsy-related infection: a systematic review of risk factors, prevention strategies, and management approaches. Urology 2017;104:11–21.
[45] Pilatz A et al. Update on strategies to reduce infectious complications after prostate biopsy. Eur Urol Focus 2019;5:20–8.
[46] Kweldam CF, Kummerlin IP, Nieboer D, et al. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. Mod Pathol 2016;29:630–6.
[47] Saeter T, Vlatkovic L, Waaler G, et al. Intraductal carcinoma of the prostate on diagnostic needle biopsy predicts prostate cancer mortality: a population-based study. Prostate 2017;77:859–65.
[48] Ploussard G et al. Decreased accuracy of the prostate cancer EAU risk group classification in the era of imaging-guided diagnostic pathway: proposal for a new classification based on MRI-targeted biopsies and early oncologic outcomes after surgery. World J Urol 2020;38:2493–500.
[49] Soeterik TFW et al. Multiparametric magnetic resonance imaging should be preferred over digital rectal examination for prostate cancer local staging and disease risk classification. Urology 2021;147:205–12.
[50] Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 2008;63:387–95.
[51] Di Pierro GB et al. Comparison of four validated nomograms (Memorial Sloan Kettering Cancer Center, Briganti 2012, 2017, and 2019) predicting lymph node invasion in patients with high-risk prostate cancer candidates for radical prostatectomy and extended pelvic lymph node dissection: clinical experience and review of the literature. Cancers (Basel) 2023;15:1683.
[52] Perera M et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol 2020;77:403–17.
[53] Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. Skelet Radiol 2014;43:1503–13.
[54] Lecouvet FE, El Mouedden J, Collette L, et al. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Eur Urol 2012;62:68–75.
[55] Pasoglou V, Larbi A, Collette L, et al. One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI): toward an upfront simplified "all-in-one" imaging approach? Prostate 2014;74:469–77.
[56] Hofman MS et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.
[57] Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001;285:2750–6.
[58] Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–8.
[59] Groome PA, Rohland SL, Siemens DR, Brundage MD, Heaton J, Mackillop WJ. Assessing the impact of comorbid illnesses on death within 10 years in prostate cancer treatment candidates. Cancer 2011;117:3943–52.
[60] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[61] Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.
[62] Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc 2003;51:1451–4.
[63] Albertsen PC et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol 2011;29:1335–41.
[64] Albertsen PC. Observational studies and the natural history of screen-detected prostate cancer. Curr Opin Urol 2015;25:232–7.
[65] Thomsen FB, Brasso K, Klotz LH, Roder MA, Berg KD, Iversen P. Active surveillance for clinically localized prostate cancer-a systematic review. J Surg Oncol 2014;109:830–5.
[66] Bruinsma SM, Roobol MJ, Carroll PR, et al. Expert consensus document: semantics in active surveillance for men with localized prostate cancer—results of a modified Delphi consensus procedure. Nat Rev Urol 2017;14:312–22.
[67] Klotz L et al. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year post biopsy follow-up. Eur Urol 2020;77:311–7.
[68] Amin A et al. The Magnetic Resonance Imaging in Active Surveillance (MRIAS) trial: use of baseline multiparametric magnetic resonance imaging and saturation biopsy to reduce the frequency of surveillance prostate biopsies. J Urol 2020;203:910–7.
[69] Hamdy FC et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2023;388:1547–58.
[70] Lam TBL, MacLennan S, Willemse PM, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE study). Eur Urol 2019;76:790–813.
[71] Ericson KJ, Wu SS, Lundy SD, Thomas LJ, Klein EA, McKenney JK. Diagnostic accuracy of prostate biopsy for detecting cribriform Gleason pattern 4 carcinoma and intraductal carcinoma in paired radical prostatectomy specimens: implications for active surveillance. J Urol 2020;203:311–9.
[72] Moreira DM et al. Baseline perineural invasion is associated with shorter time to progression in men with prostate cancer undergoing active surveillance: results from the REDEEM study. J Urol 2015;194:1258–63.
[73] Fujihara A et al. Multiparametric magnetic resonance imaging facilitates reclassification during active surveillance for prostate cancer. BJU Int 2021;127:712–21.
[74] Stavrinides V et al. Mapping PSA density to outcome of MRI-based active surveillance for prostate cancer through joint longitudinal-survival models. Prostate Cancer Prostatic Dis 2021;24:1028–31.

[75] Olivier J et al. Low-risk prostate cancer selected for active surveillance with negative MRI at entry: can repeat biopsies at 1 year be avoided? A pilot study. World J Urol 2019;37:253–9.
[76] Chu CE et al. The clinical significance of multiple negative surveillance prostate biopsies for men on active surveillance—does cancer vanish or simply hide? J Urol 2021;205:109–14.
[77] O'Connor LP et al. Changes in magnetic resonance imaging using the prostate cancer radiologic estimation of change in sequential evaluation criteria to detect prostate cancer progression for men on active surveillance. Eur Urol Oncol 2021;4:227–34.
[78] Moore CM et al. Best current practice and research priorities in active surveillance for prostate cancer—a report of a Movember International Consensus Meeting. Eur Urol Oncol 2023;6:160–82.
[79] Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014;370:932–42.
[80] Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377:132–42.
[81] Schreiber D, Wong AT, Rineer J, Weedon J, Schwartz D. Prostate biopsy concordance in a large population-based sample: a Surveillance, Epidemiology and End Results study. J Clin Pathol 2015;68:453–7.
[82] Yossepowitch O, Eggener SE, Serio AM, et al. Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. Eur Urol 2008;53:950–9.
[83] Joniau S, Briganti A, Gontero P, et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol 2015;67:157–64.
[84] Mungovan SF et al. Preoperative membranous urethral length measurement and continence recovery following radical prostatectomy: a systematic review and meta-analysis. Eur Urol 2017;71:368–78.
[85] van Dijk-de Haan MC et al. Value of different magnetic resonance imaging-based measurements of anatomical structures on preoperative prostate imaging in predicting urinary continence after radical prostatectomy in men with prostate cancer: a systematic review and meta-analysis. Eur Urol Focus 2022;8: 1211–25.
[86] Veerman H et al. A standardized method to measure the membranous urethral length (MUL) on MRI of the prostate with high inter- and intra-observer agreement. Eur Radiol 2023;33:3295–302.
[87] Walz J, Epstein JI, Ganzer R, et al. A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: an update. Eur Urol 2016;70:301–11.
[88] Vis AN et al. Selection of patients for nerve sparing surgery in robot-assisted radical prostatectomy. BJUI Compass 2022;3:6–18.
[89] de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 2016;70:233–45.
[90] Ramsay C, Pickard R, Robertson C, et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess 2012;16:1–313.
[91] Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol 2018;19:1051–60.
[92] Fossati N et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. Eur Urol 2017;72:84–109.
[93] Lestingi JFP et al. Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. Eur Urol 2021;79:595–604.
[94] Touijer KA et al. Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. Eur Urol Oncol 2021;4:532–9.
[95] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472–9.
[96] Abdollah F, Dalela D, Sood A, et al. Impact of adjuvant radiotherapy in node-positive prostate cancer patients: the importance of patient selection. Eur Urol 2018;74:253–6.
[97] Gupta M, Patel HD, Schwen ZR, Tran PT, Partin AW. Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. BJU Int 2019;123:252–60.
[98] Vale CL et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet 2020;396:1422–31.
[99] Tilki D, Chen MH, Wu J, et al. Adjuvant versus early salvage radiation therapy for men at high risk for recurrence following radical prostatectomy for prostate cancer and the risk of death. J Clin Oncol 2021;39:2284–93.
[100] Ploussard G, Staerman F, Pierrevelcin J, et al. Predictive factors of oncologic outcomes in patients who do not achieve undetectable prostate specific antigen after radical prostatectomy. J Urol 2013;190:1750–6.
[101] Wiegel T, Bartkowiak D, Bottke D, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96–02 trial. Int J Radiat Oncol Biol Phys 2015;91:288–94.
[102] Spratt DE, Dai DLY, Den RB, et al. Performance of a prostate cancer genomic classifier in predicting metastasis in men with prostate-specific antigen persistence postprostatectomy. Eur Urol 2018;74:107–14.
[103] Preisser F, Chun FKH, Pompe RS, et al. Persistent prostate-specific antigen after radical prostatectomy and its impact on oncologic outcomes. Eur Urol 2019;76:106–14.
[104] Schmidt-Hegemann NS, Fendler WP, Ilhan H, et al. Outcome after PSMA PET/CT based radiotherapy in patients with biochemical persistence or recurrence after radical prostatectomy. Radiat Oncol 2018;13:37.
[105] Choo R, Danjoux C, Gardner S, et al. Prospective study evaluating postoperative radiotherapy plus 2-year androgen suppression for post-radical prostatectomy patients with pathologic T3 disease and/or positive surgical margins. Int J Radiat Oncol Biol Phys 2009;75:407–12.
[106] Ploussard G, Staerman F, Pierrevelcin J, et al. Clinical outcomes after salvage radiotherapy without androgen deprivation therapy in patients with persistently detectable PSA after radical prostatectomy: results from a national multicentre study. World J Urol 2014;32:1331–8.
[107] Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124–9.
[108] Zapatero A et al. Reduced late urinary toxicity with high-dose intensity-modulated radiotherapy using intra-prostate fiducial markers for localized prostate cancer. Clin Transl Oncol 2017;19:1161–7.
[109] Wallis CJ, Mahar AL, Choo R, et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ 2016;352:i851.
[110] Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol 2014;110:104–9.
[111] Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: the NRG Oncology RTOG 0126 randomized clinical trial. JAMA Oncol 2018;4:e180039.
[112] Pasalic D, Kuban DA, Allen PK, et al. Dose escalation for prostate adenocarcinoma: a long-term update on the outcomes of a phase 3, single institution randomized clinical trial. Int J Radiat Oncol Biol Phys 2019;104:790–7.
[113] Kalbasi A, Li J, Berman A, et al. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. JAMA Oncol 2015;1:897–906.
[114] Kishan AU et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol 2022;23: 304–16.
[115] Krauss DJ et al. Dose-escalated radiotherapy alone or in combination with short-term androgen deprivation for intermediate-risk

prostate cancer: results of a phase III multi-institutional trial. J Clin Oncol 2023;41:3203–16.
[116] Bolla M et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009;360:2516–27.
[117] Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047–60.
[118] Syndikus I, Griffin C, Philipps L, et al. 10-Year efficacy and co-morbidity outcomes of a phase III randomised trial of conventional vs. hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CHHiP; CRUK/06/016). J Clin Oncol 2023;41(6 suppl):304.
[119] Tree AC, Ostler P, van der Voet H, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23:1308–20.
[120] van As N, Tree A, Patel J, et al. 5-Year outcomes from PACE B: an international phase III randomized controlled trial comparing stereotactic body radiotherapy (SBRT) vs. conventionally fractionated or moderately hypo fractionated external beam radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2023;117:e2–3.
[121] Moris L, Cumberbatch MG, Van den Broeck T, et al. Benefits and risks of primary treatments for high-risk localized and locally advanced prostate cancer: an international multidisciplinary systematic review. Eur Urol 2020;77:614–27.
[122] Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:275–85.
[123] Martens C et al. Relationship of the International Prostate Symptom score with urinary flow studies, and catheterization rates following 125I prostate brachytherapy. Brachytherapy 2006;5:9–13.
[124] Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int 2012;109(Suppl 1):22–9.
[125] Salembier C et al. A history of transurethral resection of the prostate should not be a contra-indication for low-dose-rate (125) I prostate brachytherapy: results of a prospective Uro-GEC phase-II trial. J Contemp Brachytherapy 2020;12:1–5.
[126] Budaus L, Bolla M, Bossi A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol 2012;61:112–27.
[127] Oh J et al. An updated analysis of the survival endpoints of ASCENDE-RT. Int J Radiat Oncol Biol Phys 2023;115:1061–70.
[128] Rodda S et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:286–95.
[129] Vordermark D, Wulf J, Markert K, et al. 3-D conformal treatment of prostate cancer to 74 Gy vs. High-dose-rate brachytherapy boost: a cross-sectional quality-of-life survey. Acta Oncol 2006;45:708–16.
[130] Parry MG et al. Impact of high-dose-rate and low-dose-rate brachytherapy boost on toxicity, functional and cancer outcomes in patients receiving external beam radiation therapy for prostate cancer: a national population-based study. Int J Radiat Oncol Biol Phys 2021;109:1219–29.
[131] Ramsay CR et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess 2015;19:1–490.
[132] Brundl J et al. Oncological long-term outcome after whole-gland high-intensity focused ultrasound for prostate cancer-21-yr follow-up. Eur Urol Focus 2022;8:134–40.
[133] Dickinson L et al. Medium-term outcomes after whole-gland high-intensity focused ultrasound for the treatment of nonmetastatic prostate cancer from a multicentre registry cohort. Eur Urol 2016;70:668–74.
[134] Lovegrove CE et al. Evaluation of functional outcomes after a second focal high-intensity focused ultrasonography (HIFU) procedure in men with primary localized, non-metastatic prostate cancer: results from the HIFU Evaluation and Assessment of Treatment (HEAT) registry. BJU Int 2020;125:853–60.
[135] Guillaumier S et al. A multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. Eur Urol 2018;74:422–9.
[136] Walz J et al. Pathological results and rates of treatment failure in high-risk prostate cancer patients after radical prostatectomy. BJU Int 2011;107:765–70.
[137] Spahn M et al. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. Eur Urol 2010;58:1–7.
[138] Ward JF et al. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005;95:751–6.
[139] Bolla M, van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066–73.
[140] Ventimiglia E, Seisen T, Abdollah F, et al. A systematic review of the role of definitive local treatment in patients with clinically lymph node-positive prostate cancer. Eur Urol Oncol 2019;2:294–301.
[141] Attard G et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022;399:447–60.