EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer

N. Mottet (Chair), P. Cornford (Vice-chair), R.C.N. van den Bergh, E. Briers, Expert Patient Advocate (European Prostate Cancer Coalition/Europa UOMO), D. Eberli, G. De Meerleer, M. De Santis, S. Gillessen, J. Grummet, A.M. Henry, T.H. van der Kwast, G.J.L.H. van Leenders, M.D. Mason, S. O'Hanlon, I.M. van Oort, D.E. Oprea-Lager, G. Ploussard, O. Rouvière, I.G. Schoots. J. Stranne, D. Tilki, T. Wiegel

Guidelines Associates: T. Van den Broeck, A. Farolfi, G. Gandaglia, N. Grivas, M. Lardas, M. Liew, E. Linares Espinós, P-P.M. Willemse

European Association of Urology

EANM — European Association of Nuclear Medicine — BIOMEDICAL IMAGING AND THERAPY FOR PERSONALIZED HEALTHCARE

SIOG — INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

European Society of Urogenital Radiology

ESTRO — European SocieTy for Radiotherapy & Oncology

EUROPA UOMO — The Voice of Men with Prostate Cancer in Europe

INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY

TABLE OF CONTENTS   PAGE

1. INTRODUCTION

1.1 Aims and scope

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, pathologists, a geriatrician and a patient representative.

All imaging sections in the text have been developed jointly with the European Society of Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM). Representatives of the ESUR and the EANM in the PCa Guidelines Panel are (in alphabetical order): Dr. A. Farolfi, Dr. D. Oprea-Lager, Prof.Dr. O. Rouvière and Dr. I.G. Schoots.

All radiotherapy (RT) sections have been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. G. De Meerleer, Prof.Dr. A.M. Henry, Prof.Dr. M.D. Mason and Prof.Dr. T. Wiegel.

The International Society of Urological Pathology is represented by Prof.Dr. T. van der Kwast and Prof.Dr. A. van Leenders.

Dr. S. O'Hanlon, consultant geriatrician, representing the International Society of Geriatric Oncology (SOIG) contributed to the sections addressing life expectancy, health status and quality of life (QoL) in particular.

Dr. E. Briers, expert Patient Advocate Hasselt-Belgium representing the patient voice as delegated by the European Prostate Cancer Coalition/Europa UOMO.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/prostate-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the PCa Guidelines. All documents can be accessed on the EAU website: http://uroweb.org/guideline/prostate-cancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU PCa Guidelines were first published in 2001. This 2023 document presents a limited update of the 2022 EAU-EANM-ESTRO-ESUR-ISUP-SIOG PCa Guidelines.

1.4.2 Summary of changes

The literature for the complete document has been assessed and updated based upon a review of all recommendations and creation of appropriate GRADE forms. Evidence summaries and recommendations have been amended throughout the current document and several new sections have been added.

All chapters of the 2022 PCa Guidelines have been updated. New data have been included in the following sections, resulting in new sections, and new and revised recommendations:

Table 4.3: 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 GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10–20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade)* cT3-4* or cN+**
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.
* Based on digital rectal examination.
** Based on CT/bone scan.

5.1.5 Guidelines for screening and individual early detection

Recommendations	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak
In asymptomatic men with a PSA level between 3–10 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • risk-calculator, provided it is correctly calibrated to the population prevalence; • magnetic resonance imaging of the prostate	Strong
• an additional serum, urine biomarker test	Weak

5.2.8.2 Summary of evidence and recommendations for performing prostate biopsy
(in line with the EAU Urological Infections Guidelines Panel)

Summary of evidence	LE
A meta-analysis of eight studies including 1,596 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight non-RCTS reported comparable rates of post-biopsy infections in patients undergoing transperineal biopsy irrespective if antibiotic prophylaxis was given or not.	1a
A meta-analysis of eleven RCTs including 2,036 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a

Figure 5.1: Prostate biopsy workflow to reduce infectious complications*
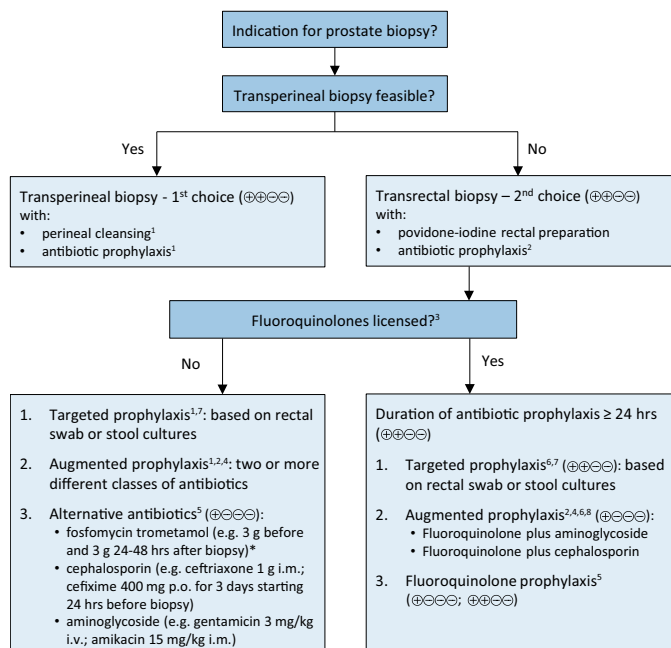
5.3.5 Summary of evidence and guidelines for staging of prostate cancer

Recommendation	Strength rating
Any risk group staging	
Treatment should not be changed based on PSMA PET/CT findings, in view of current available data.	Strong

6.1.6 General guidelines for the treatment of prostate cancer*

Recommendations	Strength rating
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Surgical treatment	
Radical prostatectomy (RP) can be safely delayed for at least 3 months from diagnosis in any risk category.	Weak
When a lymph node dissection (LND) is deemed necessary based on a nomogram, perform an extended LND template for optimal staging.	Strong
Radiotherapeutic treatment	
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease (60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks).	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low-risk or NCCN favourable intermediate-risk disease.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Only offer focal therapy with high-intensity focused ultrasound or cryotherapy within a clinical trial or prospective registry.	Strong

*All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2.1.3 Summary of evidence and guidelines for follow-up during active surveillance

Summary of evidence	LE
Serial magnetic resonance imaging can improve the detection of aggressive cancers during follow-up.	3
A progression on MRI mandates a repeat biopsy before a change in treatment strategy.	
A stationary MRI does not make repeat biopsy superfluous.	

Recommendations	Strength rating
Base follow-up during active surveillance (AS) on a strict protocol including digital rectal examination (at least once yearly), prostate-specific antigen (PSA) (at least once every 6 months) and repeated biopsy every 2 to 3 years.	Strong
Perform magnetic resonance imaging (MRI) and repeat biopsy if PSA is rising (PSA-doubling time < 3 years).	Strong
Re-classify 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 2 disease.	Weak
Base change in treatment on biopsy progression, not on progression on MRI and/or PSA.	Weak
Patients with a PI-RADS 1-2 findings on MRI and a low PSA density (< 0.15) may be excepted from repeat biopsy.	Weak

6.2.1.4 Summary of evidence and guidelines for the management of low-risk disease*

Summary of evidence	LE
Active surveillance or WW is SOC, based on life expectancy.	2a
All active treatment options present a risk of over-treatment.	1a

Recommendations	Strength rating
Watchful Waiting	
Manage patients with a life expectancy < 10 years by watchful waiting.	Strong
Active surveillance (AS)	
Manage patients with a life expectancy > 10 years and low-risk disease by AS.	Strong

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

*6.2.2.5 Guidelines for the treatment of intermediate-risk disease**

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW in asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Offer RP to patients with a life expectancy of > 10 years.	Strong
Radical prostatectomy can be safely delayed for at least 3 months.	Weak
Offer nerve-sparing surgery to patients with a low risk of extra-capsular disease on that side.	Strong
Radiotherapeutic treatment	
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 months).	Weak
Offer high-dose rate (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 months).	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

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

*6.2.3.4 Guidelines for radical and palliative treatment of high-risk localised disease**

Recommendations	Strength rating
Watchful Waiting	
Offer WW to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Radical prostatectomy can be safely delayed for at least 3 months.	Weak

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

*6.2.4.5 Guidelines for radical- and palliative treatment of locally-advanced disease**

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
Radiotherapeutic treatment	
Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 years 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 years of abiraterone to cN1M0 patients.	Strong
Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Strong

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2.5.7 Guidelines for adjuvant treatment for pN0 and pN1 disease after radical prostatectomy*

Recommendations	Strength rating
In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT).	Strong
In pN1 patients, after an extended lymph node dissection, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak

*All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.4.8 ***Guidelines for the first-line treatment of hormone-sensitive metastatic disease****

Recommendations	Strength rating
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with non-curative prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria/M1a disease.	Strong

*All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.

- Section 6.6: Two new flowcharts were introduced

Figure 6.1: Treatment non-metastasized (M0) – asymptomatic disease#

* Rule of thumb: Life expectancy 10 years.

** Recommendation based on clinical staging using digital rectal examination, not imaging.

*** Recommendation based on staging using combination of bone scan and CT.

**** See text, dependent on GG and (biopsy) volume

1EBRT: IMRT/VMAT + IGRT of the prostate

⋯⋯⋯ = weak recommendation.

ADT = androgen deprivation therapy; EBRT =external beam radiotherapy; ECE = extracapsular extension; ePLND = extended pelvic lymph node dissection; GG = grade group; HDR = high-dose rate; IDC = intraducal carcinoma; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; LDR = low-dose rate; VMAT = volumetric modulated arc therapy.

Figure 6.2: Treatment of metastasized (M1*) – disease, M+HSPC

* *Based on staging using combination of bone scan and CT.*

** *Alphabetical order*

[1]*EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).*

┌╌╌╌┐ *= weak recommendation.*

EBRT = external beam radiotherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

[#]Note: Please be aware that the various options in the following flowcharts present a generalised approach only, and cannot take the management of individual patients into account, nor the availability of resources.

*7.1.5 **Summary of evidence for follow-up after treatment with curative intent***

Summary of evidence	LE
A detectable PSA, indicating a relaps of the disease, must be differentiated from a clinically meaningful relapse. The PSA threshold that best predicts further metastases after RP is > 0.4 ng/mL and > NADIR + 2 ng/mL after IMRT/VMAT plus IGRT (± ADT].	3

2. METHODS

2.1 Data identification

For the 2023 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A number of comprehensive searches were performd, covering all sections of the PCa Guidelines. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between May 1st 2021 and April 1st 2022. A total of 2,480 unique records were identified, retrieved and screened for relevance resulting in 166 new publications having been included in the 2023 print. A detailed search strategy is available online: https://uroweb.org/guideline/prostate-cancer/?type=appendices-publications.

Changes in recommendations were generally only considered on the basis of high-level evidence (i.e. systematic reviews with meta-analysis, randomised controlled trials [RCTs], and prospective comparative studies) published in the English language. Additional information can be found in the general Methodology section of this print and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

For each recommendation within the guidelines there is an accompanying online strength rating form which includes the assessment of the benefit to harms ratio and patients' preferences for each recommendation. The strength rating forms draws on the guiding principles of the GRADE methodology but do not purport to be GRADE [3, 4]. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5];
2. the magnitude of the effect (individual or combined effects);

3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [6]. 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 nature and variability of patient values and preferences. The strength rating forms will be available online.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address. In addition, the International Society of Geriatric Oncology (SIOG), the European Society for Radiotherapy & Oncology (ESTRO), the European Society for Urogenital Radiology (ESUR), the European Association of Nuclear Medicine (EANM) and the International Society of Urological Pathology (ISUP) have endorsed the PCa Guidelines.

2.2 Review
Publications ensuing from systematic reviews have all been peer-reviewed.

2.3 Future goals
Results of ongoing and new systematic reviews will be included in the 2024 update of the PCa Guidelines:
• A systematic review assessing the performance of risk stratification tools incorporating imaging, biomarkers, biopsy involvement and/or MRI-targeted biopsies, compared to the classical risk classifications (d'Amico, EAU, CAPRA and NCCN) recommended in current guidelines for predicting biochemical recurrence, metastasis or death after local treatment for prostate cancer. Are the new stratification tools preferred above the classical risk classifications?
• A systematic review assessing the outcomes of brachytherapy boost combined with external beam RT for PCa.
• Care pathways for the various stages of PCa management are being developed. These pathways will, in due time, inform treatment flowcharts and an interactive app.
• Assessment of individual patient life expectancy – development of a calculator.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology
Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020 [7, 8]. A systematic review of autopsy studies reported a prevalence of PCa at age < 30 years of 5% (95% confidence interval [CI]: 3–8%), increasing by an odds ratio (OR) of 1.7 (1.6–1.8) per decade, to a prevalence of 59% (48–71%) by age > 79 years [9]. There is variation in the frequency of autopsy-detected PCa between men with different ethnical backgrounds and geographical areas (e.g., 83 in white US males vs. 41 in Japan at age 71–80) [10].

The variation in incidence of PCa diagnosis is even more pronounced between different geographical areas, driven by rate of prostate-specific antigen (PSA) testing and influenced by (inter)national organisations' recommendations on screening (see Section 5.1) [11]. It is highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively). The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), but rising [12]. Rates in Eastern and Southern Europe were low but have also shown a steady increase [8, 10]. Besides PSA testing, incidence is also dependent on the age of the population, geography and ethnicity.

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (e.g., Caribbean: ASR of 29 and Sub-Saharan Africa: ASRs ranging between 19 and 14), intermediate in the USA and very low in Asia (South-Central Asia: ASR of 2.9) [8, 13]. Mortality due to PCa has decreased in most Western nations but the magnitude of the reduction varies between countries [7].

3.2 Aetiology

3.2.1 *Family history/hereditary prostate cancer*

Family history and ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [14, 15]. Men of African ancestry in the Western world demonstrate more unfavourable outcomes due to a combination of biological, environmental, social, and health care factors [16]. They are more likely to be diagnosed with more advanced disease [17] and upgrade after prostatectomy was more frequent as compared to Caucasian men (49% vs. 26%) [18]. Racial disparities in development of, prevention of, and therapies for PCa may exist. It should be kept in mind that many PCa studies include either small percentages of men from other origin than Caucasians or focus on highly specific other groups [19].

Only a small subpopulation of men with PCa have true hereditary disease (≥ 3 cases in the same family, PCa in three successive generations, or ≥ 2 men diagnosed with PCa < 55 yrs). Hereditary PCa (HPCa) is associated with a six to seven year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways [14, 20]. In a large USA population database, HPCa (reported by 2.18% of participants) showed a relative risk (RR) of 2.30 for diagnosis of any PCa, 3.93 for early-onset PCa, 2.21 for lethal PCa, and 2.32 for clinically significant PCa (csPCa) [21]. These increased risks with HPCa were higher than for familial PCa (≥ 2 first- or second-degree relatives with PCa on the same side of the pedigree), or familial syndromes such as hereditary breast- and ovarian cancer and Lynch syndrome. With the father as well as two brothers affected, the probability of high-risk PCa at age 65 was 11.4% (vs. a population risk of 1.4%), and for any PCa 43.9% vs. 4.8%, in a Swedish population-based study [22].

3.2.1.1 *Germline mutations and prostate cancer*

Genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for (aggressive) PCa [23-27]. Clinical cohort studies have reported rates of 15% to 17% of cases harbour any germline mutations independent of stage [28, 29]. Based on clinical genetic data from men with PCa unselected for metastatic disease undergoing multigene testing across the US, it was found that 15.6% of men with PCa have pathogenic variants identified in genes tested ([Breast Cancer genes] *BRCA1, BRCA2, HOXB13, MLH1, MSH2, PMS2, MSH6, EPCAM, ATM, CHEK2, NBN,* and *TP53*), and 10.9% of men have germline pathogenic variants in DNA repair genes (see Table 3.1) [28]. Pathogenic variants were most commonly identified in *BRCA2* (4.5%), *CHEK2* (2.2%), *ATM* (1.8%), and *BRCA1* (1.1%) [28].

The frequency and distribution of positive germline variants of 3,607 unselected PCa patients was reported and showed that 620 (17.2%) had a pathogenic germline variant [29]. A carrier rate of 16.2% was found in unselected patients at diagnosis of metastatic castrate-resistant PCa (mCRPC) who were screened for DNA damage repair (DDR) mutations in 107 genes [30].

Among unselected men with metastatic PCa, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes [31]. Targeted genomic analysis of genes associated with an increased risk of PCa could offer options to identify families at high risk [32, 33].

A prospective cohort study of male *BRCA1* and *BRCA2* carriers confirmed *BRCA2* association with aggressive PCa [34]. An analysis of the outcomes of 2,019 patients with PCa (18 *BRCA1* carriers, 61 *BRCA2* carriers, and 1,940 non-carriers) showed that PCa with germline *BRCA1/2* mutations were more frequently associated with ISUP ≥ 4, T3/T4 stage, nodal involvement, and metastases at diagnosis than PCa in non-carriers [35]. *BRCA*-susceptibility gene mutation carriers were also reported to have worse outcome when compared to non-carriers after local therapy [36]. In a retrospective study of 313 patients who died of PCa and 486 patients with low-risk localised PCa, the combined *BRCA1/2* and *ATM* mutation carrier rate was significantly higher in lethal PCa patients (6.07%) than in localised PCa patients (1.44%) [37]. The rate of PCa among *BRCA1* carriers was more than twice as high (8.6% vs. 3.8%) compared to the general population, in contrast to findings of the prospective IMPACT study (Identification of Men With a Genetic Predisposition to ProstAte Cancer (see Chapter 5) [38].

Table 3.1: Germline mutations in DNA repair genes associated with increased risk of prostate cancer

Gene	Location	Prostate cancer risk	Findings
BRCA2	13q12.3	- RR 2.5 to 4.6 [39, 40] - PCa at 55 years or under: RR: 8–23 [39, 41]	• up to 12 % of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA2* [5.3%]) [31] • 2% of men with early-onset PCa harbour germline mutations in the *BRCA2* gene [39] • *BRCA2* germline alteration is an independent predictor of metastases and worse PCa-specific survival [35, 42]
ATM	11q22.3	RR: 6.3 for metastatic PCa [31]	• higher rates of lethal PCa among mutation carriers [37] • up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *ATM* [1.6%]) [31]
CHEK2	22q12.1	OR 3.3 [43, 44]	• up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *CHEK2* [1.9%]) [31]
BRCA1	17q21	RR: 1.8–3.8 at 65 years or under [45, 46]	• higher rates of lethal PCa among mutation carriers [37] • up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA1* [0.9%]) [31]
HOXB13	17q21.2	OR 3.4–7.9 [32, 47]	• significantly higher PSA at diagnosis, higher Gleason score and higher incidence of positive surgical margins in the radical prostatectomy specimen than non-carriers [48]
MMR genes *MLH1* *MSH2* *MSH6* *PMS2*	3p21.3 2p21 2p16 7p22.2	RR: 3.7 [49]	• Mutations in *MMR* genes are responsible for Lynch syndrome [50] • *MSH2* mutation carriers are more likely to develop PCa than other *MMR* gene mutation carriers [51]

BRCA2 = breast cancer gene 2; ATM = ataxia telangiectasia mutated; CHEK2 = checkpoint kinase 2;
BRCA1 = breast cancer gene 1; GS = Gleason score; HOXB13 = homeobox B13; MMR = mismatch repair;
MLH1 = mutL homolog 1; MSH2 = mutS homolog 2; MSH6 = mutS homolog 6; OR = odds ratio;
PMS2 = post-meiotic segregation increased 2; PCa = prostate cancer; RR = relative risk.

3.2.2 *Risk factors*

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 [52]. Asians who immigrated to the USA have approximately half the risk of PCa when compared to their US born Asian-descendant counterparts, implying a role of environmental or dietary factors [53]. However, currently there are no known effective preventative dietary or pharmacological interventions.

3.2.2.1 *Metabolic syndrome*

The single components of metabolic syndrome (MetS), hypertension (p = 0.035) and waist circumference > 102 cm (p = 0.007), have been associated with a significantly greater risk of PCa, but in contrast, having ≥ 3 components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60–0.82) [54, 55].

3.2.2.1.1 Diabetes/metformin

The association between metformin use and PCa is controversial. At population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never users (adjusted OR: 0.84, 95% CI: 0.74–0.96) [56]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with PCa and therefore not advised as a preventive measure (OR: 1.19, p = 0.50) [57].

3.2.2.1.2 Cholesterol/statins

A meta-analysis of 14 large prospective studies did not show any association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of developing either overall PCa or high-grade PCa [54]. Results from the REDUCE study also did not show a preventive effect of statins on PCa risk [55]. A meta-analysis suggested a lower risk of advanced PCa in statin users [58].

3.2.2.1.3 Obesity
Within the REDUCE study, obesity was associated with lower risk of low-grade PCa in multivariable analyses (OR: 0.79, p = 0.01), but increased risk of high-grade PCa (OR: 1.28, p = 0.042) [59]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [60]. A systematic review showed an association between obesity and increased PC-specific mortality [61].

3.2.2.2 Dietary factors
The association between a wide variety of dietary factors and PCa have been studied, but there is still a paucity of quality evidence (Table 3.2). To date, the current body of evidence will not support a causal relationship between specific (dietary and otherwise) factors and the development of PCa. Consequently, no effective preventative strategies can be suggested.

Table 3.2: Main dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [62]. A meta-analysis shows a dose-response relationship with PCa [63].
Coffee	Coffee consumption may be associated with a reduced risk of PCa; with a pooled RR of 0.91 for the highest category of coffee consumption [64].
Dairy	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [65].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [66]. A relation between intake of fried foods and risk of PCa may exist [67].
Tomatoes (lycopenes/ carotenes)	A trend towards a favourable effect of tomato intake (mainly cooked) and lycopenes on PCa incidence has been identified in meta-analyses [68, 69]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [70].
Meat	Meta-analyses show a potential association between red meat, total meat, and processed meat consumption and PCa [71, 72].
Soy (phytoestrogens [isoflavones/ coumestans])	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [73]. Total soy food intake has been associated with a reduced risk of PCa, but also with an increased risk of advanced disease [74, 75].
Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [75, 76].
Vitamin E/Selenium	An inverse association of blood, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [77, 78]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [79].

3.2.2.3 Hormonally active medication
3.2.2.3.1 5-alpha-reductase inhibitors (5-ARIs)
Although it seems that 5-ARIs have the potential of preventing or delaying the development of PCa (decreasing the risk by 25% but only for ISUP grade 1 cancer), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade PCas, although these do not seem to impact PCa mortality [80-84] None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

3.2.2.3.2 Testosterone
Hypogonadal men receiving testosterone supplements do not have an increased risk of PCa [85]. A pooled analysis showed that men with very low concentrations of free testosterone (lowest 10%) have a below average risk (OR: 0.77) of PCa [86].

3.2.2.4 Other potential risk factors
A significantly higher rate of ISUP ≥ 2 PCa (hazard ratio [HR]: 4.04) was found in men with inflammatory bowel disease when compared with the general population [87]. Balding was associated with a higher risk of PCa death [88]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31, 95%

CI: 1.14–1.52) [89]. Occupational exposure may also play a role, based on a meta-analysis which revealed that night-shift work is associated with an increased risk (2.8%, p = 0.030) of PCa [90]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24, 95% CI: 1.18–1.31) and with aggressive tumour features and worse prognosis, even after quitting smoking [91, 92]. A meta-analysis on Cadmium (Cd) found a positive association (magnitude of risk unknown due to heterogeneity) between high Cd exposure and risk of PCa for occupational exposure, but not for non-occupational exposure, potentially due to higher Cd levels during occupational exposure [93]. Men positive for human papillomavirus-16 may be at increased risk [94]. Plasma concentration of the estrogenic insecticide chlordecone is associated with an increase in the risk of PCa (OR: 1.77 for highest tertile of values above the limit of detection) [95].

A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [96] and self-reported acne [97]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa and mortality [98, 99].

Ultraviolet radiation exposure decreased the risk of PCa (HR: 0.91, 95% CI: 0.88–0.95) [100]. A review found a small but protective association of circumcision status with PCa [101]. Higher ejaculation frequency (≥ 21 times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [102].

3.2.3   Summary of evidence for epidemiology and aetiology

Summary of evidence	LE
Prostate cancer is a major health concern in men, with incidence mainly dependent on age.	3
Genetic factors are associated with risk of (aggressive) PCa.	3
A variety of dietary/exogenous/environmental factors have been associated with PCa incidence and prognosis.	3
In hypogonadal men, testosterone supplements do not increase the risk of PCa.	2a
No conclusive data exist which could support specific preventive or dietary measures aimed at reducing the risk of developing PCa.	1a

4.   CLASSIFICATION AND STAGING SYSTEMS

4.1   Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for discussion about prognosis with patients, the design of clinical trials on relatively homogeneous populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the development of recommendations for the treatment of these patient populations. Throughout these Guidelines the Union for International Cancer Control (UICC) 8th edition (2017), the Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [103] and the EAU risk group classification are used [104]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT). Changes in the diagnostic pathway, such as imaging (e.g., Magnetic Resonance Imaging [MRI], Prostate-Specific Membrane Antigen [PSMA] Positron Emission Tomography Computed Tomography [PET/CT] scan) and biopsy (e.g., increasing number of systematic biopsy cores, targeted biopsy) may cause a stage shift in risk classification systems [105].

Although the 2017 American Joint Committee on Cancer (AJCC) staging 8th edition specifically states that clinical staging should be based on digital rectal examination (DRE) only, such an explicit comment is not made by the UICC. Since clinical stage as assessed by DRE only, it is included in the EAU (D'Amico) risk group classification, cT-stage should be based on DRE findings and not on imaging. Additional staging information based on imaging should be reported separately. A non-palpable PCa with bilateral positive biopsies and extra-prostatic extension (EPE) on MRI would therefore be categorized as cT1c with a separate report of MRI findings.

Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [103]

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is **not palpable**	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends **palpably** through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*

[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1 and T2 substages. Pathological stages pT1a/b/c do not exist and histopathologically confirmed organ-confined PCas after RP are pathological stage pT2. The current UICC no longer recognise pT2 substages [103].

Of note: the EANM recently proposed a 'miTNM' (molecular imaging TNM) classification, taking into account PSMA PET/CT findings [106]. The prognosis of the miT, miN and miM substages is likely to be better than their T, N and M counterparts due to the 'Will Rogers phenomenon'; the extent of this prognosis shift remains to be assessed as well as its practical interest and impact [107]. This reclassification is not endorsed by the UICC or the AJCC.

4.2 Gleason score and International Society of Urological Pathology 2019 grade

In the original Gleason grading system, 5 Gleason grades (ranging from 1–5) based on histological tumour architecture were distinguished, but in the 2005 and subsequent 2014 ISUP consensus meetings Gleason grades 1 and 2 were eliminated [108, 109]. The 2005 ISUP modified Gleason score (GS) of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern, if two are present. If only one pattern is present, it needs to be doubled to yield the GS. For three grades, the biopsy GS comprises the most common grade plus the highest grade, irrespective of its extent. In case intraductal carcinoma is present intermixed with invasive PCa, it should be incorporated in the GS based on its underlying architectural pattern [110]. In addition to reporting of the carcinoma features for each biopsy side, an overall (or global) GS based on the carcinoma-positive biopsies can be provided. The global GS takes into account the cumulative extent of each grade from all prostate biopsies (see Section 5.2.9.2). The 2014 and 2019 ISUP endorsed grading system limits the number of PCa grades, ranging them from 1 to 5 (see Table 4.2) [109, 111].

Table 4.2: International Society of Urological Pathology 2014 grade (group) system

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 (4+5 or 5+4 or 5+5)	5

4.3 Clinically significant prostate cancer

The descriptor 'clinically significant' is widely used to differentiate PCa that may cause morbidity or death in a specific patient from types of PCa that do not. This distinction is particularly important as insignificant PCa that does not cause harm is so common [9]. Unless this distinction is made, such cancers are at high risk of being over-treated, with the treatment itself risking harmful side effects to patients. The over-treatment of insignificant PCas has also been criticised as a major drawback of PSA testing and early detection [112]. Although pathological factors are often used to delineate insignficant PCa, the definition of significant vs. insignificant is a balance between tumour and patient factors. High-risk PCa is significant in almost all men, except when life expectancy is limited. Low-risk PCa is insignificant in almost all men.

From a pathological point of view in large studies of RP specimens which showed only ISUP grade 1 disease, EPE (0.3%) [113] and biochemical recurrence (3.5%) were rare, and seminal vesicle (SV) invasion or lymph node (LN) metastasis did not occur at all [114, 115]. International Society of Urological Pathology grade 1 disease at RP itself can therefore be considered clinically insignificant. Whilst ISUP grade 1 bears the hallmarks of cancer histologically, ISUP grade 1 at RP itself does not behave in a clinically malignant fashion [116]. It is important to note that the studies showing absence of metastasis in ISUP grade 1 were all done on RP specimens; ISUP grade 1 on biopsy is associated with low risk of developing metastasis and disease-specific death, due to under-sampling of a higher grade component. Finally, modifications in PCa grading, MRI and targeted biopsies led to a grade shift during the past 10–15 years; for instance the introduction of the ISUP 2005 led to 20% of pre-ISUP 2005 GS 6 tumours being upgraded to GS 7 or higher, which has to be taken into account when interpreting older studies [117].

The current standard practice of MRI-targeted and template biopsies has reduced diagnostic inaccuracy [118], however sampling error may still occur such that higher grade cancer could be missed. This should especially be considered if the prior MRI showed a suspicious lesion, but only ISUP grade 1 was found at biopsy. Another complexity in defining insignificant cancer is that ISUP grade 1 may progress to higher grades over time, becoming clinically significant at a later biopsy [119].

Therefore, although ISUP grade 1 itself can be described as clinically insignificant, it is important to take into account other factors, including age, imaging prior to biopsy and adequate sampling core number. When combined with low-risk clinical factors (see Table 4.3), ISUP grade 1 represents low-risk PCa, with its recommendation of preferred management being active surveillance (AS) or watchful waiting (WW) (see Sections 6.1.1.1 & 6.1.1.2). It should be noted, therefore, that defining ISUP grade 1 as insignificant cancer does not mean it should be ignored, but appropriately observed.

Epidemiological and autopsy data suggest that a proportion of ISUP grade 2 PCas would remain undetectable during a man's life [120] and therefore may be over-treated. In current guidelines deferred treatment may be offered to select patients with intermediate-risk PCa [121], but clear evidence is lacking for appropriate selection criteria [122].

Recent papers have defined clinically significant cancer differently, commonly using ISUP grade 2 and above and even ISUP grade 3 and above, demonstrating the lack of consensus and evolution of its definition [123-126]. Some papers provide more than one definition within a single study [127, 128]. Since there is insufficient data to relate modern histological grading to hard clinical endpoints, it is imperative that authors define and state it in their own studies what they believe csPCa is, including exactly how the disease was diagnosed.

Table 4.3: EAU risk groups for biochemical recurrence of localised and locally-advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL	PSA 10–20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any GS (any ISUP grade)*
and cT1-2a*	or cT2b*	or cT2c*	cT3-4 or cN+**
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.
** **Based on digital rectal examination.***
*** **Based on CT/bone scan.***

4.4 Prognostic relevance of stratification

TNM staging is a schematic representation of anatomic tumour extent and pathological tumour grade is reflective of intrinsic features of tumour aggressiveness. EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, combines clinical information on tumour extent, PSA and pathology (Table 4.3) [104]. A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management [129, 130]. Specifically the National Cancer Center Network (NCCN) Guidelines subdivide intermediate-risk disease into favourable intermediate-risk and unfavourable intermediate-risk, with unfavourable features including ISUP grade 3, and/or ≥ 50% positive biopsy cores and/or at least two intermediate-risk factors [121]. However, as yet, the best stratification and optimal treatment remain controversial.

4.5 Guidelines for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Clinical stage should be based on digital rectal examination (DRE) only; additional staging information based on imaging should be reported separately.	Strong
Use the International Society of Urological Pathology (ISUP) 2019 system for grading of PCa.	Strong
Use the EAU risk group stratification for prognostic subgrouping of patients.	Strong

5. DIAGNOSTIC EVALUATION

5.1 Screening and individual early detection

5.1.1 Screening

Population or mass screening is defined as the 'systematic examination of asymptomatic men to identify individuals at risk for a specific disease' and is usually initiated by health authorities. The co-primary objectives are:
- reduction in mortality due to PCa;
- a maintained QoL as expressed by QoL-adjusted gain in life years (QALYs).

Screening for PCa still is one of the most controversial topics in the urological literature [131]. A Cochrane review of randomised PCa screening trials with PCa mortality as endpoint was published in 2013 [132] and updated in 2018 [133, 134]. The main findings of the updated publication from the results of 5 RCTs, randomising more than 721,718 men, are:
- Screening is associated with an increased diagnosis of PCa (Incidence ratio [IR]: 1.23 95% CI: 1.03–1.48).
- Screening is associated with 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]).
- No PCa-specific survival benefit was observed (IR: 0.96 [0.85–1.08]). This was the main endpoint in all trials.
- No overall survival (OS) benefit was observed (IR: 0.99, 95% CI: 0.98–1.01). None of the trials were designed/powered for this endpoint.

The included studies are different regarding multiple aspects, including: trial size, time periods, age groups, participation/compliance rates, previous screening rates (opportunistic testing in control arm, 'contamination'), one-time vs. repeat screening, and the applied diagnostic pathway. These differences account for discrepancies in results between single studies and the Cochrane review aggregated findings.

The ERSPC (European Randomized Study of Screening for Prostate Cancer) started in the early 90's, included >182K European men, found a significant reduction in PCa mortality due to screening. ERSPC applied a mainly PSA-based screening protocol (cut-off 3.0–4.0 ng/mL followed by systematic sextant prostate biopsy, every 2–4 years in men aged 50–74). The contamination rate was relatively low when compared to other large studies such as the PLCO (Prostate Lung Colorectal & Ovarian) screening trial [135]. A limitation is the heterogenity in patient groups and the applied screening protocols. Since 2013, data have been updated with 16 years of follow-up [135]. With extended follow-up, the mortality reduction (21% and 29% after non-compliance adjustment) remains unchanged. However, the number needed to screen (NNS) and to treat is decreasing and is now below the NNS observed in breast cancer trials [135, 136] (Table 5.1).

Table 5.1: Follow-up data from the ERSPC study [135]

Years of follow-up	Number needed to screen	Number needed to treat
9	1,410	48
11	979	35
13	781	27
16	570	18

In the Göteborg screening trial, with 18 years 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 it was 0.47 (95% CI: 0.29–0.78) [137]. The number needed to invite was 231; the number needed to diagnose 10.

A comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction in the systematic screening group compared to a higher over-diagnosis with only a marginal survival benefit, at best, in the opportunistic screening regimen [138].

The benefit of screening in reducing PCa-specific mortality (PCSM) and the even more favourable impact on metastases rates, is counter-balanced by the side effects of screening such as increased diagnosis rates, which has led to over-treatment of mainly low-risk PCa, and subsequent treatment-related effects [139]. Regarding QoL, the beneficial effects of screening and the side effects seem to balance out, resulting in limited overall impact on the invited population [139-141].

National USA recommendations against PSA-based screening resulted in a reduction in the use of PSA for early detection and was associated with higher rates of advanced disease [11, 112, 142-147]. Initial widespread aggressive screening in USA was associated with a decrease in PCa mortality, which has decreased for two decades since the introduction of PSA testing [148-150]. The current USA national recommendation for men < 70 years of age is that the decision to be screened should be an individual one [151-153].

Recognition of the harms of over-diagnosis and over-treatment had led to a redesign in the pathway for early detection of PCa including identification of specific risk groups, individualised re-testing interval, improved indication for biopsy using risk calculators and/or MRI, targeted biopsies, and the application of AS for low-risk disease.

The inclusion of MRI may improve a screening protocol, as it reduces the number of men that undergo biopsies while detecting more high-grade and less low-grade PCa [154-156]. The Stockholm-3 (STHLM3) screening trial randomised men with a PSA > 3 ng/mL between standard biopsies (10–12 cores) or MRI and standard plus targeted biopsies in the presence of a suspicious MRI. The percentage of men that underwent prostate biopsies in the standard group was double that of the MRI group. In this non-inferiority trial, the intention-to-treat (ITT) analysis found 18% and 21% clinically significant disease (ISUP Grade group > 1) and 12% and 4% insignificant disease in the standard and the MRI group, respectively [154]. The IP1-PROSTAGRAM study (PSA > 3 ng/mL; MRI Prostate Imaging – Reporting and Data System [PI-RADS] > 2), showed highest detection of csPCa for MRI compared to transrectal ultrasound-guided prostate (TRUS) biopsy in a population screening setting [155].

The Identification of Men With a Genetic Predisposition to ProstAte Cancer (IMPACT) study, evaluates targeted PCa screening using PSA in men aged 40–69 years with germline *BRCA1/2* mutations (annually, biopsy recommended if PSA > 3.0 ng/mL). After 3 years of screening, *BRCA2* mutation carriers were associated with a higher incidence of PCa, a younger age of diagnosis, and more clinically significant tumours compared with non-carriers [26, 157]. The influence of *BRCA1* mutations on PCa remained unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* non-carriers. The mismatch repair cohort of IMPACT in men with *MSH2* and *MSH6* pathogenic variants found a higher incidence of significant PCa vs. non-carriers [158].

5.1.2 *Individual early detection*
Early detection may be initiated on an individual level in men with risk factors (age > 50; men from 45 years of age and a family history of PCa; men of African descent from 45 years of age; men carrying *BRCA2* mutations from 40 years of age). Decreased disease-specific mortality on one side, but increased incidence with the risk of over-treatment on the other side, should be discussed with men.

5.1.2.1 *Risk assessment, co-morbidity and life-expectancy*
Data from the Goteborg arm of the ERSPC trial suggest that the age at which early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a 15-year life expectancy are unlikely to benefit, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy, co-morbidity is at least as important as age. A detailed review can be found in Section 5.4 'Estimating life expectancy and health status' and in the SIOG Guidelines [159].

5.1.2.2 *Initial risk assessment by PSA and DRE*
Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [160]. The use of DRE alone in the primary care setting had a sensitivity and specificity below 60%, possibly due to inexperience, and can therefore not be recommended to exclude PCa [161]. PSA measurement and DRE need to be repeated [162], but the optimal intervals for PSA testing and DRE follow-up are unknown as they varied between several prospective screening trials. A risk-adapted strategy might be a consideration, based on the initial PSA level. Men with a baseline PSA < 1 ng/mL at 40 years and < 2 ng/mL at 60 years are at decreased risk of PCa metastasis or death from PCa several decades later [50, 163]. The retesting interval can therefore be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk with an initial PSA < 1 ng/mL at 40 years and a PSA < 2 ng/mL at 60 years of age and a negative family history [164]. An analysis of ERSPC data supports a recommendation for an 8-year screening interval in men with an initial PSA concentration < 1 ng/mL; fewer than 1% of men with an initial PSA concentration < 1 ng/mL were found to have a concentration above the biopsy threshold of 3 ng/mL at 4-year follow-up; the cancer detection rate by 8 years was close to 1% [165]. The long-term survival and QoL benefits of extended PSA re-testing (every 8 years) remain to be proven at a population level.

5.1.2.3 *Risk assessment to determine the need for biopsy*
Multiple diagnostic tools are now available to determine the need for a biopsy to establish the diagnosis of a PCa.

Risk calculators, combining clinical data (age, DRE findings, PSA level, prostate volume, etc.) may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. The risk calculator selected should have been calibrated to the target population; lack of calibration might represent a real limiting factor for its use [166]. Several tools developed from cohort studies are available including (among others):
- the ERSPC cohort: http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators; This calculator has been updated by incorporating the 2014 ISUP Pathology Gleason Grading and Cribriform growth [167];
- the PCPT cohort: PCPTRC 2.0 http://myprostatecancerrisk.com/.

Prostate MRI stratifies patients with an indication for biopsy on a 1- to 5- risk scale of having csPCa. Prostate MRI and related MRI-directed biopsies have shown to be at least as diagnostically effective as systematic biopsies alone in diagnosing significant cancers [168] (see Section 5.2.4.2.4).

Moreover, in a prospective, multi-centre, non-randomised opportunistic early detection setting (PSA > 3 ng/mL), the MRI-directed biopsy decision strategy avoided more men biopsied in comparison to a diagnostic pathway using a risk calculator and then systematic biopsy (559/1015, 55% vs 403/950, 42%; difference -13%, 95%

CI: -17% to -8.3%; p < 0.01); it also detected less ISUP grade 1 cancers (84/1015, 8.3% vs. 121/950, 13%; difference 4.5%, 95% CI: 1.8–7.2%; p < 0.01) [169].

PSA-density (PSA-D) is the strongest predictor in risk calculators. Combinations of PSA-D and MRI have been explored [170-175], showing guidance in biopsy-decisions whilst safely avoiding redundant biopsy testing (see Section 5.2.4.2.6.3).

Urine and serum biomarkers as well as tissue-based biomarkers have been proposed for improving detection and risk stratification of PCa patients, potentially avoiding unnecessary biopsies. However, further studies are necessary to validate their efficacy [176]. At present there is too limited data to implement these markers into routine screening protocols (see Section 5.2.3).

5.1.3 *Genetic testing for inherited prostate cancer*
Increasing evidence supports the implementation of genetic counselling and germline testing in early detection and PCa management [177]. Several commercial screening panels are now available to assess main PCa risk genes [178]. However, it remains unclear when germline testing should be considered and how this may impact localised and metastatic disease management. Germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population [179]. It is important to understand the difference between somatic testing, which is performed on the tumour, and germline testing, which is performed on blood or saliva and identifies inherited mutations. Genetic counselling is required prior to and after undergoing germline testing.

Germline mutations can drive the development of aggressive PCa. Therefore, the consensus is the following men, with a personal or family history of PCa or other cancer types arising from DNA repair gene mutations should be considered for germline testing:
- Men with metastatic PCa;
- Men with high-risk PCa and a family member diagnosed with PCa at age < 60 years;
- Men with multiple family members diagnosed with csPCa at age < 60 years or a family member who died from PCa cancer;
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

Further research in this field (including not so well-known germline mutations) is needed to develop screening, early detection and treatment paradigms for mutation carriers and family members.

5.1.4 *Guidelines for germline testing**

Recommendations	Strength rating
Consider germline testing in men with metastatic PCa.	Weak
Consider germline testing in men with high-risk PCa who have a family member diagnosed with PCa at age < 60 years.	Weak
Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.	Weak
Consider germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Weak

Genetic counselling is required prior to germline testing.

5.1.5 *Guidelines for screening and individual 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 a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *BRCA2* mutations from 40 years of age.	Strong

Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up up to 8 years in those not at risk.	Weak
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak
In asymptomatic men with a PSA level between 3–10 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • risk-calculator, provided it is correctly calibrated to the population prevalence; • magnetic resonance imaging of the prostate;	Strong
• an additional serum, urine biomarker test.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

5.2 Clinical diagnosis

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores.

5.2.1 Digital rectal examination

In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [180]. A suspect DRE in patients with a PSA level ≤ 2 ng/mL has a positive predictive value (PPV) of 5–30% [180]. In the ERSPC trial, an abnormal DRE in conjunction with an elevated PSA more than doubled the risk of a positive biopsy (48.6% vs. 22.4%) [181]]. An abnormal DRE is associated with an increased risk of a higher ISUP grade, predicts csPCa in men under AS [182] and is an indication for MRI and biopsy [181, 183]. cT staging is dependent on DRE and a strong predictor of advanced PCa (OR: 11.12 for cT3 and OR: 5.28 for cT4) [184].

5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [185]. Prostate-specific antigen is organ- but not cancer specific; therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. However, PSA keeps its diagnostic value for cancer detection even in symptomatic patients [186].

PSA value is also negatively impacted by hormonal treatments, even those given for benign conditions such as finasteride or dutasteride [187]. In such cases, interpretation of PSA level should be adapted as these treatments can frequently lower the PSA level by half.

There are no agreed standards for defining PSA thresholds [188]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [189]. Table 5.2 demonstrates the occurrence of ISUP ≥ grade 2 PCa in systematic biopsies at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but csPCa. The use of nomograms and biomarkers may help in predicting indolent PCa [154, 190, 191]. In case of an elevated PSA (up to 10 ng/mL), a repeated test should be considered to confirm the increase before going to the next step.

5.2.2.1 Repeat PSA testing

A repeat PSA test before prostate biopsies in men with an initial PSA 3–10 ng/mL reduced the indication for biopsies in 16.8% of men while missing 5.4% ISUP grade > 1 in the STHLM3 trial [192]. Similarly, in the Prostate Testing for Cancer and Treatment (ProtecT) trial men with a more than 20% lower repeat-PSA analysis within 7 weeks had a lower risk of PCa (OR: 0.43, 95% CI: 0.35–0.52) as well as a lower risk of ISUP grade ≥ 2 (OR: 0.29, 95% CI: 0.19–0.44) [193]. A study with a PSA interval of 4 weeks showed similar findings of a reduced risk of PCa and ISUP grade > 1 [194]. These observations indicate that an early repeat-PSA prior to the decision of prostate biopsies has prognostic information.

Table 5.2: Risk of PCa identified by systemic PCa biopsy in relation to low PSA values [173]

PSA level (ng/mL)	Risk of PCa (%)	Risk of ISUP grade ≥ 2 PCa (%)
0.0–0.5	6.6	0.8
0.6–1.0	10.1	1.0
1.1–2.0	17.0	2.0
2.1–3.0	23.9	4.6
3.1–4.0	26.9	6.7

5.2.2.2 PSA density

Prostate-specific antigen density is the level of serum PSA divided by the prostate volume. The higher the PSA-D, the more likely it is that the PCa is clinically significant; in particular in smaller prostates when a PSA-D cut-off of 0.15 ng/mL/cc was applied [195] (see Section 5.2.4.2.6.3). Several studies found a PSA-D over 0.1–0.15 ng/mL/cc predictive of cancer [196, 197]. Patients with a PSA-D below 0.09 ng/mL/cc were found unlikely (4%) to be diagnosed with csPCa [198]. A systematic review showed heterogeneity among studies using PSA-D to select men with PI-RADS 3 category on MRI reading for biopsies but suggest a cut-off of 0.15 ng/mL/cc [196]. Others found its added value to biparametric (bp) MRI-guided biopsies unclear with an area under the curve (AUC) of 0.87–0.95 for the direction of csPCa based on bpMRI and 0.91–0.95 for the combined test of bpMRI and PSA-D [199].

5.2.2.3 Free/total PSA ratio

Free/total (f/t) PSA must be used cautiously because it may be adversely affected by several pre-analytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [200]. A systematic review including 14 studies found a pooled sensitivity of 70% in men with a PSA of 4–10 ng/mL [201]. Free/total PSA is of no clinical use if the total serum PSA is > 10 ng/mL or during follow-up of known PCa. The clinical value of f/t PSA is limited in light of the new diagnostic pathways incorporating MRI.

5.2.3 Other blood and urine biomarkers
5.2.3.1 Blood based biomarkers: PHI/4K score/IsoPSA

Several assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the U.S. Food and Drug Administration (FDA) approved Prostate Health Index (PHI) test (combining free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2] in addition to age, DRE and prior biopsy status). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multi-centre studies demonstrated that both the PHI and 4K score test out-performed f/t PSA PCa detection, with an improved prediction of csPCa in men with a PSA between 2–10 ng/mL [202-205]. In a head-to-head comparison both tests performed equally [206].

In contrast to the 4K score and PHI, which focus on the concentration of PSA isoforms, IsoPSA utilises a novel technology which focuses on the structure of PSA [207]. Using an aqueous two-phase solution, it partitions the isoforms of PSA and assesses for structural changes in PSA. In a multi-centre prospective validation in 271 men the assay AUC was 0.784 for high-grade vs. low-grade cancer/benign histology, which was superior to the AUCs of total PSA and percent free PSA [208]. In men with a negative mpMRI, PSA-D, 4K score and family history predicted the risk of csPCa on biopsy and using a nomogram reduced the number of negative biopsies and indolent cancers by 47% and 15%, respectively, while missing 10% of csPCas [209].

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 ≥ 2, and was shown to reduce the percent of clinically insignificant cancers when used in combination with MRI in a PSA screening population [268].

The Proclarix® test is a blood-based test that estimates the likelihood of csPCa according to measurement results for thrombospondin-1, cathepsin D, total PSA, percentage free PSA and patient age. This test has been correlated with the detection of significant PCa, notably in case of equivocal MRI (PI-RADS 3 lesions) [210].

5.2.3.2 Urine biomarkers: PCA3/SelectMDX/Mi Prostate score (MiPS)/ExoDX

Prostate cancer gene 3 (*PCA3*) is an overexpressed long non-coding RNA (lncRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. However, the clinical utility of the commercially available Progensa urine test for *PCA3* for biopsy decision-making remains uncertain. However, combining MRI findings with the *PCA3* score may improve risk stratification [211].

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of *HOXC6* and *DLX1* mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer [212]. A multi-centre trial evaluated SelectMDX in men with a MRI PI-RADS score < 4 or PI-RADS score < 3, and the percentage of missed csPCas was 6.5% and 3.2%, respectively, whereas 45.8% and 40% of biopsies were avoided [213]. Hendriks *et al.*, found more biopsies were avoided and more high-grade PCas detected in a MRI-based biopsy strategy compared to a SelectMDX strategy. When both tests were combined, more Gleason grade > 1 lesions were found, but the number of negative or low-grade cancer biopsies more than doubled [191]. Combining SelectMDX and MRI in men with a PSA between

3–10 ng/mL had a negative predictive value (NPV) of 93% [214]. The clinically added value of SelectMDX in the era of upfront MRI and targeted biopsies remains unclear [215].

TMPRSS2-ERG fusion, a fusion of the trans-membrane protease serine 2 (*TMPRSS2*) and the *ERG* gene can be detected in 50% of PCas [216]. When detection of *TMPRSS2-ERG* in urine was added to *PCA3* expression and serum PSA (Mi(chigan)Prostate Score [MiPS]), cancer prediction improved [217]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [218, 219]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care (SOC). However, currently, both the MiPS-score and ExoDx assay are considered investigational.

In the screening population of the ERSPC study the use of both *PCA3* and 4K panel when added to the risk calculator led to an improvement in AUC of less than 0.03 [220]. Based on the available evidence, some biomarkers could help in discriminating between aggressive and non-aggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians [221]. However, upfront MRI is also likely to affect the utility of above-mentioned biomarkers (see Section 5.2.3.2).

5.2.3.3   Biomarkers to select men for a repeat biopsy
In men with an elevated risk of PCa with a prior negative biopsy, the role of PHI, Progensa *PCA3*, and SelectMDX in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective [222]. The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. In case PCa is missed at biopsy, demonstration of epigenetic changes in the benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes (Methylated *APC*, *RASSF1* and *GSTP1*) in benign prostatic tissue. A multicentre study found a NPV of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men [223]. Given the limited available data and the fact that the role of MRI in tumour detection was not accounted for, no recommendation can be made regarding the routine application of ConfirmMDX, in particular in the light of current use of MRI before biopsy.

*5.2.4   **Imaging***
5.2.4.1   Transrectal ultrasound and ultrasound-based techniques
Standard TRUS is not reliable at detecting PCa [224] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [124]. New sonographic modalities such as micro-Doppler, sonoelastography or contrast-enhanced US provided promising preliminary findings, either alone, or combined into the so-called 'multiparametric US' [225, 226]. In the multiparametric US vs. multiparametric MRI to diagnose PCa (CADMUS) trial, 306 patients underwent both multiparametric MRI and multiparametric US composed of B-mode, Colour Doppler, real-time elastography, and contrast-enhanced US. Patients with at least one positive test underwent targeted biopsy. Multiparametric US detected 4.3% fewer csPCa while submitting 11.1% more patients to biopsy than MRI [227].

High-resolution micro-US operates at 29 MHz instead of 8-12 MHz with conventional TRUS. As high frequency ultrasonic waves are rapidly attenuated, micro-US is intrinsically limited for the exploration of the anterior part of large prostates. Several studies combined into a meta-analysis [228] obtained similar csPCa detection rates for micro-US-targeted and MRI-targeted biopsy. However, this conclusion is limited by the retrospective non-randomized design of the included studies, and by the fact that the micro-US operator was not blinded to MRI results in most of them. One prospective trial included 203 patients referred for biopsy in three centers [229]. The biopsy operator was blinded to the MRI report until after the micro-US targets had been assessed. After unblinding, micro-US and mpMRI targets were sampled, followed by systematic biopsy. Micro-US and mpMRI detected respectively 58 (73%) and 60 (76%) of the 79 csPCas, while systematic sampling detected 45/79 cases (57%). MRI-targeted biopsy detected 7 csPCas missed by micro-US; of these three were anterior lesions. Micro-US-guided biopsy detected 5 csPCas missed by MRI; of these, three were at the apex. Although these findings require further confirmation, they suggest that micro-US and MRI could complement each other. Micro-US could also be an interesting alternative to MRI/US fusion since most MRI lesions seem visible on micro-US [230]. Of note, evaluation of micro-US inter-operator variability is currently lacking.

5.2.4.2   Magnetic resonance imaging
5.2.4.2.1   MRI diagnostic performance in detecting PCa
Correlation with RP specimens shows that MRI has good sensitivity for the detection and localisation of ISUP grade ≥ 2 cancers, especially when their diameter is larger than 10 mm [231-233]. This good sensitivity was

further confirmed in patients who underwent template biopsies. In a Cochrane meta-analysis which compared MRI to template biopsies (≥ 20 cores) in biopsy-naive and repeat-biopsy settings, MRI had a pooled sensitivity of 0.91 (95% CI: 0.83–0.95) and a pooled specificity of 0.37 (95% CI: 0.29–0.46) for ISUP grade > 2 cancers [168]. For ISUP grade ≥ 3 cancers, MRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87–0.99) and 0.35 (95% CI: 0.26–0.46), respectively. MRI is less sensitive in identifying ISUP grade 1 PCa. It identifies less than 30% of ISUP grade 1 cancers smaller than 0.5 cc identified on RP specimens by histopathology analysis [231].

In a meta-analysis of 17 studies involving men with suspected or biopsy-proven PCa, the average PPVs for ISUP grade ≥ 2 cancers of lesions with a PI-RADSv2.1 score of 3, 4 and 5 were 16% (7–27%), 59% (39–78%), and 85% (73–94%), respectively, but with significant heterogeneity among studies [234].

5.2.4.2.2   Targetted biopsy improves the detection of ISUP grade ≥ 2 cancer as compared to systemic biopsy.
In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy (median number of cores: 8–15) and MRI-targeted biopsies (median number of cores: 2–7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02–1.23) for ISUP grade ≥ 2 cancers and 1.20 (95% CI: 1.06–1.36) for ISUP grade ≥ 3 cancers, and therefore in favour of MRI-targeted biopsy [168].

Another meta-analysis of studies limited to biopsy-naive patients with a positive MRI found that MRI-targeted biopsy detected significantly more ISUP grade ≥ 2 cancers than systematic biopsy (risk difference, -0.11 [95% CI: -0.2 to 0.0]; p = 0.05), in prospective cohort studies (risk difference, -0.18 [95% CI: -0.24 to -0.11]; p < 0.00001), and in retrospective cohort studies (risk difference, -0.07 [95% CI: -0.12 to -0.02]; p = 0.004) [235]. This data was confirmed in prospective multi-centre trials evaluated MRI-targeted biopsy in biopsy-naive patients [123-125].

The Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies (FUTURE) randomised trial compared three techniques of MRI-targeted biopsy in the repeat-biopsy setting [236]. In the subgroup of 152 patients who underwent both MRI-targeted biopsy and systematic biopsy, MRI-targeted biopsy detected significantly more ISUP grade ≥ 2 cancers than systematic biopsy (34% vs. 16%; p < 0.001, detection ratio of 2.1), which is a finding consistent with the Cochrane agreement analysis (detection ratio: 1.44). An ISUP grade ≥ 2 cancer would have been missed in only 1.3% (2/152) of patients, had systematic biopsy been omitted [237]. These findings support that MRI-targeted biopsy significantly out-performs systematic biopsy for the detection of ISUP grade ≥ 2 in the repeat-biopsy setting. In biopsy-naive patients, the difference appears to be less marked but remains in favour of MRI-targeted biopsy.

5.2.4.2.3   Reduced detection of ISUP grade 1 cancers by MRI-targeted biopsy without systematic biopsy
In pooled data of 25 head-to-head comparisons between systematic biopsy and MRI-targeted biopsy, the detection ratio for ISUP grade 1 cancers was 0.62 (95% CI: 0.44–0.88) in patients with prior negative biopsy and 0.63 (95% CI: 0.54–0.74) in biopsy-naive patients [168]. In the PRECISION and 4M trials, the detection rate of ISUP grade 1 patients was significantly lower in the MRI-targeted biopsy group as compared to systematic biopsy (9% vs. 22%, p < 0.001, detection ratio of 0.41 for PRECISION; 14% vs. 25%, p < 0.001, detection ratio of 0.56 for 4M) [123, 125]. In the MRI-FIRST trial, MRI-targeted biopsy detected significantly fewer patients with clinically insignificant PCa (defined as ISUP grade 1 and maximum cancer core length < 6 mm) than systematic biopsy (5.6% vs. 19.5%, p < 0.0001, detection ratio of 0.29) [124]. Consequently, MRI-targeted biopsy without systematic biopsy significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy. This seems true even when systematic biopsies are indicated after after risk stratification with a US-based risk calculator (i.e. Rotterdam Prostate Cancer Risk Calculator) [169].

5.2.4.2.4   Added value of systematic biopsy and targeted biopsy
MRI-targeted biopsies can be used in two different diagnostic pathways: 1) the 'combined pathway', in which patients with a positive MRI undergo combined systematic and targeted biopsy, and patients with a negative MRI undergo systematic biopsy; or 2) the 'MRI pathway', in which patients with a positive MRI undergo only MRI-targeted biopsy, and patients with a negative MRI who are not biopsied at all. The first diagnostic pathway focuses on maximizing the detection of significant cancers, also termed as the 'rule-in' ability. However, this pathway has the disadvantage of leading to a greater detection of insignificant cancers and of referring all patients with a clinical suspicion of cancer to biopsy. The second diagnostic pathway focuses on the 'rule-out' ability, and minimizes these disadvantages at the cost of missing a small proportion of significant cancers. Risk profiling is necessary to balance the 'rule-in' or 'rule-out' ability on an individual basis, incorporating patient and physician preference (i.e. biopsy averse/cancer averse), choosing for either adding or avoiding systematic biopsies. Table 5.3 shows the added value of systematic and MRI-targeted biopsy for ISUP grade ≥ 2 and ≥ 3 cancer detection.

Table 5.3: Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 Cancer Detection

ISUP grade		ISUP ≥ 2			ISUP ≥ 3		
		Cochrane meta-analysis* [168]	MRI-FIRST trial* [124]	4M trial [125]	Cochrane meta-analysis* [168]	MRI-FIRST trial* [124]	4M trial [125]
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)	-	-

Intervals in parenthesis are 95% CI.
The 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.
ISUP = International Society of Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

In Table 5.3, the absolute added values refer to the percentage of patients in the entire cohort; if the cancer prevalence is taken into account, the 'relative' percentage of additional detected PCa can be computed. Adding MRI-targeted biopsy to systematic biopsy in biopsy-naive patients increases the number of detected ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-targeted biopsy increases detection of ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naive patients would miss approximately 16% of all detected ISUP grade ≥ 2 PCa and 18% of all ISUP grade ≥ 3 PCa. In the repeat-biopsy setting, it would miss approximately 10% of ISUP grade ≥ 2 PCa and 9% of ISUP grade ≥ 3 PCa.

In the GÖTEBORG-2 prospective trial, 37,887 men between 50 and 60 years of age were invited to undergo regular PSA screening [238]. Participants with a PSA level above 3 ng/mL were randomly allocated to MRI and combined systematic- and targeted biopsy (reference group) or to MRI and targeted biopsy only in case of PI-RADS ≥ 3 lesions (experimental group). In the experimental group, the detection rate of ISUP 1 cancers was reduced by half (detection ratio: 0.46, 95% CI: 0.33–0.64, p < 0.001); that of ISUP ≥ 2 cancers was lower but not significantly (detection ratio: 0.81, 95% CI: 0.60 to 1.1). In the reference group, 10 of the 68 men with ISUP ≥ 2 cancer were diagnosed by systematic biopsy only. All these 10 patients were of intermediate risk. Thus, in a screening setting, the 'MRI pathway' may reduce the risk of over-diagnosis by half, at the cost of delaying detection of intermediate-risk tumours in a small percentage of patients. However, these good results were obtained at a single academic centre with double reading of the MRI, which may limit their generalisability in less experienced centers (see Sections 5.2.4.2.6.1 and 5.2.4.2.6.2).

5.2.4.2.5   Avoiding biopsies in the 'MR pathway'
The diagnostic yield and number of biopsy procedures potentially avoided by the 'MR pathway' depends on the Likert/PI-RADS threshold used to define a positive MRI. In pooled studies on biopsy-naive patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of ≥ 3 would have avoided 30% (95% CI: 23–38) of all biopsy procedures while missing 11% (95% CI: 6–18) of all detected ISUP grade ≥ 2 cancers (relative percentage) [168]. Increasing the threshold to ≥ 4 would have avoided 59% (95% CI: 43–78) of all biopsy procedures while missing 28% (95% CI: 14–48) of all detected ISUP grade ≥ 2 cancers [168]. Of note, the percentages of negative MRI (Likert/PI-RADS score ≤ 2) in the MRI-FIRST, PRECISION and 4M trials were 21.1%, 28.9% and 49%, with related ISUP grade ≥ 2 cancer prevalences of 27.7% (23.7–32.6), 37.5% (31.4–43.8), and 30% (ND) respectively [123-125].

5.2.4.2.6   Practical considerations
5.2.4.2.6.1 Prostate MRI reproducibility
Despite the use of the PI-RADSv2 scoring system [239], MRI inter-reader reproducibility remains moderate at best which currently limits its broad use by non-dedicated radiologists [240]. However, significant improvement in the accuracy of MRI and MRI-targeted biopsy can be observed over time, both in academic and community hospitals, especially after implementation of PI-RADSv2 scoring and multidisciplinary meetings using pathological correlation and feedback [241-244]. An updated version of the PI-RADS score (PI-RADSv2.1) has been published to improve reader reproducibility, showing improved diagnostic performance [234] but it has not yet been fully evaluated [245]. It is still too early to predict whether quantitative approaches and computer-aided diagnostic systems will improve the characterisation of lesions seen at MRI [246]. Standardisation of MRI interpretation and quality check of acquisition and of MRI-targeted biopsy technique is required to optimise the 'MRI pathway' in large-volume and small-volume (non-expert) centres [247-249].

5.2.4.2.6.2 Targeted biopsy accuracy and reproducibility
Clinically significant PCa not detected by the 'MRI pathway' can be missed because of MRI failure (invisible cancer or reader's misinterpretation) or because of targeting failure (target missed or under sampled by MRI-targeted biopsy).

The accuracy of MRI-targeted biopsy is substantially impacted by the experience of the biopsy operator [240], and two retrospective studies on patients with a unilateral lesion found that the added value of systematic biopsy was higher in the MRI-positive lobe than in the MRI-negative lobe [250, 251]. This suggests that a substantial part of the added value of systematic biopsies is due to mistargeting issues (i.e., the lesion has been correctly identified by MRI but missed by MRI-targeted biopsy and detected by systematic sampling).

Increasing the number of cores taken per target may partially compensate for guiding imprecision, and a minimum of 3 to 5 cores is required for proper sampling of the lesions [252-254]. Consequently, some authors have suggested MRI-directed biopsy approaches using targeted biopsies combined with peri-lesional/ regional systematic biopsies, rather than standard sextant-based systematic biopsies. This could decrease the number of cores taken (by avoiding systematic biopsies in MRI-negative lobes) and improve the detection of csPCa (by improving the lesional and peri-lesional sampling). A recent meta-analysis of 8 retrospective studies showed a nonsignificant difference in detection of ISUP grade ≥ 2 PCa in the MRI-directed targeted- and regional biopsy approach, compared to the recommended practice of MRI-directed targeted- and systematic biopsy approach (RR: 0.95, 95% CI: 0.90–1.01; p = 0.09). However MRI-directed targeted- and regional biopsy approach detected significantly more csPCa than MRI-targeted biopsy alone (RR: 1.18, 95% CI: 1.10–1.25; p < 0.001) [255]. However, due to the heterogeneity of the retrospective studies, prospective clinical studies are needed before the role of this biopsy approach can be assessed. The impact of per-lesional sampling on non-significant (ISUP 1) cancer has not been fully assessed either.

5.2.4.2.6.3 Risk-stratification
Using risk-stratification to avoid biopsy procedures
Prostate-specific antigen density may help refine the risk of csPCa in patients undergoing MRI as PSA-D and the PI-RADS score are significant independent predictors of csPCa at biopsy [256, 257]. In a meta-analysis of 8 studies, pooled MRI NPV for ISUP grade ≥ 2 cancer was 84.4% (95% CI: 81.3–87.2) in the whole cohort, 82.7% (95% CI: 80.5–84.7) in biopsy-naive men and 88.2% (95% CI: 85–91.1) in men with prior negative biopsies. In the subgroup of patients with PSA-D < 0.15 ng/mL, NPV increased to respectively 90.4% (95% CI: 86.8–93.4), 88.7% (95% CI: 83.1–93.3) and 94.1% (95% CI: 90.9–96.6) [258]. In contrast, the risk of csPCa is as high as 27–40% in patients with negative MRI and PSA-D > 0.15–0.20 ng/mL/cc [125, 172, 257, 259-261].

Based on a meta-analysis of > 3,000 biopsy-naive men, a risk-adapted data table of csPCa was developed, linking 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 5.4) [170]. For example, the risk of having ISUP grade ≥ 2 cancer in biopsy-naive men with a PI-RADS 1–2 assessment score and PSA-D below 0.10 is 3–4%, in a below-average-risk population of < 5% [170]. This risk-adapted matrix table based on PSA-D and on MRI risk assessments may guide the decision to perform a biopsy.

These data are applicable for a mean ISUP grade ≥ 2 cancer prevalence of 35% (range 28–46%) in biopsy-naive men, and would need to be adjusted to other populations' prevalence. Awaiting validation of MRI-based multivariate risk-prediction tools, corroboration linking MRI findings to PSA-D values for biopsy decisions is beginning to emerge which may promote their routine use in clinical practice [20, 262]. It must be emphasised, however, that the use of PSA-D remains currently limited due to the lack of standardisation of prostate volume measurement (assessed by DRE or by imaging [TRUS or MRI using various techniques such as ellipsoid formula or planimetry]). The impact of this lack of standardisation on the volume estimation remains underevaluated.

Table 5.4: 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 [170]*

Detection of clinically significant prostate cancer (ISUP grade 2 and higher)					
		PSA-density risk groups			
PI-RADS risk categories	Prevalence ISUP ≥ 2 PCa	Low < 0.10	Intermediate-low 0.10–015	Intermediate-high 0.15–0.20	High ≥ 0.20
		31% (678/2199)	28% (612/2199)	16% (360/2199)	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

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

\# Thompson IM *et al.* N Engl J Med. 2004 May 27;350(22):2239-46. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng/mL.
\#\# 2019 EAU guidelines: csPCa 9% (95% CI: 6–14%).

Table adapted from: Schoots, IG and Padhani AR. BJU Int 2021 127(2):175. 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, with permission from Wiley.

Several groups have developed comprehensive risk calculators which combine MRI findings with simple clinical data as a tool to predict subsequent biopsy results [263]. At external validation, they tended to outperform risk calculators not incorporating MRI findings (ERSPC and Prostate Cancer Prevention Trial) with good discriminative power (as measured by the AUC). However, they also tended to be miscalibrated with under- or over-prediction of the risk of ISUP grade ≥ 2 cancer [264, 265]. In one study that externally assessed four risk calculators combining MRI findings and clinical data, only two demonstrated a distinct net benefit when a risk of false-negative prediction of 15% was accepted. The others were harmful for this risk level, as compared to the 'biopsy all' strategy [264]. This illustrates the prevalence-dependence of risk models. Recalibrations taking into account the local prevalence are possible, but this approach is difficult in routine clinical practice as the local prevalence is difficult to estimate and may change over time.

Using risk-stratification to avoid MRI scans and biopsy procedures
A retrospective analysis including 200 men from a prospective database of patients who underwent MRI and combined systematic and targeted biopsy showed that upfront use of the Rotterdam Prostate Cancer Risk Calculator would have avoided MRI and biopsy in 73 men (37%). Of these 73 men, 10 had ISUP grade 1 cancer and 4 had ISUP grade ≥ 2 cancer [266]. A prospective multi-centre study evaluated several diagnostic pathways in 545 biopsy-naive men who underwent MRI and systematic and targeted biopsy. Using a PHI

threshold of > 30 to perform MRI and biopsy would have avoided MRI and biopsy in 25% of men at the cost of missing 8% of the ISUP grade ≥ 2 cancers [267]. Another prospective multi-centre trial including 532 men (with or without history of prostate biopsy) showed that using a threshold of ≥ 10% for the Stockholm3 test to perform MRI and biopsy would have avoided MRI and biopsy in 38% of men at the cost of missing 8% of ISUP grade ≥ 2 cancers [268].

5.2.4.2.6.4 Potential cancer grade shift, induced by improved diagnosis by MRI and MRI-targeted biopsy
MRI findings are significant predictors of adverse pathology features on prostatectomy specimens, and of survival-free BCR after RP or RT [105, 269-271]. In addition, tumours visible on MRI are enriched in molecular hallmarks of aggressivity, as compared to invisible lesions [272]. Thus, MRI does identify aggressive tumours.

Nonetheless, as MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer, ISUP grade ≥ 2 cancers detected by MRI-targeted biopsy are, on average, of better prognosis than those detected by the classical diagnostic pathway (Will Rogers phenomenon [107]). This is illustrated in a retrospective series of 1,345 patients treated by RP which showed that, in all risk groups, patients diagnosed by MRI-targeted biopsy had better BCR-free survival than those diagnosed by systematic biopsy only [105]. To mitigate this grade shift, in case of targeted biopsies, the 2019 ISUP consensus conference recommended using an aggregated ISUP grade summarizing the results of all biopsy cores from the same MR lesion, rather than using the result from the core with the highest ISUP grade [110]. When long-term follow-up of patients who underwent MRI-targeted biopsy is available, a revision of the risk-groups definition will become necessary. In the meantime, results of MRI-targeted biopsy must be interpreted in the context of this potential grade shift [273].

5.2.4.3 Guidelines for MRI imaging in biopsy decision

Recommendations for all patients	Strength rating
Do not use magnetic resonance imaging (MRI) as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for MRI acquisition and interpretation and evaluate MRI results in multidisciplinary meetings with pathological feedback.	Strong

Recommendations in biopsy-naïve patients	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e., PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (e.g., PSA density < 0.15 ng/mL), omit biopsy based on shared decision-making with the patient.	Weak

Recommendations in patients with prior negative biopsy	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e., PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared decision-making with the patient.	Strong

5.2.5 Baseline biopsy decision
The need for prostate biopsy is based on PSA level, PSA density, other biomarkers and/or suspicious DRE and/or imaging (see Section 5.2.4). Age, potential co-morbidity and therapeutic consequences should also be considered and discussed beforehand [241]. Risk stratification is a potential tool for reducing unnecessary biopsies [274].

Limited PSA elevation alone should not prompt immediate biopsy. Prostate-specific antigen level should be verified after a few weeks, in the same laboratory using the same assay under standardised conditions (i.e. no ejaculation, manipulations, and urinary tract infections [UTIs]) [275, 276]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [277].

Ultrasound (US)-guided and/or MRI-targeted biopsy is now the SOC. Prostate biopsy is performed by either the recommended transperineal approach or the transrectal one. Cancer detection rates, when performed without prior imaging with MRI, are comparable between the two approaches [246], however, evidence suggests reduced infection risk with the transperineal route (see Section 5.2.8.1.1) [278, 279]. Transurethral resection of the prostate (TURP) should not be used as a tool for cancer detection [280].

5.2.6 **Repeat biopsy decision**

5.2.6.1 *Repeat biopsy after previously negative biopsy*

Men with a previous negative systematic biopsy should be offered a prostate MRI and in case of PI-RADS > 3 findings, a repeat (targeted) biopsy should be done. Other indications for repeat biopsy should be discussed on an individual basis taking into account PSA level and its evolution, DRE, PSA density and pathological findings on the previous biopsy.

In a contemporary series of biopsies the likelihood of finding a csPCa after follow-up biopsy after a diagnosis of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia (PIN) was only 6-8%, not significantly different from follow-up biopsies after a negative biopsy [281, 282].

The added value of other biomarkers remains unclear (see Sections 5.2.3.1 and 5.2.3.2).

5.2.6.2 *Saturation biopsy*

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30–43% and depends on the number of cores sampled during earlier biopsies [283]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention varies substantially from 1.2% to 10% [284-287].

However, given the very low risk of subsequent csPCa after a negative biopsy and/or in case of negative MRI, the clinical utility of saturation biopsy in the repeat biopsy setting remains uncertain in the current MRI-driven diagnostic pathway and such schemes should not be routinely used [288].

5.2.7 **Prostate biopsy procedure**

For systematic biopsies, where no prior imaging is used for targeting, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland regardless of the approach used. A 2006 systematic review showed that 12 is the minimum number of cores for systematic biopsies, with > 12 cores not increasing cancer detection rate significantly [289].

Additional cores should be obtained from suspect areas identified by DRE or on pre-biopsy MRI; multiple cores (3–5) should be taken from each MRI-visible lesion.

Where MRI has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique over another [236, 290-293]. However, regarding approach, the only systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%) [294]. This benefit was especially pronounced for anterior tumours. Multiple cores (3–5) should be taken from each lesion (see Section 5.2.4.2.6.2).

As detailed in Section 5.2.4.2.6.2, the added value of systematic biopsy is partially explained by the fact that they compensate for guiding imprecisions of targeted biopsy. Therefore, biopsy strategies with multiple peri-lesional (regional) targeted cores obtained in addition of MRI-directed targeted cores are being investigated [250, 251, 295-298]. Prospective clinical trials are needed to evaluate whether these strategies can replace the combination of systematic and targeted biopsy currently recommended as the diagnostic work-up in men with positive MRI scans.

5.2.8 **Summary of evidence and guidelines for prostate biopsies**

Summary of evidence	LE
Literature review including multiple biopsy schemes suggests that a minimum 12-core scheme is optimal in the majority of initial and repeat biopsy patients, dependent on prostate size. These biopsy schemes should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [299].	3
Systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%).	2
Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique (cognitive guidance, US/MR fusion software or direct in-bore guidance) over the other.	2

Recommendations	Strength rating
When performing systematic biopsy only, at least 12 cores are recommended.	Strong
Systematic transperineal biopsies are preferred over systematic transrectal biopsies for detection of clinically significant PCa.	Strong
Where magnetic resonance imaging (MRI) has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak

5.2.8.1   Antibiotics prior to biopsy
5.2.8.1.1   Transperineal prostate biopsy
A total of eight randomised studies including 1,596 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (48 events among 789 men) compared to transperineal biopsy (22 events among 807 men) (RR: 95% CI: 2.48 [1.47–4.2]) [300, 301]. In addition, a systematic review including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [302]. Finally, a population-based study from the UK (n = 73,630) showed lower re-admission rates for sepsis in patients who had transperineal vs. transrectal biopsies (1.0% vs. 1.4%, respectively) [303]. The available evidence demonstrates that the transrectal approach should be abandoned in favour of the transperineal approach despite any possible logistical challenges. A systematic review and meta-analysis of eight non-RCTs reported no significant differences between patients receiving or not receiving antibiotic prophylaxis in terms of post-biopsy infection (0,11% vs. 0.31%) and sepsis (0.13% vs. 0,09%), for the transperineal approach [304]. This is in line with another systematic review and meta-analysis of 112 individual patient cohorts which also showed no significant difference in the number of patients experiencing post-transperineal-biopsy infection 1.35% of 29,880 patients receiving antibiotic prophylaxis and 1.22% of 4,772 men not receiving antibiotic prophylaxis (p = 0.8) [305]. In addition, two recently published RCTs have reported comparably low post-biopsy infection rates for transperineal biopsy regardless of whether antibiotic prophylaxis was administered or not [306, 307].

There is a growing body of evidence to suggest that antibiotic prophylaxis may not be required for transperineal biopsy; however the Panel has chosen to wait until a number of ongoing RCTs report their study findings before making a recommendation on this.

5.2.8.1.2   Transrectal prostate biopsy
An updated meta-analysis of eleven RCTs including 2,237 men showed that use of a rectal povidone-iodine preparation before biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications (RR: 95% CI: 0.47 [0.36–0.61]) [301, 308-310]. Single RCTs showed no evidence of benefit for perineal skin disinfection [311], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [312].

A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications (RR: 95% CI: 0.96 [0.64–1.54]) [301].

An updated meta-analysis of 28 RCTs with 4,027 patients found no evidence that use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than no injection (RR: 95% CI: 1.08 [0.79–1.48]) [300, 301, 313]. A meta-analysis of 9 RCTs including 2,230 patients found that extended biopsy templates showed comparable infectious complications to standard templates (RR: 95% CI: 0.80 [0.53–1.22]) [301]. Additional meta-analyses found no difference in infectious complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. non-coaxial), needle size (large vs. small), and number of injections for peri-prostatic nerve block (standard vs. extended) [301].

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control (RR: 95% CI: 0.56 [0.40–0.77]) [314].

Fluoroquinolones have been traditionally used for antibiotic prophylaxis in this setting; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones resulting in the suspension of the indication for peri-operative antibiotic prophylaxis including prostate biopsy [315].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, or augmented prophylaxis (combination of two or more different classes of

antibiotics) is recommended [314]. In countries where use of fluoroquinolones are suspended, cephalosporins or aminoglycosides can be used as individual agents with comparable infectious complications based on meta-analysis of two RCTs [314]. A meta-analysis of three RCTs reported that fosfomycin trometamol was superior to fluoroquinolones (RR: 95% CI: 0.49 [0.27–0.87]) [314], but routine general use should be critically assessed due to the relevant infectious complications reported in non-randomised studies [316]. Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swap/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See figure 5.1 for prostate biopsy workflow to reduce infections complications.

5.2.8.2 Summary of evidence and recommendations for performing prostate biopsy (in line with the EAU Urological Infections Guidelines Panel)

Summary of evidence	LE
A meta-analysis of eight studies including 1,596 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight non-RCTS reported comparable rates of post-biopsy infections in patients undergoing transperineal biopsy irrespective if antibiotic prophylaxis was given or not.	1a
A meta-analysis of eleven RCTs including 2,036 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

Recommendations	Strength rating*
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong
Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g., fosfomycin trometamol**, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong

* Note on strength ratings:
The above strength ratings are explained here due to the major clinical implications of these recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its Strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy as, although quality of data is low, the clinical benefit is high and practical application simple. A 'Strong' rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.
** The indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.

Figure 5.1: Prostate biopsy workflow to reduce infectious complications*
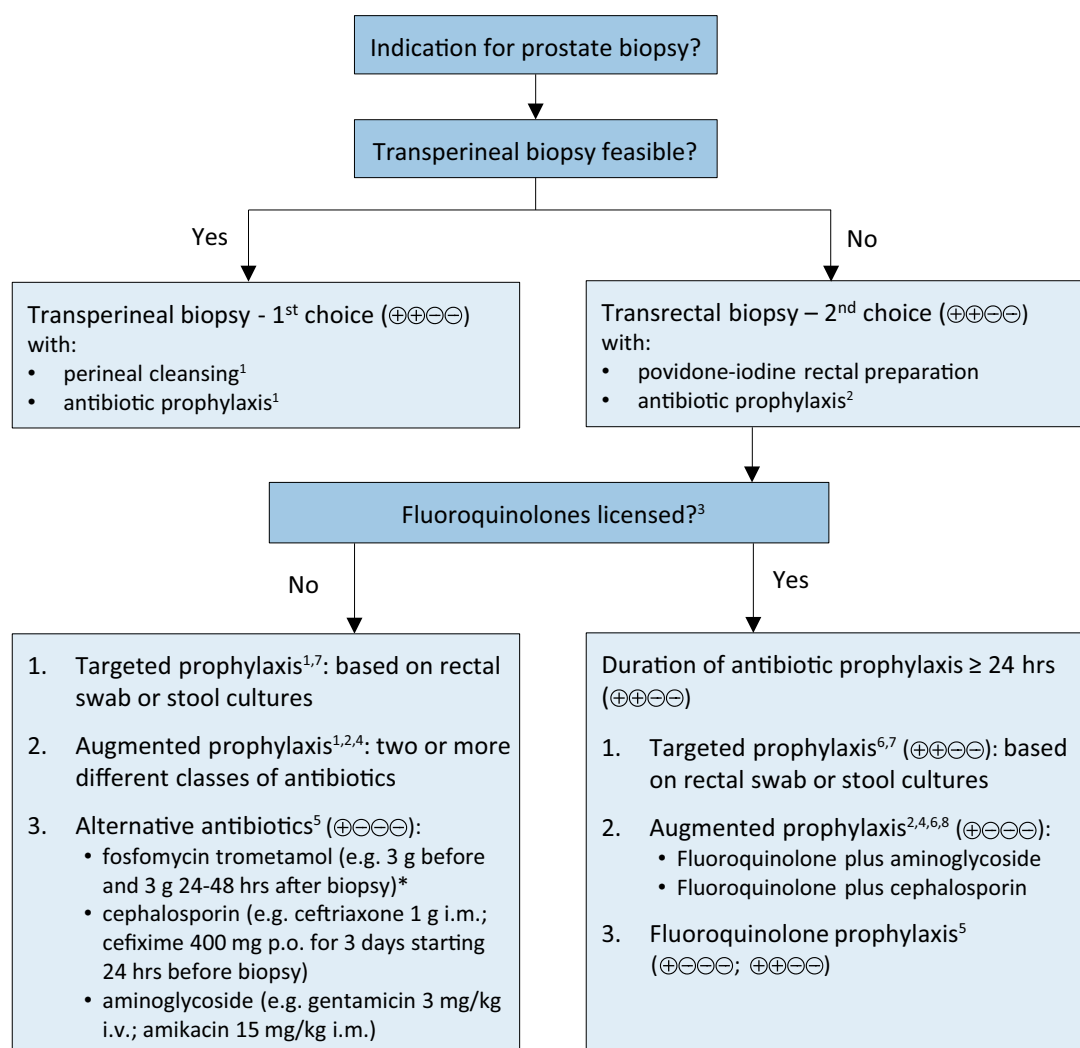
Suggested workflow on how to reduce post biopsy infections.
1. *Two systematic reviews including non-RCTs and two RCTs describe comparable rates of post-transperineal biopsy infection in patients with and without antibiotic prophylaxis.*
2. *Be informed about local antimicrobial resistance.*
3. *Banned by European Commission due to side effects.*
4. *Contradicts principles of Antimicrobial Stewardship.*
5. *Fosfomycin trometamol (3 RCTs), cephalosporins (2 RCTs), aminoglycosides (2 RCTs).*
6. *Only one RCT comparing targeted and augmented prophylaxis.*
7. *Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.*
8. *Various schemes: fluoroquinolone plus aminoglycoside (3 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).*

GRADE Working Group grades of evidence. High certainty: (⊕⊕⊕⊕) very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: (⊕⊕⊕⊖) moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: (⊕⊕⊖⊖) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Figure adapted from Pilatz et al., [314] with permission from Elsevier.

* *Of note: local guidance in relation to the use of fosfomycin trometamol for prostate biopsy needs to be checked.*

5.2.8.3 Local anaesthesia prior to biopsy

Ultrasound-guided peri-prostatic block is recommended [317]. Ten mL of 2% lidocaine is infiltrated bilaterally along the apex to base. Intra-rectal instillation of local anaesthesia is inferior to peri-prostatic infiltration [318]. Local anaesthesia can also be used effectively for MRI-targeted and systematic transperineal biopsy [319]. Patients are placed in the lithotomy position. Twenty mL of 0.5% bupivacaine with adrenaline (1 in 200,000) is injected into the perineal skin and subcutaneous tissues anterior to the anus, followed two minutes later by a peri-prostatic block. A systematic review evaluating pain in 3 studies comparing transperineal vs. transrectal biopsies found that the transperineal approach significantly increased patient pain (RR: 1.83 [1.27–2.65]) [320]. In a randomised comparison a combination of peri-prostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to peri-prostatic anaesthesia only [321]. Targeted biopsies can then be taken via a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [319, 322, 323].

5.2.8.4 Complications

Complications of TRUS biopsy are listed in Table 5.5 [324]. Mortality after prostate biopsy is extremely rare and most are consequences of sepsis [325]. Low-dose aspirin is no longer an absolute contra-indication [326]. A systematic review found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haematospermia and urinary retention [327]. A meta-analysis of 4,280 men randomised between transperineal vs. TRUS biopsies in 13 studies found no significant differences in complication rates, however, data on sepsis compared only 497 men undergoing TRUS biopsy to 474 having transperineal biopsy. The transperineal approach required more (local) anaesthesia [328].

Table 5.5: Adverse events of three groups of targeted biopsy [324]*

	Overall (n = 234)	Transrectal MRI-TB (n = 77)	Transperineal FUS-TB (n = 79)	Transrectal COG-TB (n = 78)	p value
Clavien-Dindo grade					< 0.001
No adverse events	30.3 (71)	47.4 (36)	29.1 (23)	15.4 (12)	
Grade 1	63.2 (148)	50.0 (38)	65.8 (52)	74.4 (58)	
Grade 2	6.0 (14)	2.6 (2)	5.1 (4)	10.3 (8)	
Grades 3, 4, 5	–	–	–	–	
Haematuria	53.4 (125)	35.5 (27)	50.6 (40)	74.4 (58)	< 0.001
Haematospermia	37.2 (87)	26.3 (20)	35.4 (28)	50.0 (39)	< 0.01
Rectal bleeding	3.4 (8)	2.6 (2)	2.5 (2)	5.1 (4)	0.59
UTI	3.4 (8)	2.6 (2)	1.3 (1)	6.4 (5)	0.21
Fever	3 (7)	1.3 (1)	2.5 (2)	5.1 (4)	0.46
Urinary retention	3 (7)	–	3.8 (3)	5.1 (4)	0.15
Haematoma	1.3 (3)	–	3.8 (3)	–	0.29
Other					0.56
Lower back pain	0.9 (2)	1.3 (1)	1.3 (1)	–	
Atrial fibrillation	0.4 (1)	–	1.3 (1)	–	

COG-TB = cognitive registration TRUS targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI targeted biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection. Data are presented as % (n).
With permission by Elsevier.

5.2.8.5 Seminal vesicle biopsy

Indications for SV (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20–25% [329]. A SV staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent RT. Its added value compared with MRI is questionable.

5.2.8.6 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to MRI-detected lesions or repeat template biopsies [330].

5.2.9 Pathology of prostate needle biopsies

5.2.9.1 Processing

Prostate core biopsies from different sites are processed separately, as delivered by the biopsy operator. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [331]. In case individual cores can clearly be identified in submitted jars, a maximum of three cores should be embedded per tissue cassette, and sponges or paper should be used to keep the cores stretched and flat to achieve optimal flattening and alignment [332-334]. To optimise detection of small lesions and improve accuracy of grading, paraffin blocks should be cut at three levels and intervening unstained sections may be kept for immunohistochemistry (IHC) [335].

5.2.9.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [335]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [335]. Sections 5.2.9.2.1 and 5.2.9.2.2 list the recommended terminology and item list for reporting prostate biopsies [332]. Type and subtype of PCa should be reported such as for instance acinar adenocarcinoma, ductal adenocarcinoma and small or large cell neuroendocrine carcinoma, even if representing a small proportion of the PCa. The distinct aggressive nature of small/large cell neuroendocrine carcinoma should be commented upon in the pathology report [332]. Apart from grading acinar and ductal adenocarcinoma, the percentage of Gleason grade 4 component should be reported in Gleason score 7 (3+4 and 4+3) PCa biopsies. Percentage Gleason grade 4 has additional prognostic value and is considered in some AS protocols [336-338]. Considerable evidence has been accumulated in recent years supporting that among the Gleason grade 4 patterns, cribriform pattern carries an increased risk of biochemical recurrence, metastatic disease and death of disease [339, 340]. Reporting of this sub-pattern based on established criteria is recommended [110, 341]. Intraductal carcinoma, defined as an extension of cancer cells into pre-existing prostatic ducts and acini, distending them, with preservation of basal cells [110], should be distinguished from high-grade PIN [342] as it conveys unfavourable prognosis in terms of biochemical recurrence and cancer-specific survival (CSS) [343, 344]. Its presence should be reported, whether occurring in isolation or associated with adenocarcinoma [110].

5.2.9.2.1 Recommended terminology for reporting prostate biopsies [287]

Benign/negative for malignancy; if appropriate, include a description
Active inflammation
Granulomatous inflammation
High-grade prostatic intraepithelial neoplasia (PIN)
High-grade PIN with atypical glands, suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern
Intraductal carcinoma

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2019 grade [110, 345, 346]. For MRI targeted biopsies consisting of multiple cores per target the aggregated (or composite) ISUP grade should be reported per targeted lesion [110]. If the targeted biopsies are negative, presence of specific benign pathology should be mentioned, such as dense inflammation, fibromuscular hyperplasia or granulomatous inflammation [110, 347]. A global ISUP grade comprising all systematic (non-targeted) and targeted biopsies is also reported (see Section 4.2). The global ISUP grade takes into account all biopsies positive for carcinoma, by estimating the total extent of each Gleason grade present. For instance, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site of Gleason grade 4 only, the global ISUP grade would be 2 (i.e. GS 7[3+4]) or 3 (i.e. GS 7[4+3]), dependent on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the worst grade would be ISUP grade 4 (i.e. GS 8[4+4]). Neither global nor worst ISUP grade is clearly superior over the other [348]. The majority of clinical studies have not specified whether global or worst biopsy grade was taken into account. In addition to Gleason score/ISUP grade, the presence/absence of intraductal/invasive cribriform pattern should be reported [110, 345, 346]. Furthermore, in biopsy Gleason score 7 (ISUP grade 2 and 3) percentage Gleason grade 4 should be monitored at the case and/or biopsy level [110, 346]. Lymphovascular invasion (LVI) and EPE must each be reported, if identified, since both carry unfavourable prognostic information [349-351].

Recently, a series of studies have demonstrated that computer-assisted PCa grading artificial intelligence algorithms can perform grading at the level of experienced genito-urinary pathologists. These algorithms have potential in supporting grading of less experienced pathologist, by reducing inter-observer variability, and in quantitative analyses. However, more extensive and prospective validation of these algorithms is needed for implementation in daily clinical practise [110, 345, 346].

The proportion of systematic (non-targeted) carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP grade, tumour volume, surgical margins and pathological stage in RP specimens and predict BCR, post-prostatectomy progression and radiotherapy (RT) failure. These parameters are included in nomograms created to predict pathological stage and SV invasion after RP and RT failure [352, 353]. A pathology report should therefore provide both the number of carcinoma-positive cores and the extent of cancer involvement for each core. The length in mm and percentage of carcinoma in the biopsy have equal prognostic impact [354]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [355] triggering immediate treatment vs. AS in patients with ISUP grade 1 (see Section 6.1.1.1).

5.2.9.2.2   Recommended item list for reporting prostate cancer biopsies [110, 345, 346]

Type of carcinoma
Primary and secondary Gleason grade, per biopsy site and global
International Society of Urological Pathology (ISUP) grade
Percentage of global Gleason grade 4 in GS 7 biopsies
Presence/absence of intraductal/invasive cribriform carcinoma
Number of cancer-positive biopsy cores
Extent of cancer (in mm or percentage)
For MRI-targeted biopsies with multiple cores aggreggate (or composite) ISUP grade per lesion
For carcinoma-negative MRI-targeted biopy, specific benign pathology, e.g. fibrouscular hyperplasia or granulamatous inflammation
If present, lymphovascular invasion, extra-prostatic extension and ejaculatory duct/seminal vesicle involvement

5.2.9.3   Tissue-based prognostic biomarker testing

After a comprehensive literature review and several panel discussions an ASCO-EAU-AUA multidisciplinary expert panel made recommendations regarding the use of tissue-based PCa biomarkers. The recommendations were limited to 5 commercially available tests (Oncotype Dx®, Prolaris®, Decipher®, Decipher PORTOS and ProMark®) with extensive validation in large retrospective studies and evidence that their test results might actually impact clinical decision-taking [356]. The selected commercially available tests significantly improved the prognostic accuracy of clinical multivariable models for identifying men who would benefit of AS and those with csPCa requiring curative treatment, as well as for guidance of patient management after RP. Few studies showed that tissue biomarker tests and MRI findings independently improved the detection of csPCa in an AS setting, but it remains unclear which men would benefit of both tests. Decipher® test outcome has been associated with presence of intraductal/invasive cribriform carcinoma, but retains independent value in multivariable analysis [357-359]. Since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa scheduled for radiotherapy (RT) to decide on treatment intensification with hormonal therapy (HT).

5.2.9.4   Histopathology of radical prostatectomy specimens
5.2.9.4.1   Processing of radical prostatectomy specimens
Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most widely accepted method includes complete embedding of the posterior prostate and a single mid-anterior left and right section. Compared with total embedding, partial embedding with this method missed 5% of positive margins and 7% of EPE [360].

The entire RP specimen should be inked upon receipt in the laboratory to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before

slicing. After fixation, the apex and the base (bladder neck) are removed and cut into (para)sagittal or radial sections; the shave method is not recommended [108]. The remainder of the specimen is cut in transverse, 3–4 mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with pre-operative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.2.9.4.2   Radical prostatectomy specimen report
The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.6). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended. Synoptic reporting results in more transparent and complete pathology reporting [361].

Table 5.6: Mandatory elements provided by the pathology report

Histopathological (sub)type
Type of carcinoma, e.g., conventional acinar adenocarcinoma, (small cell) neuroendocrine cell carcinoma or ductal carcinoma
Subtype and unusual variants, e.g., pleomorphic giant cell or mucinous
Histological grade
Primary (predominant) Gleason grade
Secondary Gleason grade
Tertiary Gleason grade (if applicable)
Global ISUP grade
Approximate percentage of Gleason grade 4 or 5
Tumour quantitation (optional)
Percentage of prostate involved
Size/volume of dominant tumour nodule
Pathological staging (pTNM)
If extraprostatic extension is present: • indicate whether it is focal or extensive (see Section 5.2.9.4.4); • specify sites; • indicate whether there is seminal vesicle invasion. *If applicable, regional lymph nodes:* • location; • number of nodes retrieved; • number of nodes involved.
Surgical margins
If carcinoma is present at the margin: • specify sites; • extent: focal or extensive (see Section 5.2.9.4.6) • (highest) grade at margin.
Other
Presence of lymphovascular/angio-invasion
Location of dominant tumour
Presence of intraductal carcinoma/cribriform architecture

5.2.9.4.3   ISUP grade in prostatectomy specimens
Grading of conventional prostatic adenocarcinoma using the Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [109]. The Gleason score is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [362-364]. The ISUP grade in prostatectomy specimens is determined mostly in a similar way as in biopsies, with a minor exception; i.e. the exclusion of minor (< 5%) high-grade components from the ISUP grade. For instance, in a carcinoma almost entirely composed of Gleason grade 3 the presence of a minor (< 5%) Gleason grade 4 or 5 component is not included in the Gleason score (ISUP grade 1), but its presence is commented upon [110]. In case of multifocality the ISUP grade of the index lesion i.e. the tumour having the highest grade, stage or volume, is given.

5.2.9.4.4   Definition of extra-prostatic extension
Extra-prostatic extension is defined as carcinoma mixed with peri-prostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE because the latter is related to recurrence risk [365].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [366] or < 1 high-power field in one or at most two sections whereas others measure the depth of extent in millimetres [366].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e. not as pT4, because it does not carry independent prognostic significance for PCa recurrence and should be recorded as EPE (pT3a) [367, 368]. Stage pT4 is assigned when the tumour invades the bladder muscle wall as determined macroscopically [103].

5.2.9.4.5   PCa volume
Although PCa volume at RP correlates with tumour grade, stage and surgical margin status, the independent prognostic value of PCa volume has not been established [366, 369-372]. Improvement in prostatic radio-imaging allows more accurate pre-operative measurement of cancer volume. Since the independent value of pathological tumour volume at RP has not been established, reporting of the diameter/volume of the dominant tumour nodule, or a rough estimate of the percentage of cancer tissue, is optional [373].

5.2.9.4.6   Surgical margin status
Surgical margin status is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [370] or at the surface of the tissue lacking ink. In tissues that have severe crush artefacts, it may not be possible to determine margin status [374].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [375]. There is evidence for a relationship between margin extent and recurrence risk [376, 377]. However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in mm of involvement: focal, $\leq$ 1 mm vs. extensive, > 1 mm [378], or number of blocks with positive margin involvement. Gleason score at the positive margin was found to correlate independently with outcome, and should be reported [361, 376, 379].

5.3   Diagnosis - Clinical Staging
5.3.1   *T-staging*
The cT category listed in Table 4.1 (TNM Classification) only relies on DRE findings. Imaging parameters and biopsy results for local staging are, so far, not part of the risk category stratification [380].

5.3.1.1   *US-based techniques and CT*
Transrectal US has limited accuracy for PCa local staging [381]. More advanced US-based techniques have not yet been tested in large-scale studies. In case of locally-advanced cancers, abdominopelvic US or CT may show rectal or bladder invasion and dilatation of the upper collecting systems [381].

5.3.1.2   *MRI*
T2-weighted imaging remains the most useful method for local staging on MRI. Pooled data from a meta-analysis showed a sensitivity and specificity of 0.57 (95% CI: 0.49–0.64) and 0.91 (95% CI: 0.88–0.93), 0.58 (95% CI: 0.47–0.68) and 0.96 (95% CI: 0.95–0.97), and 0.61 (95% CI: 0.54–0.67) and 0.88 (95% CI: 0.85–0.91), for EPE, SVI, and overall stage T3 assessment, respectively [382].

Detection of EPE and SVI seems more accurate at high field strength (3 Tesla) [382], while the added value of functional imaging remains debated [382, 383].

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 using MRI findings rather than DRE findings showed better BCR-free survival due to improved discrimination and the Will Roger's phenomenon [384].

Traditionally, EPE/SVI is assessed visually using qualitative signs (e.g., capsular disruption, visible tumour within peri-prostatic fat). Inter-reader agreement with such subjective reading is moderate, with kappa (k) values ranging from 0.41 to 0.68 [385]. The length of tumour capsule contact (LCC) is also a significant predictor of EPE; it has the advantage of being quantitative, although the ideal cut-off value remains debated [386, 387].

Several grading systems combining subjective qualitative signs and/or LCC into a score have shown good sensitivity for EPE (0.68–0.82) with substantial inter-reader agreement (κ = 0.63–0.74), but at the expense of decreased specificity (0.71–0.77); none of these scores has shown definitive superiority over the others [388].

Magnetic resonance imaging findings can improve the prediction of the pathological stage when combined with clinical and biopsy data. As a result, several groups developed multivariate risk calculators for predicting EPE/SVI or positive surgical margins [389]. In external validation cohorts, these risk calculators showed significantly better discrimination than nomograms without MRI-based features [390-392]. However, they remain limited by substantial miscalibration and therefore their results must be interpreted with care.

Given its low sensitivity for focal (microscopic) EPE, MRI is not recommended for local staging in low-risk patients. However, MRI can still be useful for treatment planning.

5.3.2 *N-staging*

5.3.2.1 *Computed tomography and MRI*
Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of non-metastatic LNs varies widely and may overlap the size of LN metastases. Usually, LNs with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are considered malignant. Decreasing these thresholds improves sensitivity but decreases specificity. As a result, the ideal size threshold remains unclear [393, 394]. Computed tomography and MRI sensitivity is less than 40% [395, 396]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade < 4 cancer, PSA < 20 ng/mL, or localised disease [393, 397].

Diffusion-weighted MRI (DW-MRI) may detect metastases in normal-sized nodes, but a negative DW-MRI cannot rule out the presence of LN metastases, and DW-MRI provides only modest improvement for LN staging over conventional imaging [398].

5.3.2.2 *Risk calculators incorporating MRI findings and clinical data*
Because 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 [399-401]. Although these nomograms are associated with good performance, they have been developed using systematic biopsy findings and may therefore not be appropriate for patients diagnosed with combined MRI-targeted biopsy and systematic biopsy.

Two models incorporating MRI-targeted biopsy findings and MRI-derived findings recently underwent external validation [364, 402]. One model was tested on an external cohort of 187 patients with a prevalence of LN invasion of 13.9% (vs. 16.9% in the development cohort). The C-index was 0.73 (vs. 0.81 in the development cohort); at calibration analysis, the model tended to overpredict the actual risk [402]. The other model was validated in an external multi-centre cohort of 487 patients with a prevalence of 8% of LN invasion (vs. 12.5% in the development cohort). The AUC was 0.79 (vs. 0.81 in the development cohort). Using a risk cut-off of 7% would have avoided LN dissection in 273 (56% of the cohort), while missing LN invasion in 7 patients (2.6% of the patients below the 7% threshold; 18% of the 38 patients with LN invasion) [403]. Therefore, this nomogram and a 7% threshold should be used after MRI-targeted biopsy to identify candidates for extended LN dissection (eLND).

5.3.2.3 *Choline PET/CT*
In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51–66%) and 92% (95% CI: 89–94%), respectively [404]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10–35%), the sensitivity was only 8.2% at region-based analysis and 18.9% at patient-based analysis, which is too low to be of clinical value [405]. The sensitivity of choline PET/CT increases to 50% in patients at high risk and to 71% in patients at very high risk [406].

Due of its low sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases, or to rule out a nodal dissection based on risk factors or nomograms (see Section 6.3.4.1.2).

5.3.2.4 *Prostate-specific membrane antigen-based PET/CT*
Prostate-specific membrane antigen PET/CT uses several different radiopharmaceuticals; most published studies used ^{68}Ga-labelling for PSMA PET imaging, but some used ^{18}F-labelling. PSMA is also an attractive target because of its specificity for prostate tissue, even if the expression in other non-prostatic malignancies or benign conditions may cause incidental false-positive findings [407-411].

A multi-centre prospective phase III imaging trial, investigating men with intermediate- and high-risk PCa who underwent RP and PLND, showed a sensitivity and specificity of ^{68}Ga-PSMA-11 PET of 0.40

(95% CI: 0.34-0.46), and 0.95 (95% CI: 0.92-0.97), respectively [412]. This is line with previous results from prospective, multi-centre studies addressing the accuracy of ^{68}Ga-PSMA and ^{18}F-DCFPyL PET/CT for LN staging in patients with newly diagnosed PCa [413, 414]. Comparable results were also demonstrated in a phase II/III prospective, multi-centre study (OSPREY) with a median specificity of 97.9% (95% CI: 94.5–99.4%) and median sensitivity of 40.3% (28.1–52.5%) for pelvic nodal involvement [415]. This suggests that current PSMA-based PET/CT imaging cannot yet replace diagnostic ePLND (see also Section 6.1.2.3.2).

Prostate-specific antigen may be a predictor of a positive PSMA PET/CT. In the primary staging cohort from a meta-analysis, however, no robust estimates of positivity were found [416].

Comparison between PSMA PET/CT and MRI was performed in a systematic review and meta-analysis including 13 studies (n = 1,597) [417]. ^{68}Ga-PSMA was found to have a higher sensitivity and a comparable specificity for staging pre-operative LN metastases in intermediate- and high-risk PCa [418].

PSMA PET/CT has a good sensitivity and specificity for LN involvement, possibly impacting clinical decision-making. 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 ^{68}Ga-PSMA PET were 77% and 97%, respectively, after eLND at the time of RP. On a per-lesion-based analysis, sensitivity and specificity were 75% and 99%, respectively [416].

In summary, PSMA PET/CT is more sensitive in N-staging as compared to MRI, abdominal contrast-enhanced CT or choline PET/CT; however, small LN metastases, under the spatial resolution of PET (~5 mm), may still be missed.

5.3.2.5 Risk calculators incorporating MRI and PSMA findings
Recently, an international, multi-centre study incorporated PSMA PET into existing nomograms in order to predict pelvic LN metastatic disease in PCa patients. Performance of 3 nomograms was assessed in 757 patients undergoing RARP and ePLND. Addition of PSMA PET to the nomograms substantially improved the discriminative ability of the models yielding cross-validated AUCs of 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively [419].

5.3.3 **M-staging**
5.3.3.1 Bone scan
[99m]Tc-Bone scan is a highly sensitive conventional imaging technique, evaluating the distribution of active bone formation in the skeleton related to malignant and benign disease. A meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%) at patient level [420]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade [393, 421]. A retrospective study investigated the association between age, PSA and GS in 703 newly diagnosed PCa patients who were referred for bone scintigraphy. The incidence of bone metastases increased substantially with rising PSA and upgrading GS [422]. In two studies, a dominant Gleason pattern of 4 was found to be a significant predictor of positive bone scan [423, 424]. Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP grade or clinical stage [393].

5.3.3.2 Fluoride PET/CT, choline PET/CT and MRI
[18]F-sodium fluoride (^{18}F-NaF) PET or PET/CT, similarly to bone scintigraphy, only assesses the presence of bone metastases. The tracer was reported to have similar specificity and superior sensitivity to bone scintigraphy for detecting bone metastases in patients with newly diagnosed high-risk PCa [425, 426]. Inter-observer agreement for the detection of bone metastases was excellent, demonstrating that ^{18}F-NaF PET/CT is a robust tool for the detection of osteoblastic lesions in patients with PCa [427].

It remains unclear whether choline PET/CT is more sensitive than bone scan but it has higher specificity with fewer indeterminate bone lesions [428-430]. Choline PET/CT has also the advantage of detecting visceral and nodal metastases.

Diffusion-weighted whole-body and axial skeleton MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa. Whole-body MRI can also detect visceral and nodal metastases; it was shown to be more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [431]. A meta-analysis found that whole-body MRI is more sensitive than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity [420].

5.3.3.3 PSMA PET/CT
A systematic review including 12 studies (n = 322) reported high variation in ^{68}Ga-PSMA PET/CT sensitivity for initial staging (range 33–99%; median sensitivity on per-lesion analysis 33–92%, and on per-patient

analysis 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) [432].

In a prospective multi-centre study in patients with high-risk PCa before curative surgery or RT (proPSMA), 302 patients were randomly assigned to conventional imaging or ^{68}Ga-PSMA-11 PET/CT [433]. The primary outcome focused on the accuracy of first-line imaging for the identification of pelvic LN 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 a 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 as compared to conventional imaging (41 [28%] men [95% CI: 21–36] vs. 23 [15%] men [95% CI: 10–22], p = 0.08), with less equivocal findings (7% [95% CI: 4–13] vs. 23% [95% CI: 17–31]) and lower radiation exposure (8.4 mSv vs. 19.2 mSv; p < 0.001) [433].The comparison of whole body MRI and PSMA PET/CT in detecting bone metastases has led to inconclusive opposite results in two small cohorts [418, 434].

5.3.4   Summary of evidence and practical considerations on initial N/M staging
The field of non-invasive N- and M-staging of PCa patients is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN- and bone metastases than the classical work-up with bone scan and abdominopelvic CT. In view of the evidence offered by the randomised, multi-centre proPSMA trial [433], replacing bone scan and abdominopelvic CT by more sensitive imaging modalities may be a consideration in patients with high-risk PCa undergoing initial staging. However, in absence of prospective studies demonstrating survival benefit, caution must be used when taking therapeutic decisions [435]. The prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. In particular, it is unclear whether patients with metastases detectable only with PET/CT or whole-body MRI should be managed using systemic therapies only, or whether they should be subjected to aggressive local and metastases-directed therapies [436].

Results from RCTs evaluating the management and outcome of patients with (and without) metastases detected by choline PET/CT, PSMA PET/CT and MRI are awaited before a recommendation can be made to treat patients based on the results of these tests [437].

5.3.5   Summary of evidence and guidelines for staging of prostate cancer

Summary of evidence	LE
PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management.	1b

Recommendations	Strength rating
Any risk group staging	
Use pre-biopsy MRI for local staging information.	Weak
Treatment should not be changed based on PSMA PET/CT findings, in view of current available data.	Strong
Low-risk localised disease	
Do not use additional imaging for staging purposes.	Strong
Intermediate-risk disease	
In ISUP grade 3, include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	Weak
High-risk localised disease/locally-advanced disease	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong
When using PSMA-PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

5.4   Estimating life expectancy and health status
5.4.1   Introduction
Evaluation of life expectancy and health status is important in clinical decision-making for screening, diagnosis, and treatment of PCa. Prostate cancer is common in older men (median age 68) and diagnoses in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the USA [438, 439].

Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over 10 years life expectancy is considered mandatory for any benefit from local treatment and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCSM and life expectancy of surgery vs. AS [440]. Although in a RCT the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR: 0.45), RP was associated with a reduced risk of metastases and use of androgen deprivation therapy (ADT) among older men (RR: 0.68 and 0.60, respectively) [441]. External beam RT shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [442].

Older men have a higher incidence of PCa and may be under-treated despite the high overall mortality rates [443, 444]. Of all PCa-related deaths 71% occur in men aged > 75 years [445], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [446-448]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease received curative treatment compared to 88% aged 65–74 [449].

5.4.2 Life expectancy

Life expectancy tables for European men are available online: https://ec.europa.eu/eurostat/web/productsdatasets/-/tps00205. Survival may be variable and therefore estimates of survival must be individualised. Gait speed is a good single predictive method of life expectancy (from a standing start, at usual pace, generally over 6 meters). For men at age 75, 10-year survival ranged from 19% < 0.4 m/s to 87%, for ≥ 1.4 m/s [450].

Figure 5.2: Predicted Median Life Expectancy by Age and Gait Speed for males* [450]
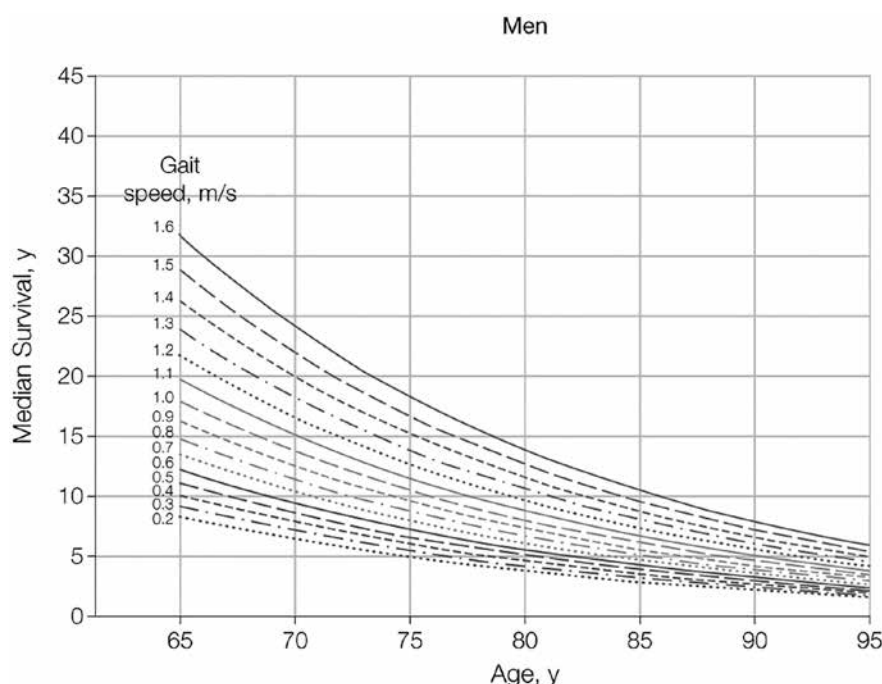
Figure reproduced with permission of the publisher, from Studenski S, et al. JAMA 2011 305(1)50.

5.4.3 Health status screening

Heterogeneity increases with advancing age, so it is important to use measures other than just age or performance status (PS) when considering treatment options. The International SIOG PCa Working Group recommends that treatment for adults over 70 years of age should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (see Table 5.7) [159]. This tool helps to discriminate between those who are fit and those with frailty, a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and negative side effects of cancer treatment [451]. Healthy patients with a G8 score > 14 or vulnerable patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Frail patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (see Figure 5.3) [159]. Patients with a G8 score ≤ 14 should undergo a comprehensive geriatric assessment (CGA) as this score is associated with 3-year mortality. A CGA is a multi-domain assessment that includes co-morbidity, nutritional status, cognitive and physical function, and social supports to determine if

impairments are reversible [452]. A systematic review of the effect of geriatric evaluation for older cancer patients showed improved treatment tolerance and completion [453].

The Clinical Frailty Scale (CFS) is another screening tool for frailty (see Figure 5.4) [454]. Although not frequently used in the cancer setting, it is considered to be a common language for expressing degree of frailty. The scale runs from 1 to 9, with higher scores indicating increasing frailty. Patients with a higher CFS score have a higher 30-day mortality after surgery and are less likely to be discharged home [455].

It is important to use a validated tool to identify frailty, such as the G8 or CFS, as clinical judgement has been shown to be poorly predictive of frailty in older patients with cancer [456].

5.4.3.1 Co-morbidity

Co-morbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [457, 458]. Ten years after not receiving active treatment for PCa, most men with a high co-morbidity score had died from competing causes, irrespective of age or tumour aggressiveness [457]. Measures for co-morbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [459, 460] (Table 5.8) and Charlson Co-morbidity Index (CCI) [461].

5.4.3.2 Nutritional status

Malnutrition can be estimated from body weight during the previous 3 months (good nutritional status < 5% weight loss; risk of malnutrition: 5–10% weight loss; severe malnutrition: > 10% weight loss) [462].

5.4.3.3 Cognitive function

Cognitive impairment can be screened for using the mini-COG (https://mini-cog.com/) which consists of three-word recall and a clock-drawing test and can be completed within 5 minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an increasingly important factor in health status assessment [463-465]. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [466].

5.4.3.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [467]. Measures for dependence in daily activities include: Activities of Daily Living (ADL; basic activities) and Instrumental Activities of Daily Living (IADL; activities requiring higher cognition and judgement) [468-470].

5.4.3.5 Shared decision-making

The patient's own values and preferences should be taken into account as well as the above factors. A shared decision-making process also involves anticipated changes to QoL, functional ability, and a patient's hopes, worries and expectations about the future [471]. Particularly in older and frail patients, these aspects should be given equal importance to disease characteristics during the decision-making process [472]. Older patients may also wish to involve family members, and this is particularly important where cognitive impairment exists.

5.4.4 Conclusion

Individual life expectancy, health status, frailty, and co-morbidity, not only age, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of 10 years is most commonly used as a threshold for benefit of local treatment. Older men may be under-treated. Patients aged 70 years of age or older who have frailty should receive a comprehensive geriatric assessment. Resolution of impairments in vulnerable men allows a similar urological approach as in fit patients.

Table 5.7: G8 screening tool (adapted from [473]**)**

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80-85
		2 = < 80
	Total score	**0-7**

Figure 5.3: Decision tree for health status screening (men > 70 years)** [159]
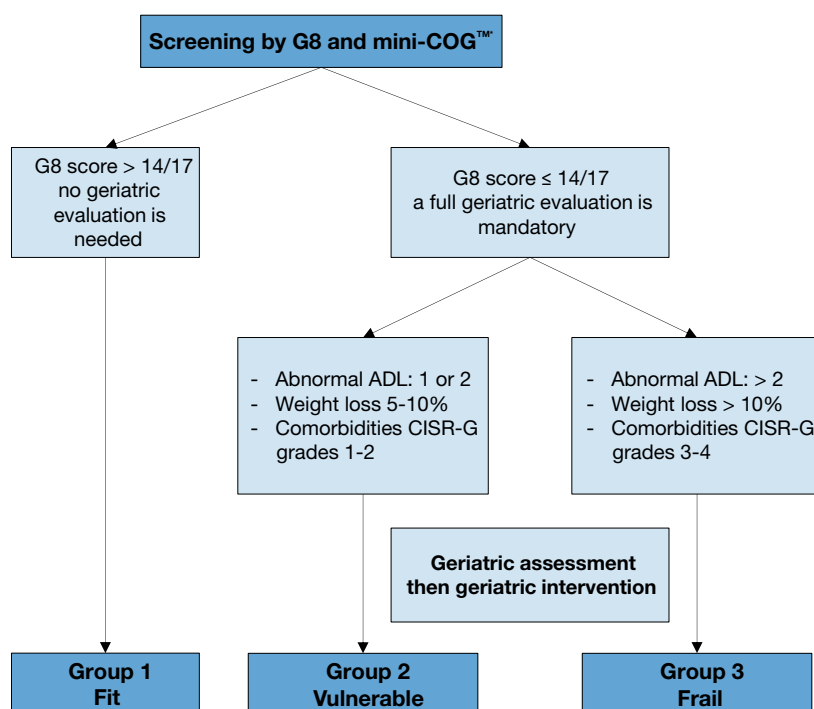
Mini-COG^{TM} = Mini-COG^{TM} cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.

* For Mini-COG™, a cut-off point of ≤ 3/5 indicates a need to refer the patient for full evaluation of potential dementia.

**Reproduced with permission of Elsevier, from Boyle H.J., et al. Eur J Cancer 2019:116; 116 [159].

Figure 5.4: The Clinical Frailty Scale version 2.0 [454]*

CLINICAL FRAILTY SCALE

	1	**VERY FIT**	People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	2	**FIT**	People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.
	3	**MANAGING WELL**	People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.
	4	**LIVING WITH VERY MILD FRAILTY**	Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.
	5	**LIVING WITH MILD FRAILTY**	People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
	6	**LIVING WITH MODERATE FRAILTY**	People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.
	7	**LIVING WITH SEVERE FRAILTY**	**Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
	8	**LIVING WITH VERY SEVERE FRAILTY**	Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	9	**TERMINALLY ILL**	Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

DALHOUSIE UNIVERSITY
www.geriatricmedicineresearch.ca

Clinical Frailty Scale ©2005–2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: **www.geriatricmedicineresearch.ca** Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

*Permission to reproduce the CFS was granted by the copyright holder.

Table 5.8: Cumulative Illness Score Rating-Geriatrics (CISR-G)

1	Cardiac (heart only)
2	Hypertension (rating is based on severity; affected systems are rated separately)
3	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics)
4	Respiratory (lungs, bronchi, trachea below the larynx)
5	ENT (eye, ear, nose, throat, larynx)
6	Upper GI (esophagus, stomach, duodenum. Biliar and parcreatic trees; do not include diabetes)
7	Lower GI (intestines, hernias)
8	Hepatic (liver only)
9	Renal (kidneys only)
10	Other GU (ureters, bladder, urethra, prostate, genitals)
11	Musculo-Skeletal-Integumentary (muscles, bone, skin)
12	Neurological (brain, spinal cord, nerves; do not include dementia)
13	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)
14	Psychiatric/Behavioural (includes dementia, depression, anxiety, agitation, psychosis)
	All body systems are scores on a 0 - 4 scale. - 0: No problem affecting that system. - 1: Current mild problem or past significant problem. - 2: Moderate disability or morbidity and/or requires first line therapy. - 3: Severe problem and/or constant and significant disability and/or hard to control chronic problems. - 4: Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.
Total score 0-56	

Recommendations	Strength rating
Use individual life expectancy, health status, and co-morbidity in PCa management.	Strong
Use the Geriatric-8, mini-COG and Clinical Frailty Scale tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak
Offer adapted treatment to patients with irreversible impairment.	Weak
Offer symptom-directed therapy alone to frail patients.	Strong

6.   TREATMENT

This chapter reviews the available treatment modalities, followed by separate sections addressing treatment for the various disease stages.

6.1   Treatment modalities

6.1.1   *Deferred treatment (active surveillance/watchful waiting)*

As PCa is such a common disease, and with the increased rate of early detection of small tumours after the introduction of PSA, there is a distinct risk of over-diagnosis and subsequent over-treatment of the disease [474]. As all available curative treatment options for PCa carry a risk of significant side effects there is a need for conservative treatment options for patients with low risk of dying from their PCa. Data from studies conducted on patients who did not undergo local treatment with up to 25 years of follow-up, with endpoints of OS and CSS, are available. Several series have shown a consistent CSS rate of 82–87% at 10 years [475-478], and 80–95% for T1/T2 and ISUP grade ≤ 2 PCas [479]. In three studies with data beyond 15 years, the CSS was 80%, 79% and 58% respectively [475, 477, 478], and two reported 20-year CSS rates of 57% and 32% [475, 477]. The observed heterogeneity in outcomes is due to different inclusion criteria, with some older studies from the pre-PSA era showing worse outcomes [477]. In addition, many patients classified as ISUP grade 1 would now be classified as ISUP grade 2–3 based on the 2005 Gleason classification, suggesting that the above-mentioned results should be considered as minimal. Patients with well-, moderately- and poorly-differentiated tumours had 10-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from a pooled analysis [479]. Observation is most effective in men aged 65–75 years with low-risk PCa [480]. In screen-detected localised PCa there is also a lead-time bias, resulting in a higher rate of early detected PCa, but also an even higher risk of detecting clinically insignificant PCa that never would have caused any problems [474]. Cancer-specific survival from untreated screen-detected PCa in patients with ISUP grade 1–2 is therefore likely to be even higher than for PCa detected of other reasons. Consequently, a high proportion of men with PSA-detected PCa are suitable for conservative treatment.

The high CSS rates of localised PCa leads to a life expectancy of at least 10 years to be considered mandatory for any benefit from active treatment. Co-morbidity is as important as age in predicting life expectancy in men with PCa. Increasing co-morbidity greatly increases the risk of dying from non-PCa-related causes. In an analysis of 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI score ≥ 2 had died from competing causes at 10 years follow-up regardless of their age at time of diagnosis. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at 10 years, especially for well- or moderately-differentiated lesions [457]. This highlights the importance of assessing co-morbidity even before considering a biopsy, but also before advising a patient with a PCa diagnosis on the optimal treatment for him.

There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and WW (Table 6.1.1).

Table 6.1.1: Definitions of active surveillance and watchful waiting [481]

	Active surveillance	**Watchful waiting**
Treatment intent	Curative	Palliative
Follow-up	Pre-defined schedule	Patient-specific
Assessment/markers used	DRE, PSA, MRI at recruitment, re-biopsy	Not pre-defined, but dependent on development of symptoms of progression
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Eligible patients	Mostly low-risk patients	Can apply to patients with all stages

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

6.1.1.1   Active surveillance

Active surveillance aims to avoid unnecessary treatment, and consequently unnecessary side effects, in men with clinically localised PCa, and a life expectancy of 10 years or more, who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [482]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up consisting of PSA testing, clinical examination, MRI imaging and repeat prostate biopsies, with curative treatment being prompted by pre-defined thresholds indicative of potentially life-threatening disease, which is still curable, while considering individual life expectancy.

No formal RCT is available comparing AS to curative treatment. Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review [483]. More recently, the largest prospective series of men with low-risk PCa managed by AS was published [484]. Table 6.1.2 summarises the results of selective AS cohorts. It is clear that the long-term OS and CSS of patients on AS are extremely good. However, more than one-third of patients are 'reclassified' during follow-up, most of whom undergo curative treatment due to disease upgrading, increase in disease extent, disease stage, progression or patient preference. There is considerable variation and heterogeneity between studies regarding patient selection and eligibility, follow-up policies (including frequency and type of imaging such as MRI imaging, type and frequency of repeat prostate biopsies, such as MRI-targeted biopsies or transperineal template biopsies, use of PSA kinetics and density, and frequency of clinical follow-up), when active treatment should be instigated (i.e., reclassification criteria) and which outcome measures should be prioritised [482]. For specific guidelines on inclusion criteria and follow-up strategies for AS, see Sections 6.2.1.1, 6.2.1.3 and 6.2.2.1 and 6.2.2.5.

In the ProtecT-trial, a RCT, 1,643 patients were randomised into one of three arms: active treatment with either RP or EBRT or active monitoring (AM) [485]. Even though the ProtecT trial is a RCT it does not include a formal AS strategy as described above and in Sections 6.2.1.1.4 and 6.2.1.3, but rather AM, a significantly less stringent surveillance strategy in terms of clinical follow-up, imaging and repeat biopsies. Fifty-six percent of the patients had low-risk disease, with 90% having a PSA < 10 ng/mL, 77% ISUP grade 1 (20% ISUP grade 2–3), and 76% had T1c disease. The remaining patients had mainly intermediate-risk disease. The key finding was that AM was as effective as active treatment at 10 years (CSS = 99% vs. 98.8%), but at a cost of increased metastatic progression risk (2.6% vs. 6%). Metastases, although rare, were more frequent than seen with comparable AS protocols [483]. Recently, a comprehensive characterisation of the ProtecT study cohort was performed, stratifying patients at baseline according to risk of progression using clinical stage, grade at diagnosis and PSA level [486]. Additionally, detailed clinico-pathological information on participants who received RP were analysed. The authors aimed to test the hypothesis that the clinico-pathological features of participants with disease progression differed from those with stable disease in order to identify prognostic markers. The results showed that out of all patients who had been randomised (n = 1,643), 34% (n = 505) had intermediate- or high-risk disease, and 66% (n = 973) had low-risk disease. Of all patients who had received AM, RP or RT within 12 months of randomisation (n = 1,607), 12% (n = 198) developed progression at a median follow-up of 10 years, of which 72% (n = 142) had undergone AM. Treatment received, age (65–69 vs. 50–64 years), PSA, ISUP grade at diagnosis, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs. 3.0 mm), aggregate length of tumour (median 8.0 vs. 4.0 mm), and presence of perineural invasion were each associated with increased risk of disease progression (p < 0.001 for each). However, these factors could not reliably predict progression in individuals. Notably, 53% (n = 105) of patients who progressed had biopsy ISUP grade 1 disease, although,

conversely, none of the participants who received RP and subsequently progressed had pathological ISUP grade 1 tumours. This discrepancy in progression and metastases rate between the AM arm of the ProtecT-study and comparable AS protocols can, most likely, be explained by inadequate sampling by PSA testing and 10-core TRUS-guided biopsies and differences in intensity of surveillance.

It is important to note that the AM arm in ProtecT represented an intermediate approach between contemporary AS protocols and WW in terms of a monitoring strategy based almost entirely on PSA measurements alone; there was no use of MRI scan, either at recruitment or during the monitoring period, nor were there any protocol-mandated repeat prostate biopsies at regular intervals. In addition, approximately 40% of randomised patients had intermediate-risk disease. Nevertheless, the ProtecT study has reinforced the role of deferred active treatment (i.e., either AS or some form of initial AM) as a feasible alternative to active curative interventions in patients with low-grade and low-stage disease. Beyond 10 years, no RCT-data is available, as yet, although AS is likely to give more reassurance especially in younger men, based on more accurate risk stratification at recruitment and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must continuously be evaluated before considering any active treatment in low-risk patients and in those with up to 10 years' individual life expectancy [486].

Table 6.1.2: Active surveillance in screening-detected prostate cancer
(large cohorts with longer-term follow-up)

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [487]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [488]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [489]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [490]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [491]	278	41	-	89	100
Godtman, *et al.* 2013 [492]	439	72	-	81	99.5
Klotz, *et al.* 2015 [493]	993	77	-	85	98.1
Tosoian, *et al.* 2020 [494]	1,818	60	-	93	99.9
Carlsson, *et al.* 2020 [495]	2,664	52	-	94	100
Total	**7,557-8,024**	**50.8**	**-**	**92**	**99.6**

* Patients receiving active therapy following initial active surveillance.
CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported;
OS = overall survival; RP = radical prostatectomy.

6.1.1.2   Watchful Waiting
Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment from the outset, and patients are clinically 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms in order to maintain QoL.

There are two RCTs and one Cochrane review comparing the outcomes of WW to RP. The SPCG-4 study was a RCT from the pre-PSA era, randomising patients to either WW or RP [496]. The study found RP to provide superior CSS, OS and PFS compared to WW at a median follow-up of 23.6 years (range 3 weeks–28 years). However, the benefit in favour of RP over WW was only apparent after 10 years. The PIVOT trial, a RCT conducted in the early PSA era, made a similar comparison between RP vs. WW in 731 men (50% with non-palpable disease) but in contrast to the SPCG-4, it found little, to no, benefit of RP (cumulative incidence of all-cause death, RP vs. observation: 68% vs. 73%; RR: 0.92, 95% CI: 0.84–1.01) within a median follow-up period of 18.6 years (interquartile range, 16.6 to 20 years) [497]. Exploratory subgroup analysis showed that the borderline benefit from RP was most marked for intermediate-risk disease (RR: 0.84, 95% CI: 0.73–0.98) but there was no benefit in patients with low- or high-risk disease. Overall, no adverse effects on health-related QoL (HRQoL) and psychological well-being was apparent in the first 5 years [498]. However, one of the criticisms of the PIVOT trial is the relatively high overall mortality rate in the WW group compared with more contemporary series. A Cochrane review performed a pooled analysis of RCTs comparing RP vs. WW [499]. Three studies were included; the previously mentioned SPCG-4 [496] and PIVOT [497] and the Veteran's Administration Cooperative Urological Research Group (VACURG) study which was conducted in the pre-PSA era [500]. The authors found that RP compared with WW reduced time to death by any cause (HR: 0.79, 95% CI: 0.70–0.90), time to death by PCa (HR: 0.57, 95% CI: 0.44–0.73) and time to metastatic

progression (HR: 0.56, 95% CI: 0.46–0.70) at 29 years' follow-up. However, RP was associated with higher rates of urinary incontinence (RR: 3.97, 95% CI: 2.34–6.74) and erectile dysfunction (ED) (RR: 2.67, 95% CI: 1.63–4.38).

The overall evidence indicates that for men with asymptomatic, clinically localised PCa, and with a life expectancy of < 10 years based on co-morbidities and/or age, the oncological advantages of active treatment over WW are unlikely to be relevant to them. Consequently, WW should be adopted for such patients. For assistance in estimating life expectancy and health status see Section 5.4.

6.1.2 *Radical prostatectomy*
6.1.2.1 *Introduction*
The goal of RP by any approach is the eradication of cancer while, whenever possible, preserving pelvic organ function [501]. The procedure involves removing the entire prostate with its capsule intact and SVs, followed by vesico-urethral anastomosis. Surgical approaches have expanded from perineal and retropubic open approaches to laparoscopic and robotic-assisted techniques; anastomoses have evolved from Vest approximation sutures to continuous suture watertight anastomoses under direct vision and mapping of the anatomy of the dorsal venous complex (DVC) and cavernous nerves has led to excellent visualisation and potential for preservation of erectile function [502]. The main results from multi-centre RCTs involving RP are summarised in Table 6.1.3.

Table 6.1.3: Oncological results of radical prostatectomy in organ-confined disease in RCTs

Study	Acronym	Population	Treatment period	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [496]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [503]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk and intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2016 [485]	ProtecT	Screened population	1999-2009	120	Mainly low- and intermediate-risk	99 (at 10 yr.)

CSS = cancer-specific survival; FU = follow-up; mo = months; PSA = prostate-specific antigen; yr. = year.

6.1.2.2 *Pre-operative preparation*
6.1.2.2.1 Pre-operative patient education
As before any surgery appropriate education and patient consent is mandatory prior to RP. Peri-operative education has been shown to improve long-term patient satisfaction following RP [504]. Augmentation of standard verbal and written educational materials such as use of interactive multimedia tools [505, 506] and pre-operative patient-specific 3D printed prostate models has been shown to improve patient understanding and satisfaction and should be considered to optimise patient-centred care [507].

6.1.2.2.2 Pre-operative pelvic floor exercises
Although many patients who have undergone RP will experience a return to urinary continence [508], temporary urinary incontinence is common early after surgery, reducing QoL. Pre-operative pelvic floor exercises (PFE) with, or without, biofeedback have been used with the aim of reducing this early post-operative incontinence. A systematic review and meta-analysis of the effect of pre-RP PFE on post-operative urinary incontinence showed a significant improvement in incontinence rates at 3 months post-operatively with an OR of 0.64 (p = 0.005), but not at 1 month or 6 months [509]. Pre-operative PFE may therefore provide some benefit, however the analysis was hampered by the variety of PFE regimens and a lack of consensus on the definition of incontinence.

6.1.2.2.3 Prophylactic antibiotics
Prophylactic antibiotics should be used; however, no high-level evidence is available to recommend specific prophylactic antibiotics prior to RP (See EAU Urological Infections Guidelines [510]). In addition, as the susceptibility of bacterial pathogens and antibiotic availability varies worldwide, any use of prophylactic antibiotics should adhere to local guidelines.

6.1.2.2.4 Neoadjuvant androgen deprivation therapy
Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of these using a 3-month period.

The main findings were summarised in a 2006 Cochrane review [511]. Neoadjuvant ADT is associated with a decreased rate of pT3 (downstaging), decreased positive margins, and a lower incidence of positive LNs. These benefits are greater with increased treatment duration (up to 8 months). However, since neither the PSA relapse-free survival nor CSS were shown to improve, neoadjuvant ADT should not be considered as standard clinical practice. These findings were supported by a 2021 systematic review and meta-analysis [512]

One recent RCT compared neoadjuvant luteinising hormone-releasing hormone (LHRH) alone vs. LHRH plus abiraterone acetate plus prednisone (AAP) prior to RP in 65 localised high-risk PCa patients [513]. Patients in the combination arm were found to have both significantly lower tumour volume and significantly lower BCR at > 4 years follow-up (p = 0.0014). A pooled analysis of 3 RCTs, including 117 patients and assessing the impact of intense neoadjuvant deprivation therapy has reported a complete pathological response rate of 9.4%, with improved BCR outcomes in complete responders [514]. Further supportive evidence is required before recommending combination neoadjuvant therapy including abiraterone prior to RP. Another RCT (CALGB 90203), comparing RP alone to RP with neoadjuvant chemo-hormonal therapy (CHT) including docetaxel for clinically high-risk localised PCa did not meet the study's primary endpoint of biochemical PFS at 3 years post-operatively, due to contamination with early salvage RT (SRT). As a result, CHT is not currently recommended unless longer-term data show a survival benefit using clinical endpoints [515].

6.1.2.2.5   Timing of radical prostatectomy
The effect of the COVID-19 pandemic on healthcare prompted a systematic review of whether delayed surgery for intermediate and high-risk localised PCa affected oncological outcomes [516]. Evidence in the 19 studies included was hampered by variation in definitions of delay from diagnosis to surgery, but oncological outcomes, including adverse pathology, BCR, additional treatment and survival, were no worse with delays of up to 3 months. Heterogeneity of data prevented any meaningful analysis of delays beyond 3 months.

6.1.2.3   Surgical techniques
Prostatectomy can be performed by open-, laparoscopic- or robot-assisted (RARP) approaches. The initial open technique of RP described by Young in 1904 was via the perineum [502] but suffered from a lack of access to pelvic LNs. If lymphadenectomy is required during perineal RP it must be done via a separate open retropubic (RRP) or laparoscopic approach. The open retropubic approach was popularised by Walsh in 1982 following his anatomical description of the DVC, enabling its early control, and of the cavernous nerves, permitting a bilateral nerve-sparing procedure [517]. In 2002, RARP was introduced using the da Vinci Surgical System® by Binder [518]. This technology combined the minimally-invasive advantages of laparoscopic RP with improved surgeon ergonomics and greater technical ease of suture reconstruction of the vesicourethral anastomosis and has now become the preferred minimally-invasive approach when available.

In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss, but not earlier (12 weeks) functional or oncological outcomes compared to open RP [519]. An updated analysis with follow-up at 24 months did not reveal any significant differences in functional outcomes between the approaches [520]. Increased surgical experience has lowered the complication rates of RP and improved cancer cure [477-480]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, can improve cancer control with RP [521-523]. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [476, 498, 503, 524]. A 2016 systematic review and meta-analysis included two small RCTs comparing RARP vs. laparoscopic RP (LRP) [525]. The results suggested higher rates of return of erectile function (RR: 1.51, 95% CI: 1.19–1.92) and return to continence function (RR: 1.14, 95% CI: 1.04–1.24) in the RARP group. However, a Cochrane review comparing either RARP or LRP vs. open RP included two RCTs and found no significant differences between the comparisons for oncological-, urinary- and sexual function outcomes, although RARP and LRP both resulted in statistically significant improvements in duration of hospital stay and blood transfusion rates over open RP [526]. Therefore, no surgical approach can be recommended over another.

Outcome after prostatectomy has been shown to be dependent on both surgeon [527] as well as hospital volume [528]. Although various volume criteria have been set worldwide, the level of evidence is insufficient to pinpoint a specific lower volume limit.

6.1.2.3.1   Robotic anterior versus Retzius-sparing dissection
Robot-assisted RP has typically been performed via the anterior approach, first dropping the bladder to expose the space of Retzius. However, the posterior approach (Retzius-sparing [RS-RARP]) has been used to minimise injury to support structures surrounding the prostate.

Galfano *et al.*, first described RS-RARP in 2010 [529]. This approach commences dissection posteriorly at the pouch of Douglas, first dissecting the SVs and progressing caudally behind the prostate. All of the anterior support structures are avoided, giving rise to the hypothetical mechanism for improved early post-operative continence. RS-RARP thus offers the same potential advantage as the open perineal approach, but without disturbance of the perineal musculature.

Retzius-sparing-RARP has been recently investigated in RCTs leading to four systematic reviews and meta-analyses [530-532] including a 2020 Cochrane systematic review [533] and a large propensity score matched analysis [534]. The Cochrane review used the most rigorous methodology and analysed 5 RCTs with 502 patients. It found with moderate certainty that RS-RARP improved continence at 1 week post catheter removal compared to standard RARP (RR: 1.74). Continence may also be improved at 3 months post-operatively (RR: 1.33), but this was based on low-certainty data. Continence outcomes appeared to equalise by 12 months (RR: 1.01). These findings matched those of the other systematic reviews. However, a significant concern was that RS-RARP appears to increase the risk of positive margins (RR: 1.95) but this was also low-certainty evidence. A single-surgeon propensity score matched analysis of 1,863 patients reached the same conclusion as the systematic reviews regarding earlier return to continence but did not show data on margin status [534].

Based on these data, recommendations cannot be made for one technique over another. However, the trade-offs between the risks of a positive margin vs. earlier continence recovery should be discussed with prospective patients. Furthermore, no high-level evidence is available on high-risk disease with some concerns that RS-RARP may confer an increased positive margin rate based on pT3 results. In addition, RS-RARP may be more technically challenging in various scenarios such as anterior tumours, post-TURP, a grossly enlarged gland, or a bulky median lobe [535].

6.1.2.3.2   Pelvic lymph node dissection
A systematic review has demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [536]. Moreover, two RCTs have failed to show a benefit of an extended approach vs. a limited PLND on early oncologic outcomes [537, 538].

Extended PLND 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. With this template, 94% of patients are correctly staged [539] and as such, ePLND provides the most accurate information for staging and prognosis [536].

The individual risk of patients harbouring positive LNs can be estimated based on validated nomograms. The Briganti [400, 401], Partin and MSKCC nomograms [540] have shown similar diagnostic accuracy in predicting LN invasion [541-543]. However, these nomograms were developed in the pre-MRI setting based on systematic random biopsy.

An updated nomogram has been externally validated in men diagnosed based on MRI followed by MRI-targeted biopsy [401]. Using this nomogram, patients could be spared an ePLND if their risk of nodal involvement was less than 7%; which would result in missing only 1.5% of patients with nodal invasion [401, 403]. However, 70% of patients would still undergo an unnecessary ePLND as they would have no LN involvement [364]. This is problematic due to the risk of complications of PLND (see below) as well as the additional operative time required.

A 2021 systematic review and meta-analysis of 27 studies showed that PSMA PET had a significantly higher sensitivity (93% vs. 54%, p = 0.008) and NPV (96% vs. 83%, p = 0.044) for LN positivity in intermediate-risk vs. high-risk groups [544]. This suggests that, given a lack of survival benefit of PLND, it might be safely omitted in intermediate-risk patients whose staging PSMA PET is negative. However, only 1 of the 27 studies with only 42 patients had focused on intermediate-risk cancer, indicating a need for further data in this risk group. The authors conclude that PLND should still be performed in high-risk patients with *negative* PSMA PET, however this should also be balanced against the risk of morbidity of PLND (see Section 5.3.2.4). For patients with *positive* pelvic LNs on PSMA PET only, evidence is currently unavailable on the best treatment strategy.

6.1.2.3.2.1 Early complications of extended pelvic lymph node dissection
Extended PLND increases morbidity in the treatment of PCa [536]. Overall complication rates of 19.8% vs. 8.2% were noted for ePLND vs. limited PLND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event (AE). Other authors have reported lower complication rates [545]. Similar rates of lymphoceles have been observed in RALP series; however, in one subgroup analysis lymphoceles were more

common with the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [546, 547]. Briganti *et al.*, [548] also showed more complications after extended compared to limited PLND. Twenty percent of men suffer a complication of some sort after ePLND. Thromboembolic events occur in less than 1% of cases overall, but the RR of DVT and PE associated with PLND has been found to be 7.8 and 6.3, respectively [549] (See section 6.1.2.4.2)

6.1.2.3.2.2 Sentinel node biopsy analysis
The rationale for a sentinel node biopsy (SNB) is based on the concept that a sentinel node is the first to be involved by migrating tumour cells. Therefore, when this node is negative it is possible to avoid an ePLND [550]. Intraprostatic injections of indocyanine green (ICG) have been used to visualise prostate-related LNs for SNB. In a randomised comparison, Harke *et al*, found more cancer-containing LNs in men who underwent a PLND guided by ICG but no difference in BCR at 22.9-month follow-up [551]. A systematic review of 21 studies showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at ePLND [552]. However, this review was hampered by widespread heterogeneity of both definitions and how SNB is performed. This prompted the development of an expert consensus report to guide further research [550]. There currently remains insufficient evidence supporting SNB for nodal staging.

6.1.2.3.3   Prostatic anterior fat pad dissection and histologic analysis
Several multi-centre and large single-centre series have shown the presence of lymphoid tissue within the fat pad anterior to the endopelvic fascia; the prostatic anterior fat pad (PAFP) [553-559]. This lymphoid tissue is present in 5.5–10.6% of cases and contains metastatic PCa in up to 1.3% of intermediate- and high-risk patients.
When positive, the PAFP is often the only site of LN metastasis. The PAFP is therefore a rare but recognised route of spread of disease. Unlike PLND, there is no morbidity associated with removal of the PAFP. The PAFP is always removed at RP for exposure of the endopelvic fascia and should be sent for histologic analysis as per all removed tissue.

6.1.2.3.4   Management of the dorsal venous complex
Since the description of the anatomical open RP by Walsh and Donker in the 1980s, various methods of controlling bleeding from the DVC have been proposed to optimise visualisation [517]. In the open setting, blood loss and transfusion rates have been found to be significantly reduced when ligating the DVC prior to transection [560]. However, concerns have been raised regarding the effect of prior DVC ligation on apical margin positivity and continence recovery due to the proximity of the DVC to both the prostatic apex and the urethral sphincter muscle fibres. In the robotic-assisted laparoscopic technique, due to the increased pressure of pneumoperitoneum, whether prior DVC ligation was used or not, blood loss was not found to be significantly different in one study [561]. In another study, mean blood loss was significantly less with prior DVC ligation (184 vs. 176 mL, p = 0.033), however it is debatable whether this was clinically significant [562]. The positive apical margin rate was not different, however, the latter study showed earlier return to full continence at 5 months post-operatively in the no prior DVC ligation group (61% vs. 40%, p < 0.01).

Ligation of the DVC can be performed with standard suture or using a vascular stapler. One study found significantly reduced blood loss (494 mL vs. 288 mL) and improved apical margin status (13% vs. 2%) when using the stapler [563].
Given the relatively small differences in outcomes, the surgeon's choice to ligate prior to transection or not, or whether to use sutures or a stapler, will depend on their familiarity with the technique and the equipment available.

6.1.2.3.5   Nerve-sparing surgery
During prostatectomy, preservation of the neurovascular bundles (NVB) with parasympathetic nerve branches of the pelvic plexus can spare erectile function [564, 565].

Extra-, inter-, and intra-fascial dissection planes can be planned, with those closer to the prostate and performed bilaterally associated with superior (early) functional outcomes [566-569]. Furthermore, many different techniques are propagated such as retrograde approach after anterior release (vs. antegrade), and athermal and traction-free handling of bundles [570-572]. Nerve-sparing (NS) surgery may be performed using clips or low bipolar energy without clear benefit favouring one technique over another regarding functional outcomes [573].

A 2021 large retrospective study of high-risk patients also found that NS did not affect BCR, risk of metastasis, or of death [574]. Notably, clinical and pathological stage T3 and ISUP Grade 5 did not impact these oncological outcomes. However, as a retrospective study, it was subject to selection bias, whereby patients with unfavourable characteristics were more likely to have undergone non-nerve-sparing surgery.

A 2021 systematic review of 19 studies analysing the parameters used for 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. As with all nomograms, the question remains as to where to set the cut-off point [575].

A 2022 systematic review of 18 comparative studies (no RCTs) of NS vs. non-nerve-sparing RP showed a RR of side-specific positive margins of 1.5, but none of them included patients with high-risk PCa [576]. There was no effect seen of NS on BCR. However, follow-up was short and studies were subject to selection bias with mainly low-risk patients. For those patients with high-risk PCa, side-specific NS was avoided if disease was palpable or EPE was present on MRI. Indeed, a 2019 systematic review showed that MRI affected the decision to perform NS or not in 35% of cases without any negative impact on surgical margin rate [577] (See Section 5.3.1.2).

Although age and pre-operative function may remain the most important predictors for post-operative erectile function, NS has also been associated with improved continence outcomes and may therefore still be relevant for men with poor erectile function [578, 579]. The association with continence may be mainly due to the dissection technique used during NS surgery, and not due to the preservation of the NVB themselves [578].

In summary, the quality of data is not adequate to permit a strong recommendation in favour of NS or non-nerve-sparing, but pre-operative risk factors for side-specific EPE such as PSA, PSA density, clinical stage, ISUP grade, and PI-RADS score, EPE and capsule contact length on MRI, should be taken into account.

6.1.2.3.6   Lymph-node-positive patients during radical prostatectomy
Although no RCTs are available, data from prospective cohort studies comparing survival of pN+ patients (as defined following pathological examination after RP) support that RP may have a survival benefit over abandonment of RP in node-positive cases [580]. As a consequence there is no role for performing frozen section of suspicious LNs.

6.1.2.3.7   Removal of seminal vesicles
The more aggressive forms of PCa may spread directly into the SVs. For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen [581]. However, in some patients the tips of the SVs can be challenging to dissect free. Furthermore, the cavernous nerves run past the SV tips such that indiscriminate dissection of the SV tips could potentially lead to ED [582]. However, a RCT comparing nerve-sparing RP with and without a SV-sparing approach found no difference in margin status, PSA recurrence, continence or erectile function outcomes. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement.

6.1.2.3.8   Techniques of vesico-urethral anastomosis
Following prostate removal, the bladder neck is anastomosed to the membranous urethra. The objective is to create a precisely aligned, watertight, tension-free, and stricture-free anastomosis that preserves the integrity of the intrinsic sphincter mechanism. Several methods have been described, based on the direct or indirect approach, the type of suture (i.e. barbed vs. non-barbed/monofilament), and variation in suturing technique (e.g., continuous vs. interrupted, or single-needle vs. double-needle running suture). The direct vesico-urethral anastomosis, which involves the construction of a primary end-to-end inter-mucosal anastomosis of the bladder neck to the membranous urethra by using 6 interrupted sutures placed circumferentially, has become the standard method of reconstruction for open RP [583].

The development of laparoscopic- and robotic-assisted techniques to perform RP have facilitated the introduction of new suturing techniques for the anastomosis. A systematic review and meta-analysis compared unidirectional barbed suture vs. conventional non-barbed suture for vesico-urethral anastomosis during robotic-assisted laparoscopic prostatectomy (RALP) [584]. The review included 3 RCTs and found significantly reduced anastomosis time, operative time and posterior reconstruction time in favour of the unidirectional barbed suture technique, but there were no differences in post-operative leak rate, length of catheterisation and continence rate. However, no definitive conclusions could be drawn due to the relatively low quality of the data. In regard to suturing technique, a systematic review and meta-analysis compared continuous vs.

interrupted suturing for vesico-urethral anastomosis during RP [585]. The study included only one RCT with 60 patients [586]. Although the review found slight advantages for continuous suturing over interrupted suturing in terms of catheterisation time, anastomosis time and rate of extravasation, the overall quality of evidence was low and no clear recommendations were possible. A recent RCT [587] compared the technique of suturing using a single absorbable running suture vs. a double-needle single-knot running suture (i.e. Van Velthoven technique) in laparoscopic RP [588]. The study found slightly reduced anastomosis time with the single running suture technique, but anastomotic leak, stricture, and continence rates were similar.

Overall, although there are a variety of approaches, methods and techniques for performing the vesico-urethral anastomosis, no clear recommendations are possible due to the lack of high-certainty evidence. In practice, the chosen method should be based on surgeon experience and individual preference [583-588].

6.1.2.3.9   Bladder neck management
Bladder neck mucosal eversion
Some surgeons perform mucosal eversion of the bladder neck as its own step in open RP with the aim of securing a mucosa-to-mucosa vesico-urethral anastomosis and avoiding anastomotic stricture. Whilst bringing bladder and urethral mucosa together by the everted bladder mucosa covering the bladder muscle layer, this step may actually delay healing of the muscle layers. An alternative is to simply ensure bladder mucosa is included in the full thickness anastomotic sutures. A non-randomised study of 211 patients with and without bladder neck mucosal eversion showed no significant difference in anastomotic stricture rate [589]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [590], but it is also 2.2 higher in open RP than RARP [591].

Bladder neck preservation
Whilst the majority of urinary continence is maintained by the external urethral sphincter at the membranous urethra (see below), a minor component is contributed by the internal lissosphincter at the bladder neck [592]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. A RCT assessing continence recovery at 12 months and 4 years showed improved objective and subjective urinary continence in both the short- and long term without any adverse effect on oncological outcome [593]. These findings were confirmed by a systematic review [594]. However, concern remains regarding margin status for cancers located at the prostate base.

A systematic review addressing site-specific margin status found a mean base-specific positive margin rate of 4.9% with bladder neck preservation vs. only 1.9% without [592]. This study was inconclusive, but it would be sensible to exercise caution when considering bladder neck preservation if significant cancer is known to be at the prostate base. Bladder neck preservation should be performed routinely when the cancer is distant from the base. However, bladder neck preservation cannot be performed in the presence of a large median lobe or a previous TURP.

6.1.2.3.10   Urethral length preservation
The membranous urethra sits immediately distal to the prostatic apex and is chiefly responsible, along with its surrounding pelvic floor support structures, for urinary continence. It consists of the external rhabdosphincter which surrounds an inner layer of smooth muscle. Using pre-operative MRI, the length of membranous urethra has been shown to vary widely. Two systematic reviews and meta-analyses found that every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post-RP [595, 596]. 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 pre-operatively to facilitate counselling of patients on their relative likelihood of early post-operative continence.

6.1.2.3.11   Cystography prior to catheter removal
Cystography may be used prior to catheter removal to check for a substantial anastomotic leak. If such a leak is found, catheter removal may then be deferred to allow further healing and sealing of the anastomosis. However, small comparative studies suggest that a cystogram to assess anastomotic leakage is not indicated as SOC before catheter removal 8 to 10 days after surgery [597]. If a cystogram is used, men with LUTS, large prostates, previous TURP or bladder neck reconstruction, may benefit as these factors have been associated with leakage [598, 599]. Contrast-enhanced transrectal US is an alternative [600].

6.1.2.3.12   Urinary catheter
A urinary catheter is routinely placed during RP to enable bladder rest and drainage of urine while the vesicourethral anastomosis heals. Compared to a traditional catheter duration of around 1 week, some centres remove the transurethral catheter early (post-operative day 2–3), usually after thorough anastomosis with

posterior reconstruction or in patients selected peri-operatively on the basis of anastomosis quality [601-604]. No higher complication rates were found. Although shorter catheterisation has been associated with more favourable short-term functional outcomes, no differences in long-term function were found [605]. One RCT has shown no difference in rate of UTI following indwelling catheter (IDC) removal whether prophylactic ciprofloxacin was given prior to IDC removal or not, suggesting antibiotics should not be given at catheter removal [606].

As an alternative to transurethral catheterisation, suprapubic catheter insertion during RP has been suggested. Some reports suggest less bother regarding post-operative hygiene and pain [607-611], while others did not find any differences [612, 613]. No impact on long-term functional outcomes were seen.

6.1.2.3.13 Use of a pelvic drain
A pelvic drain has traditionally been used in RP for potential drainage of urine leaking from the vesico-urethral anastomosis, blood, or lymphatic fluid when a PLND has been performed. Two RCTs in the robotic-assisted laparoscopic setting have been performed [614, 615]. Patients with urine leak at intra-operative anastomosis watertight testing were excluded. Both trials showed non-inferiority in complication rates when no drain was used. When the anastomosis is found to be watertight intra-operatively, it is reasonable to avoid inserting a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

6.1.2.4 Acute and chronic complications of radical protatectomy
Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [616-620], and can be compared with contemporaneous reports after RRP [621]. A prospective controlled non-RCT of patients undergoing RP in 14 centres using RALP or RRP showed that 12 months after RALP, 21.3% of patients were incontinent, as were 20.2% after RRP (adjusted OR: 1.08, 95% CI: 0.87–1.34) [622]. Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66–0.98) [622].

A systematic review and meta-analysis of unplanned hospital visits and re-admissions post-RP analysed 60 studies with over 400,000 patients over a 20-year period up to 2020. It found an emergency room visit rate of 12% and a hospital re-admission rate of 4% at 30 days post-operatively [623].

A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at 2 years [519]. Urinary function scores did not differ significantly between RRP vs. RALP at 6 and 12 weeks post-surgery (74–50 vs. 71–10, p = 0.09; 83–80 vs. 82–50, p = 0.48), with comparable outcomes for sexual function scores (30–70 vs. 32–70, p = 0.45; 35–00 vs. 38–90, p = 0.18). In the RRP group 14 (9%) patients had post-operative complications vs. 6 (4%) in the RALP group. The intra- and peri-operative complications of RRP and RALP are listed in Table 6.1.4. Table 6.1.5 lists the Clavien-Dindo definition of surgical complications. The early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation remains controversial resulting in a lack of clear recommendations (see Section 8.3.2.1).

Table 6.1.4: Intra-and peri-operative complications of retropubic RP, laparoscopic RP and RALP
          (Adapted from [555])

Predicted probability of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep-vein thrombosis	0.6	0.2	1.4
Predicted rates of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Clavien-Dindo I	2.1	4.1	4.2
Clavien-Dindo II	3.9	7.2	17.5
Clavien-Dindo IIIa	0.5	2.3	1.8
Clavien-Dindo IIIb	0.9	3.6	2.5
Clavien-Dindo IVa	0.6	0.8	2.1
Clavien-Dindo V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

Table 6.1.5: Clavien-Dindo grading of surgical complications [624]

Grade	Definition
I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g., antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
IIIa	Complications requiring surgical, endoscopic or radiological intervention - intervention not under general anaesthetic
IIIb	Complications requiring surgical, endoscopic or radiological intervention - intervention under general anaesthetic
IVa	Life-threatening complications; this includes CNS complications (e.g., brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) - single-organ dysfunction (including dialysis)
IVb	Life-threatening complications; this includes CNS complications (e.g., brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) - multi-organ dysfunction
V	Death of the patient

6.1.2.4.1 Effect of anterior and posterior reconstruction on continence

Preservation of integrity of the external urethral sphincter is critical for continence post-RP. Less clear is the effect of reconstruction of surrounding support structures to return to continence. Several small RCTs have been conducted, however, pooling analyses is hampered by variation in the definitions of incontinence and surgical approach, such as open vs. robotic and intra-peritoneal vs. extra-peritoneal. In addition, techniques used to perform both anterior suspension or reconstruction and posterior reconstruction are varied. For example, anterior suspension is performed either through periosteum of the pubis or the combination of ligated DVC and puboprostatic ligaments (PPL). Posterior reconstruction from rhabdosphincter is described to either Denonvilliers fascia posterior to bladder or to posterior bladder wall itself.

Two trials assessing posterior reconstruction in RALRP found no significant improvement in return to continence [625, 626]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to 1 pad per day (median 18 vs. 30 days, p = 0.024) [627]. When combining both anterior and posterior reconstruction, where for anterior reconstruction the PPL were sutured to the anterior bladder neck, another RCT found no improvement compared to a standard anastomosis with no reconstruction [628].

Four RCTs including anterior suspension have also shown conflicting results. Anterior suspension alone through the pubic periosteum, in the setting of extra-peritoneal RALRP, showed no advantage [629]. However, when combined with posterior reconstruction in RRP, one RCT showed significant improvement in return to continence at one month (7.1% vs. 26.5%, p = 0.047) and 3 months (15.4% vs. 45.2%, p = 0.016), but not at 6 months (57.9% vs. 65.4%, p = 0.609) [630]. Another anterior plus posterior reconstruction RCT using the Advanced Reconstruction of VesicoUrethral Support (ARVUS) technique and the strict definition of continence of 'no pads', showed statistically significant improvement in continence at 2 weeks (43.8% vs. 11.8%), 4 weeks (62.5% vs. 14.7%), 8 weeks (68.8% vs. 20.6%), 6 months (75% vs. 44.1%) and 12 months (86.7% vs. 61.3%), when compared to standard posterior Rocco reconstruction [631]. Anterior suspension alone through the DVC and PPL combined without posterior construction in the setting of RRP has shown improvement in continence at one month (20% vs. 53%, p = 0.029), 3 months (47% vs. 73%, p = 0.034) and 6 months (83% vs. 100%, p = 0.02), but not at 12 months (97% vs. 100%, p = 0.313) [632]. Together, these results suggest a possible earlier return to continence, but no long-term difference.

As there is conflicting evidence on the effect of anterior and/or posterior reconstruction on return to continence post-RP, no recommendations can be made. However, no studies showed an increase in adverse oncologic outcome or complications with reconstruction.

6.1.2.4.2 Deep venous thrombosis prophylaxis

For EAU Guidelines recommendations on post-RP deep venous thrombosis prophylaxis, please see the Thromboprophylaxis Guidelines Section 3.1.6 [633]. However, these recommendations should be adapted based on national recommendations, when available.

6.1.3 **Radiotherapy**

Intensity-modulated RT (IMRT) or volumetric arc radiation therapy (VMAT) with image-guided RT (IGRT) is currently widely recognised as the standard treatment approach for EBRT.

6.1.3.1 *External beam radiation therapy*

6.1.3.1.1 Technical aspects

Intensity-modulated RT and VMAT employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. Viani *et al*., show significantly reduced acute and late grade ≥ 2 genito-urinary (GU) and gastro-intestinal (GI) toxicity in favour of IMRT, while BCR-free rates did not differ significantly when comparing IMRT with three-dimensional conformal radiation therapy (3D-CRT) in a RCT comprising 215 patients [634]. A meta-analysis by Yu *et al.*, (23 studies, 9,556 patients) concluded that IMRT significantly decreases the occurrence of grade 2–4 acute GI toxicity, late GI toxicity and late rectal bleeding, and achieves better PSA relapse-free survival in comparison with 3D-CRT. Intensity-modulated EBRT and 3D-CRT show comparable acute rectal toxicity, late GU toxicity and OS, while IMRT slightly increases the morbidity of acute GU toxicity [635]. Zapatero *et al*., found, based on 733 consecutive patients (295 IMRT vs. 438 3D-CRT), that compared with 3D-CRT, high-dose IMRT/IGRT is associated with a lower rate of late urinary complications despite a higher radiation dose [636]. In conclusion, IMRT plus IGRT remain the SOC for the treatment of PCa.

The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes in total. Both techniques allow for a more complex distribution of the dose to be delivered and provide concave isodose curves, which are particularly useful as a means of sparing the rectum. Radiotherapy treatment planning for IMRT and VMAT differs from that used in conventional EBRT, requiring a computer system capable of 'inverse planning' and the appropriate physics expertise. Treatment plans must conform to pre-specified dose constraints to critical organs at risk of normal tissue damage and a formal quality assurance process should be routine.

With dose escalation using IMRT/VMAT, organ movement becomes a critical issue in terms of both tumour control and treatment toxicity. Techniques will therefore combine IMRT/VMAT with some form of IGRT (usually gold marker or cone-beam CT), in which organ movement can be visualised and corrected for in real time, although the optimum means (number of applications per week) of achieving this is still unclear [637, 638]. Tomotherapy is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

While image-guided radiotherapy (IGRT) for PCa has resulted in lower rates of toxicity, the use of MR-guided adapted RT is still investigational [639]. Planning studies confirm that MR-based adaptive RT significantly reduces doses to organs at risk (OAR) and this should translate into a meaningful clinical benefit in due course [640]. Although the rates of acute GI- and GU toxicity appear low, mostly on the basis of patients treated with stereotactic RT [641], follow-up is too short for definitive conclusions [639]. Of interest, in one series, 36% of patients treated with SBRT needed a catheter insertion for acute grade 2 urinary retention [642]. Above that, the daily fraction time of up to 45 minutes [639, 641], the heavy MR-workflow and the limited field size (rendering most pelvic fields too large) make its implementation not yet a routine [639]. Results of prospective RCTs such as the MIRAGE trial (CT-guided Stereotactic Body Radiation Therapy and MRI-guided Stereotactic Body Radiation Therapy for Prostate Cancer) will have to be awaited [643].

6.1.3.1.2 Dose escalation

Local control is a critical issue for the outcome of RT of PCa. It has been shown that local failure due to insufficient total dose is prognostic for death from PCa as a second wave of metastases is seen 5 to 10 years later on [644]. Several RCTs have shown that dose escalation (range 74–80 Gy) has a significant impact on 10-year biochemical relapse as well as metastases and disease-specific mortality [645-652]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant HT has varied (see Table 6.1.6). The best evidence of an OS benefit in patients with intermediate- or high-risk PCa, but not with low-risk PCa, derives from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database by Kalbasi *et al*., including a total of 42,481 patients [653]. The concept of a focal boost to the dominant intraprostatic lesion visible on MRI has been successfully validated in a RCT of 571 intermediate- and high-risk patients [654]. Patients were randomised between 77 Gy in 35 fractions of 2.2 Gy and the same dose plus a focal boost up to 18 Gy. Additional ADT was given to 65% of patients in both arms. However, the duration of the ADT was not reported. With a median follow-up of 72 months there was a moderate improvement of biochemical PFS (primary endpoint). In addition, focal boosting decreased local failure (HR: 0.33) and increased the rate of regional + distant MFS (HR: 0.58) [655]. No significant difference

for late GU- or GI toxicity grade ≥ 2 (23% and 12% vs. 28% and 13%) was documented. For grade ≥ 3 GU-toxicity these numbers were 3.5% and 5.6% ($p > 0.05$). However, longer follow-up is needed to assess late GU-toxicity [655]. Of note, there was a clear decrease in biochemical failure with increasing boost dose, individually given up to 18 Gy. If IMRT/VMAT and IGRT are used for dose escalation, rates of severe late side effects (> grade 3) for the rectum are 2–4% and for the GU tract 2–6% [647, 654]. These data do not apply to focal boost therapy.

Table 6.1.6: Randomised trials of dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
MD Anderson study 2011 [652]	301	T1-T3, N0, M0, PSA $\leq$ 10 ng/mL PSA 10-20 ng/mL PSA > 20 ng/mL	70 vs.78 Gy	15 yr.	DM, DSM, FFF	All patients: 18.9% FFF at 70 Gy 12% FFF at 78 Gy ($p = 0.042$) 3.4% DM at 70 Gy 1.1% DM at 78 Gy ($p = 0.018$) 6.2% DSM at 70 Gy 3.2% DSM at 78 Gy ($p = 0.043$) No difference in OS ($p > 0.05$)
PROG 95-09 2010 [646]	393	T1b-T2b PSA $\leq$ 15 ng/mL 75% low-risk pts. Low-risk: T1-2a, PSA < 10 mg/mL, GS $\leq$ 6 Interm-risk: PSA 10-15 ng/mL or GS 7 or T2b High-risk: GS 8-10	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	8.9 yr.	10-yr. ASTRO BCF	All patients: 32% BF at 70.2 Gy 17% BF at 79.2 Gy ($p < 0.0001$) Low-risk patients: 28% BF at 70.2 Gy 7% BF at 79.2 Gy ($p < 0.0001$)
MRC RT01 2014 [651]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	10 yr.	BFS, OS	43% BFS at 64 Gy 55% BFS at 74 Gy ($p = 0.0003$) 71% OS both groups ($p = 0.96$)
Dutch randomised phase III trial 2014 [650]	664	T1b-T4 143 pts. with (neo) adjuvant HT	68 vs. 78 Gy	110 mo.	Freedom biochemical (Phoenix) and/or clinical failure at 10 yr.	43% FFF at 68 Gy 49% FFF at 78 Gy ($p = 0.045$)
GETUG 06 2011 [649]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	61 mo.	BCF (ASTRO)	39% BF at 70 Gy 28% BF at 80 Gy
RTOG 0126 2018 [645]	1,532	T1b-T2b ISUP grade 1 + PSA 10-20 ng/mL or ISUP grade 2/3 + PSA < 15 ng/mL	70.2 vs. 79.2 Gy	100 mo.	OS, DM, BCF (ASTRO)	75% OS at 70.2 Gy 76% OS at 79.2 Gy 6% DM at 70.2 Gy 4% DM at 79.2 Gy ($p = 0.05$) 47% BCF at 70.2 Gy 31% BCF at 79.2 Gy ($p < 0.001$; Phoenix, $p < 0.001$)

| FLAME Trial [654, 655] | 571 | EAU risk classification: Intermediate risk (15%) High risk (84%) | 77 Gy (35 fx. 2.2 Gy) vs. 77 Gy (35 Fx.) + focal boost (up to 18 Gy) ADT (65% both arms – duration unknown) | 72 mo. (median) | BFS (5 yr.) DSM (5 yr.) | BFS: 92% at 77 Gy + boost 85% at 77 Gy (p < 0.001, HR: 0.45) DSM: p = 0.49 Focal boost in favour of: Local control (HR: 0.33) Distant MFS (HR: 0.58) |

BF = biochemical failure; BFS = biochemical progression-free survival; DM = distant metastases; DSM = disease specific mortality; FFF = freedom from biochemical or clinical failure; HT = hormone therapy; MFS = metastasis-free survival; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; yr. = year.

6.1.3.1.3   Hypofractionation

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue and slowly proliferating cells are very sensitive to an increased dose per fraction [656]. A meta-analysis of 25 studies including > 14,000 patients concluded that since PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8–2 Gy [657]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at lower cost.

Moderate HFX is defined as RT with 2.5–3.4 Gy/fx. Several studies report on moderate HFX applied in various techniques also including HT in part [658-665]. A systematic review concluded that studies on moderate HFX (2.5–3.4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy but long-term efficacy data are still lacking [664]. These results were confirmed by a recent Cochrane review on moderate HFX for clinically localised PCa [666]. Eleven studies were included (n = 8,278) with a median follow-up of 72 months showing little or no difference in PCa-specific survival (HR: 1.00). Based on 4 studies (n = 3,848), HFX probably makes little or no difference to late radiation GU toxicity (RR: 1.05) or GI toxicity (RR: 1.1), but this conclusion is based on relatively short follow-up, and 10 to 15-year data will be required to confirm these findings.

Moderate HFX should only be done by experienced teams using high-quality EBRT using IGRT and IMRT/ VMAT and published phase III protocols should be adhered to (Table 6.1.7).

Table 6.1.7: Major phase III randomised trials of moderate hypofractionation for primary treatment

Study/ Author	n	Risk, ISUP grade, or NCCN	ADT	RT Regimen	BED, Gy	Median FU, mo	Outcome
Lee, *et al.* 2016 [660]	550 542	low risk	None	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	**5 yr. DFS 86.3%** (n.s.) **5 yr. DFS 85.3%**
Dearnaley, *et al.* CHHiP 2016 [661]	1,077/19 fx 1,074/20 fx 1,065/37 fx	15% low 73% intermediate 12% high	3-6 mo. before and during EBRT	57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx	73.3 77.1 74	62	**5 yr. BCDF 85.9% (19 fx) 90.6% (20 fx) 88.3% (37 fx)**
De Vries, *et al.*, 2020 [667]	403 392	30% ISUP grade 1 45% ISUP grade 2-3, 25% ISUP grade 4-5	None	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	89	**8-yr. OS 80.8% vs. 77.6%** (p = 0.17) **8 yr. TF 24.4% vs. 26.3%**

| Catton, et al. 2017 [663] | 608 | intermediate risk 53% T1c 46% T2a-c | None | 60 Gy/20 fx | 77.1 | 72 | **5 yr. BCDF both arms 85%** HR: 0.96 (n.s) |
| | 598 | 9% ISUP grade 1 63% ISUP grade 2 28% ISUP grade 3 | | 78 Gy/39 fx | 78 | | |

ADT = androgen deprivation therapy; BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/ß of 1.5 Gy; DFS = disease-free survival; EBRT = external beam radiotherapy; FU = follow-up; fx = fractions; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo. = month; n = number of patients; NCCN = National Comprehensive Cancer Network; n.s. = not significant; TF = treatment failure; yr. = year.

Ultra-HFX has been defined as RT with > 3.4 Gy per fraction [665]. It requires IGRT and (ideally) stereotactic body RT (SBRT). Table 6.1.8 provides an overview of selected studies. Short-term biochemical control (5-years) is comparable to conventional fractionation. However, there are concerns about high-grade GU and rectal toxicity and full long-term side effects may not yet be known [664, 668]. In the HYPO-RT-PC randomised trial by Widmark *et al*., (n = 1,200), no difference in failure-free survival was seen for conventional or ultra-HFX but acute grade ≥ 2 GU toxicity was 23% vs. 28% (p = 0.057), favouring conventional fractionation. There were no significant differences in long-term toxicity [668]. A systematic review by Jackson *et al*., included 38 studies with 6,116 patients who received RT with < 10 fractions and ≥ 5 Gy per fraction. Five and 7-year biochemical recurrence-free survival (BRFS) rates were 95.3% and 93.7%, respectively, and estimated late grade ≥ 3 GU and GI toxicity rates were 2.0% and 1.1%, respectively [669]. The authors conclude that there is sufficient evidence to support SBRT as a standard treatment option for localised PCa, even though the median follow-up in this review was only 39 months and it included at least one trial (HYPO-RT-PC) which used 3D-CRT in 80% and IMRT/VMAT in the remainder for ultra-HFX. In their review on SBRT, Cushman *et al*., evaluated 14 trials, including 2,038 patients and concluded that despite a lack of long-term follow-up and the heterogeneity of the available evidence, prostate SBRT affords appropriate biochemical control with few high-grade toxicities [670]. In the Intensity-modulated fractionated RT vs. stereotactic body RT for PCa (PACE-B) trial, acute grade > 2 GU or GI toxicities did not differ significantly between conventional fractionation and ultra- HFX [671]. Adopting planning dose constraints to the penile bulb might minimise ED, especially in younger patients (Table 6.1.8) [672].

First results of a small (n = 30) randomised phase-II trial in intermediate-risk PCa of 'ultra-high single dose RT' (SDRT) with 24 Gy compared with an ultra HFX stereotactic body RT regime with 5x9 Gy, have been published recently [673].

Table 6.1.8: Selected trials on ultra-hypofractionation for intact localised PCa

Study	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark *et al.* 2019 HYPO-RT-PC [668]	1,200	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
Brand *et al.* 2019 PACE-B [671]	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 12% vs. 10%, p = 0.38 Grade ≥ 2 acute GU 27% vs. 23%, p = 0.16

FFS = failure-free survival; FU = follow-up; fx = number fractions; GI = gastro-intestinal toxicity; GU = genito-urinary toxicity; mo. = months; n = number of patients; TD = total dose; SBRT = stereotactic body radiotherapy; wk. = weeks; yr. = years.

6.1.3.1.4   Neoadjuvant or adjuvant hormone therapy plus radiotherapy
The combination of RT with LHRH ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [674-678] (Table 6.1.9). The main message is that for all intermediate-risk disease a short duration of 4-6 months is optimal while a longer one, around 3 years,

is needed for high-risk patients. The OS impact of adding short-term ADT for favourable intermediate-risk disease, however, remains a matter of debate [121].

Table 6.1.9: Selected studies of use and duration of ADT in combination with RT for PCa

Study	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [675]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65–70 Gy	**Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade 2-5**
RTOG 94-13 2007 [679]	T1c–4 N0–1 M0	1,292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	**No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)**
RTOG 86-10 2008 [676]	T2–4 N0–1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65–70 Gy RT	**No significant difference at 10 yr.**
D'Amico AV, *et al.* 2008 [677]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	**Significant benefit that may pertain only to men with no or minimal co-morbidity** (HR: 0.55, 95% CI: 0.34–0.90, p = 0.01)
RTOG 92-02 2008 [680]	T2c–4 N0–1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65–70 Gy	p = 0.73, p = 0.36 **overall; significant benefit** (p = 0.044) (p = 0.0061) **in subset with ISUP grade 4–5**
EORTC 22961 2009 [681]	T1c–2ab N1 M0, T2c–4 N0–1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70 Gy 3D-CRT	**Better result with 3 yr. treatment than with 6 mo.** (3.8% improvement in survival at 5 yr.)
EORTC 22863 2010 [674]	T1–2 poorly differentiated and M0, or T3–4 N0–1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70 Gy RT	**Significant benefit at 10 yr. for combined treatment** (HR: 0.60, 95% CI: 0.45–0.80, p = 0.0004).
TROG 96-01 2011 [678]	T2b–4 N0 M0	802	Neoadjuvant ADT Duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	**No significant difference in OS reported; benefit in PCa-specific survival** (HR: 0.56, 95% CI: 0.32–0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65–1.08, p = 0.18)
RTOG 99-10 2015 [682]	intermediate risk 94% T1–T2, 6% T3–4	1,579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk.	70.2 Gy 2D/3D	**67 vs. 68%,** p = 0.62, confirms 8 + 8 wk. LHRH as a standard

| PCSIII 2020 [683] | Intermediate risk | 600 | 76 Gy alone vs. 76 Gy + ADT vs. 70 Gy + ADT | LHRH + bicalutamide 6 mo. 4 mo. prior to RT | 70 vs. 76 Gy | **Significantly improved biochemical failure-free and PCa-specific survival for ADT arms, with no difference in OS.** |

ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiotherapy in standard fractionation; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; wk = week; yr. = year.

The question of the added value of EBRT combined with ADT has been clarified by 3 RCTs. All showed a clear benefit of adding EBRT to long-term ADT (Table 6.1.10).

Table 6.1.10: Selected studies of ADT in combination with, or without, RT for PCa

Study	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [684]	T1b–2 WHO Grade 1–3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. plus continuous flutamide	70 Gy 3D-CRT vs. no RT	34% (95% CI: 29–39%) vs. 17% (95% CI: 13–22% CSM at 12 (15) yr. favouring combined treatment (p < 0.0001 for 15-yr. results) NCIC CTG PR.3/MRC
PRO7/NCIC 2015 [685]	T3–4 (88%), PSA > 20 ng/mL (64%), ISUP grade 4–5 (36%) N0 M0	1,205	ADT ± EBRT	Continuous LHRH agonist	65–70 Gy 3D-CRT vs. no RT	10-yr. OS = 49% vs. 55% favouring combined treatment HR: 0.7, p < 0.001)
Sargos, *et al.* 2020 [686]	T3–4 N0 M0	273	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr. OS 71.4% vs. 71.5%

ADT = androgen deprivation therapy; CSM = cancer-specific mortality; EBRT = external beam radiotherapy; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy.

6.1.3.1.5   Combined dose-escalated radiotherapy and androgen-deprivation therapy
The combination of ADT with various forms of RT has been extensively studied, with extremely strong evidence for the use of such combined modality therapy in several settings. The MARCAP (Individual Patient Data Meta-Analysis of Randomized Trials in Cancer of the Prostate) consortium recently conducted a meta-analysis of trials using individual patient data (IPD), and a primary endpoint of MFS, a validated surrogate for OS. Trials were eligible if they studied the use or prolongation of ADT in patients receiving definitive RT, and included 12 trials with 10,853 patients. Median follow-up was over 11 years. The use of ADT was clearly associated with significant improvements in BCR, metastatic recurrence, MFS, and OS. The benefits of ADT were independent of RT dose, age, and risk groups comparing NCCN unfavourable intermediate-risk (see Sections 4.2 and 6.2.2.3), high-risk and locally-advanced disease. There were no demonstrable benefits from the extension of duration of neoadjuvant ADT [687].

Three RCTs have shown that the benefits of ADT are independent of dose escalation, and that the use of ADT would not compensate for a lower RT dose:
1.   The GICOR study shows a better biochemical DFS in high-risk patients for 3D-CRT radiation dose > 72 Gy when combined with long-term ADT [688].
2.   DART01/05 GICOR shows improved OS in high-risk patients after ten years if 2 years of adjuvant ADT is combined with high-dose RT [689].
3.   EORTC trial 22991 shows that 6 months ADT improves biochemical and clinical DFS irrespective of the dose (70, 74, 78 Gy) in intermediate-risk and low-volume high-risk localised PCa patients [690].

A meta-analysis based on IPD from two RCTs (RTOG 9413 and Ottawa 0101) has compared neoadjuvant/ concomitant vs. adjuvant ADT (without substratifying between favourable- and unfavourable intermediate-risk disease) in conjunction with prostate RT and reported superior PFS with adjuvant ADT, but the data heterogeneity means that this observation is hypothesis-generating only [691].

In addition, a Canadian two-arm dose-escalated (76 Gy) RCT compared neoadjuvant and concomitant with adjuvant short-term ADT in 432 patients with intermediate-risk PCa. After 10 years no significant difference in OS or RT-related grade ≥ 3 GI or GU toxicity was seen [692]. Therefore both regimen in combination with dose escalation are reasonable standards.

6.1.3.2   Proton beam therapy

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

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose but it cannot be used as evidence for the superiority of proton therapy [646]. Thus, unequivocal information showing an advantage of protons over IMRT photon therapy is still not available. Studies from the SEER database and from Harvard describing toxicity and patient-reported outcomes do not point to an inherent superiority of protons [693, 694]. In terms of longer-term GI toxicity, proton therapy might even be inferior to IMRT [694].

A RCT comparing equivalent doses of proton-beam therapy with IMRT is underway. Meanwhile, proton therapy must be regarded as an experimental alternative to photon-beam therapy.

6.1.3.3   Spacer during external beam radiation therapy

Biodegradable spacer insertion involves using a liquid gel or balloon to increase the distance between the prostate and rectum and consequently reduce the amount of radiation reaching the rectum. Various materials have been used with most evidence available for CE-marked hydrogel spacers [695]. A meta-analysis including one RCT and six cohort studies using the hydrogel spacer demonstrated a 5–8% reduction in the rectal volume receiving high-dose radiation, although heterogeneity between studies is found [696]. In the final analysis of the RCT with a median follow-up of 37 months and with approximately two-thirds of patients evaluable, those treated with spacer *in situ* had no deterioration from baseline bowel function whilst those treated without spacer had a lower mean bowel summary score of 5.8 points which met the threshold for a minimally important difference of 4–6 points [697].

This meta-analysis highlights inconsistent reporting of procedural complications. In addition, with more widespread clinical use safety reports describe uncommon, but severe and life changing, complications including prostatic abscess, fistulae and sepsis [698]. Implantation is associated with a learning curve and should only be undertaken by teams with experience of TRUS and transperineal procedures with robust audit reporting in place [699]. Its role in the context of moderate or extreme HFX is as yet unclear.

6.1.3.4   Brachytherapy
6.1.3.4.1   Low-dose rate brachytherapy

Low-dose rate (LDR) brachytherapy uses radioactive seeds permanently implanted into the prostate. In patients declining or unsuitable for AS LDR monotherapy [700] can be offered to those with low-risk or NCCN favourable intermediate-risk (see Section 4.2) and good urinary function defined as an International Prostatic Symptom Score (IPSS) < 12 and maximum flow rate > 15 mL/min on urinary flow tests [701]. In addition, with due attention to dose distribution, patients having had a previous TURP can undergo brachytherapy without an increase in risk of urinary toxicity. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the postero-lateral sides of the prostate and there should be at least a 3-month interval between TURP and brachytherapy to allow for adequate healing [702-705].

The only available RCT comparing RP and LDR brachytherapy as monotherapy was closed due to poor accrual [706]. Outcome data are available from a number of large population cohorts with mature follow-up [707-711]. The biochemical DFS for ISUP grade 1 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [707-711]. A significant correlation has been shown between the implanted dose and biochemical control [712]. A D90 (dose covering 90% of the prostate volume) of > 140 Gy leads to a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years (92 vs. 68%). There is no OS benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [713].

Low-dose rate brachytherapy can be combined with EBRT in NCCN unfavourable intermediate-risk PCa (see Section 4.2) and high-risk patients. External beam RT (total dose of 78 Gy) has been compared with EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy) in intermediate-risk and high-risk patients in the ASCENDE-RT randomised trial with 12 months of ADT in both arms [714]. The LDR boost resulted

in 5- and 7-year PSA PFS increase (89% and 86%, respectively, compared to 84% and 75%). This improvement was achieved at a cost of increased late grade 3+ GU toxicity (18% compared to 8%) [715]. Toxicity resulted mainly in the development of urethral strictures and incontinence and great care should be taken during treatment planning.

6.1.3.4.2   High-dose rate brachytherapy
High-dose rate (HDR) brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in Table 6.1.11. The use of the GEC (Groupe Europeen de Curietherapie)/ESTRO Guidelines is strongly recommended [716]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [717]. A systematic review of non-RCTs and data from population studies suggest outcomes with EBRT plus HDR brachytherapy are superior to EBRT alone [718, 719].

A single-centre RCT of EBRT (55 Gy in 20 fractions) vs. EBRT (35.75 Gy in 13 fractions), followed by HDR brachytherapy (17 Gy in two fractions over 24 hours) has been reported [720]. In 218 patients with T1–3 N0M0 PCa the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical disease-free rate (p = 0.04) at 5 and 10 years (75% and 46% compared to 61% and 39%). However, an unexpectedly high rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to a dose lower than the current standard used [720].

Supporting, but not definitive, evidence of the benefit of HDR boost is available from the TROG 03.04 RADAR trial. This multi-centre study had upfront radiation dose escalation (non-randomised) with dosing options of 66, 70, or 74 Gy EBRT, or 46 Gy EBRT plus HDR brachytherapy boost and randomised men with locally-advanced PCa to 6 or 18 months ADT. After a minimum follow-up of 10 years HDR boost significantly reduced distant progression, the study primary endpoint (sub HR: 0.68, 95% CI: 0.57–0.80; p < 0.0001), when compared to EBRT alone and, independent of duration of ADT, HDR boost was associated with increased IPSS of 3 points at 18 months post-treatment resolving by 3 years but decreased rectal symptoms when compared to EBRT [721]. Although radiation dose escalation using brachytherapy boost provides much higher biological doses, the TROG 03.04 RADAR RCT and systematic reviews show ADT use independently predicts better outcomes regardless of radiation dose intensification [713, 721, 722]. Omitting ADT may result in inferior OS and based on current evidence ADT use and duration should be in line with that used when delivering EBRT alone.

Fractionated HDR brachytherapy as monotherapy can be offered to patients with low- and intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres. Five-year PSA control rates of 97.5% and 93.5% for low- and intermediate-risk PCa, respectively, are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [723]. Single fraction HDR monotherapy should not be used as it has inferior biochemical control rates compared to fractionated HDR monotherapy [724].

Table 6.1.11: Difference between LDR and HDR brachytherapy

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	• Permanent seeds implanted • Uses Iodine-125 (I-125) (most common), Palladium-103 (^{103}Pd-) or Cesium-131 isotopes • Radiation dose delivered over weeks and months • Acute side effects resolve over months • Radiation protection issues for patient and carers
High dose rate (HDR)	• Temporary implantation • Iridium-192 (IR-192) isotope introduced through implanted needles or catheters • Radiation dose delivered in minutes • Acute side effects resolve over weeks • No radiation protection issues for patient or carers

6.1.3.5   *Acute side effects of external beam radiotherapy and brachytherapy*
Gastro-intestinal and urinary side effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of grade 1, 20% of grade 2, and 2% grade 3. In the same trial, approximately 30% of patients reported acute grade 1 GI toxicity, 10% grade 2, and less than

1% grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [725]. In addition, general side effects such as fatigue are common. It should be noted that the incidence of acute side effects is greater than that of late effects (see Section 8.2.2.1), implying that most acute effects resolve. In a RCT of conventional dose EBRT vs. EBRT and LDR brachytherapy the incidence of acute proctitis was reduced in the brachytherapy arm, but other acute toxicities were equivalent [714]. Acute toxicity of HDR brachytherapy has not been documented in a RCT, but retrospective reports confirm lower rates of GI toxicity compared with EBRT alone and grade 3 GU toxicity in 10%, or fewer, patients, but a higher incidence of urinary retention [726]. Similar findings are reported using HFX; in a pooled analysis of 864 patients treated using extreme HFX and stereotactic RT, declines in urinary and bowel domains were noted at 3 months which returned to baseline, or better, by 6 months [727].

6.1.4 *Hormonal therapy*
6.1.4.1 *Introduction*
6.1.4.1.1 Different types of hormonal therapy
Androgen deprivation can be achieved by suppressing the secretion of testicular androgens in different ways. This can be combined with inhibiting the action of circulating androgens at the level of their receptor which has been known as complete (or maximal or total) androgen blockade (CAB) using the old-fashioned antiandrogens [728].

6.1.4.1.1.1 Testosterone-lowering therapy (castration)
6.1.4.1.1.1.1 Castration level
The castration level of testosterone is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15 ng/dL [729]. Therefore, a more appropriate level should be defined as < 20 ng/dL (< 0.7 nmol/L). This definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [730-732]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still the historical < 50 ng/dL (1.7 nmol/L).

6.1.4.1.1.1.2 Bilateral orchiectomy
Bilateral orchiectomy or subcapsular pulpectomy is still considered the primary treatment modality for ADT. It is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia, and it is the quickest way to achieve a castration level which is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment [733].

6.1.4.1.1.1.3 Oestrogens
Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [734]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses these drugs are not considered as standard first-line treatment [735, 736]. Oestrogen patches are under investigation [737].

6.1.4.1.1.1.4 Luteinising-hormone-releasing hormone agonists
Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon which starts two to three days after administration and lasts for about one week. This may lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [738]. Patients at risk are usually those with high-volume symptomatic bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare but does not completely remove the risk. Anti-androgen therapy is usually continued for 4 weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare up' is unknown [739].

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within 2 to 4 weeks [740]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [741]. So far, no survival difference between LHRH agonists and orchiectomy has been reported due to the lack of high-quality trials [742].

The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.1.4.1.1.1.5 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone-releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available. Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [740]. A phase III RCT compared degarelix to monthly leuprorelin following up patients for 12 months, suggesting a better PSA PFS for degarelix 240/80 mg compared to monthly leuprorelin [743]. A systematic review did not show a major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond 12 months as well as the lack of survival data [744]. Its definitive superiority over the LHRH analogues remains to be proven. Short-term follow-up data from a meta-analysis indicate that the use of LHRH antagonist is associated with significantly lower overall mortality and cardiovascular events as compared with agonists. On the other hand, other adverse effects such as decreased libido, hot flushes, ED, weight gain, and injection site reactions are seen less often with the agonists [745, 746].

Relugolix is an oral LHRH antagonist. It was compared to the LHRH agonist leuprolide in a randomised phase III trial [747]. The primary endpoint was sustained testosterone suppression to castrate levels through 48 weeks. There was a significant difference of 7.9 percentage points (95% CI: 4.1–11.8) showing non-inferiority and superiority of relugolix. The incidence of major adverse cardiovascular events was significantly lower with relugolix (prespecified safety analysis). Relugolix has been approved by the FDA [748] and EMA [749] for hormone sensitive PCa.

6.1.4.1.1.1.6 Anti-androgens

These oral compounds are classified according to their chemical structure as:
- steroidal, e.g., cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g., nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal anti-androgens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

6.1.4.1.1.1.6.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side effects are secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side effects are cardiovascular toxicity (4–40% for CPA) and hepatotoxicity.

Cyproterone acetate was the first licensed anti-androgen but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31–41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT CPA showed a poorer OS when compared with LHRH analogues [750]. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in DSS and OS at a median follow-up of 8.6 years [751]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.1.4.1.1.1.6.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy with e.g., nilutamide, flutamide or bicalutamide does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [752]. Non-androgen-related pharmacological side effects differ between agents. Bicalutamide shows a more favourable safety and tolerability profile than flutamide and nilutamide [753]. The dosage licensed for use in CAB is 50 mg/day, and 150 mg/day for monotherapy. The non-steroidal anti-androgens pharmacological side effects are mainly gynaecomastia (70%) and breast pain (68%). However, non-steroidal anti-androgen monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [752, 754]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.1.4.1.1.2 New androgen receptor pathway inhibitors (ARPis)

Once on ADT the development of castration-resistance (CRPC) is only a matter of time. It is considered to be mediated through two main overlapping mechanisms: androgen-receptor (AR)-independent and AR-dependent mechanisms (see Section 6.5 - Castrate-resistant PCa). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells and an over-expression of the AR has been observed, suggesting an adaptive mechanism [755]. This has led to the development of several new compounds targeting the androgen

axis. In mCRPC, abirateron acetate and enzalutamide have been approved. In addition to ADT (sustained castration), abiraterone acetate, apalutamide and enzalutamide have been approved for the treatment of metastatic hormone sensitive PCa (mHSPC) by the FDA and the EMA. For the updated approval status see EMA and FDA websites [756-760]. Finally, apalutamide, darolutamide and enzalutamide have been approved for non-metastatic CRPC (nmCRPC) at high risk of further metastases [761-765].

6.1.4.1.1.2.1 Abiraterone acetate
Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-hydrolase and 17,20-lyase inhibition). By blocking CYP17, abiraterone acetate significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone to prevent drug-induced hyperaldosteronism [756, 759].

6.1.4.1.1.2.2 Apalutamide, darolutamide, enzalutamide (alphabetical order)
These agents are novel non-steroidal anti-androgens with a higher affinity for the AR receptor than bicalutamide. While previous non-steroidal anti-androgens still allow transfer of ARs to the nucleus and would act as partial agonists, all three agents also block AR transfer and therefore suppress any possible agonist-like activity [760-762]. Darolutamide has structurally unique properties [761]. In particular, in preclinical studies, it showed not to cross the blood-brain barrier [766, 767].

6.1.4.2 Non-hormonal non-cytotoxic drug treatments
6.1.4.2.1 PARP inhibitors
Poly (ADP-ribose) polymerase inhibitors (PARPi) block the enzyme poly ADP-ribose polymerase (PARP) and were developed aiming to selectively target cancer cells harbouring *BRCA* mutations and other mutations inducing homologous recombination deficiency and high level of replication pressure with a sensitivity to PARPi treatment. Due to the oncogenic loss of some DNA repair effectors and incomplete DNA repair repertoire, some cancer cells are addicted to certain DNA repair pathways such as Poly (ADP-ribose) polymerase (PARP)-related single-strand break repair pathway. The interaction between *BRCA* and PARP is a form of synthetic lethal effect which means the simultaneously functional loss of two genes leads to cell death, while a defect in any single gene only has a limited effect on cell viability [768]. The therapeutic indication for PCa is discussed in Section 6.5.8.1.

6.1.4.2.2 Immune checkpoint inhibitors
Checkpoint inhibitors target the molecules CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). For advanced PCa patients that are microsatellite instability-high/deficient mismatch repair (MSI-H/*dMMR*), the PD-1 inhibitor pembrolizumab has been approved by the FDA but not by the EMA. The label is tumour agnostic [769, 770]. See also Section 6.5.2.1

AKT inhibitors are small molecules which are designed to target and bind to all three isoforms of AKT, which is a key component of the PI3K/AKT pathway. In clinical trials, ipatasertib, an oral, highly specific, AKT inhibitor was used and showed significant activity when combined with abiraterone acetate in patients with loss of the tumour suppressor protein PTEN on immunohistochemistry within the tumour [771, 772]. Currently, there are no approved AKT inhibitors.

6.1.4.3 Radiopharmaceutical therapy
Radiopharmaceutical therapy (RPT) is based on the delivery of radioactive atoms to tumour-associated targets. The mechanism of action for RPT is radiation-induced killing of cells. Radionuclides with different emission properties are used to deliver radiation. The most commonly used radionuclides are represented by β-particles (e.g., ^{177}Lu) or α-particles (e.g., [223]Ra, [225]Ac). [177]Lu is increasingly used because of its optimal imaging range (100–200 keV), favourable half time (6.6 days) and appropriate β-particle energy for therapy. The short path of the α-particles (0.05–0.08 mm) results in minimal toxic effects in adjacent healthy tissue. These properties enable such radionuclides to be used as theranostics (i.e., the same radionuclide may be used for both diagnostic and therapeutic purposes). However an essential requirement prior to any RPT is to assess the targeting of the agent, mainly using PET techniques which show the tumour expression and the extent of cancer [773]. [177]Lu has been approved by the FDA for the treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy [774]. Clinical details are discussed in Section 6.5.6.

6.1.5 Investigational therapies
6.1.5.1 Background
Besides RP, EBRT and brachytherapy, other modalities have emerged as potential therapeutic options in patients with clinically localised PCa [775-777]. These new modalities have been developed as minimally-

invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity, and improved functional outcomes. In this section, both whole gland- and focal treatment [778, 779] will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy (PDT), as sufficient data are available to form the basis of some initial judgements. Other options such as radiofrequency ablation (RFA) and electroporation, among others, are considered to be in the early phases of evaluation [778].

6.1.5.2   Whole-gland therapies
6.1.5.2.1   Cryotherapy for whole-gland treatment
Cryotherapy uses freezing techniques to induce cell death by dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals and vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [775-777]. 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 mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryotherapy devices are mainly used. Since its inception, cryotherapy has been used for whole-gland treatment in PCa either as a primary or salvage treatment option.

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 recto-urethral fistula formation (0–6%) [780]. 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 non-comparative single-arm case series with short follow-up [780].

6.1.5.2.2   High-intensity focused ultrasound for whole-gland treatment
High-intensity focused US consists of focused US waves emitted from a transducer that cause tissue damage by mechanical and thermal effects as well as by cavitation [781]. The goal of HIFU is to heat malignant tissue above 65°C, so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anesthesia, with the patient lying in the lateral or supine position. High-intensity focused US has previously been widely used for whole-gland therapy with the following adverse effects: acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), recto-urethral fistula (0–5%) and urinary incontinence (10%) [780].

Since the ultrasound energy is most often delivered from the rectal cavity, HIFU faces challenges in delivering energy to the anterior part in large prostates.
Similar to cryosurgery, the lack of any long-term prospective comparative data on oncological outcomes, without significant reduction of side effects, prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [780].

6.1.5.3   Focal therapy for whole-gland treatment
During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness leading to the adoption of both formal and informal screening strategies. The effect of this has been that men are identified at an earlier stage with smaller tumours, with a greater propensity for unifocal disease potentially suitable for focal therapy [782-784]. There is also greater awareness of the risks of over-treatment leading to attempts to ablate only a region of the prostate containing the tumour thereby limiting toxicity by sparing the neurovascular bundles, sphincter and urethra [785-787]. Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU, PDT, irreversible electroporation (IRE), and focal RT.
Despite these therapies having less impact on urogenital function, AS should remain the primary option for patient with low-risk PCa.

A recent systematic review included data from 5,827 patients across 72 studies and covered different energy sources including HIFU, cryotherapy, PDT, laser interstitial thermotherapy, focal brachytherapy, IRE and radiofrequency ablation (RFA) [788]. The review favours HIFU and PDT for their higher quality data, over 95% of pad-free incontinence and 85–90% of patients without clinical significant cancer in short-term analysis.
This has to be critially analysed, because 45% of all patients with a focal approach included in this systematic review had an ISUP 1 cancer. The overall quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and retrospective in design, heterogeneity of definitions and approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review finds high-

quality evidence that focal therapy has favourable functional outcomes and minimises AEs, definitive proof of oncological effectiveness of focal therapy compared to standard treatments remains unavailable.

The currently largest analysis on oncologic outcomes following focal HIFU includes 625 patients, with 70% having ISUP 2/3 disease, followed for 5 years with an 88% failure-free survival (FFS), defined as the need for salvage treatment or systemic therapy [789]. In this study one repeated focal HIFU session was allowed and performed in 25% of all patients. Follow-up was driven by PSA and clinics, with re-biopsies performed only in 36% of patients after a significant PSA rise and suspicious MRI.

The guideline Panel acknowledges the challenges for interventional RCTs [790-792]. The interim analysis and meeting reports demonstrate slow recruitment, patients declining consent and rejecting their treatment allocation into the RP group.

Propensity-matched analysis using prospective multi-centre databases are available for comparison of focal therapy vs. radical therapy [793, 794]. Oncological follow-up data up to 8 years can be used to counsel patients in treatment decisions [793]. Patients were managed by focal therapy had a HIFU or cryotherapy, with one retreatment, if needed. 17.1% of patients in the focal arm received a retreatment. The primary outcome was FFS defined as "need for local or systemic salvage treatment or metastasis". Both groups included 246 patients with an average PSA of 7.9 ng/mL and 60% ISUP 2/3 cancers. The cancer core length was 5–6 mm with 45% having bilateral cancer. The authors report similar cancer control 8 years after therapy, with FFS and BCR of 83% and 23.9% for focal therapy vs. 79% and 24.8% for RP, respectively. Similar results were demonstrated in a cohort-based analysis with a follow-up of 6 years [794].

The use of different definitions for oncological failure in the two arms is a limitation of these studies. While any recurrence after RP was seen as failure, a second HIFU was permitted in the focal group. The current data from the HIFU Evaluation and Assessment of Treatment (HEAT) registry indicates that a repeat-HIFU does not significantely decrease urinary or erectile function [795]. However, this change of failure definition will have to be re-evaluated.

It is important to note, that these results were achieved in centres with a dedicated focal program where all patients had a mpMRI with targeted and systematic biopsies or full template mapping biopsies.

The prospective HEAT registry recently analysed over 800 men undergoing focal HIFU for localised PCa [795]. The functional data indicate low treatment-related toxicity with less than 4% decrease in pad-free incontinence and a reduction in IIEF of 0.4 points. The low percentage of side effects was also maintained if a second round of focal therapy was needed.

One comparative RCT was conducted in a very-low risk population, for which there is currently a strong movement away from any form of active treatment. This study was comparing padeliporfin-based vascular-targeted PDT vs. AS and found at a median follow-up of 24 months that less patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24–0.46), and needed less radical therapy (6% vs. 29%, p < 0.0001). Updated results were published in 2018 showing that these benefits were maintained after four years [796]. Nevertheless, limitations of the study include an unusually high observed rate of disease progression in the AS arm (58% in two years) and more patients in the AS arm chose to undergo radical therapy without a clinical indication which may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy or any MRI scanning, which is not representative of contemporary practice.

In order to update the evidence base, a systematic review incorporating a narrative synthesis was performed by the Panel, including comparative studies assessing focal ablative therapy vs. radical treatment, AS or alternative focal ablative therapy, published between 1st January 2000 and 12th June 2020 [797]. In brief, out of 1,119 articles identified, 4 primary studies (1 RCT and 3 retrospective cohort studies) [796, 798-801] recruiting 3,961 patients, and 10 systematic reviews were included [780]. Only qualitative synthesis was possible due to clinical heterogeneity. Comparative effectiveness data regarding focal therapy were inconclusive. Data quality and applicability were poor due to clinical heterogeneity, RoB and confounding, lack of long-term data, inappropriate outcome measures and poor external validity.

The impact of salvage therapies after focal therapy was investigated in smaller series [802, 803]. If a salvage RP is necessary, the reported functional and oncological outcomes are comparable to treatment-naïve patients [802, 803].

The available evidence indicates that focal therapy is associated with less AEs than whole gland or radical treatments. Robust prospective trials reporting standardised 10-year oncological outcomes [804] are needed before unrestricted recommendations in support of focal therapy for routine clinical practice can be made [778, 789, 804]. Currently, focal therapy using HIFU or cryotherapy should be performed within the context of a prospective registry. All other ablative modalites should only be offered in well-designed prospective trial setting.

6.1.6   General guidelines for the treatment of prostate cancer*

Recommendations	Strength rating
No active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all local treatments have side effects.	Strong
Surgical treatment	
Radical prostatectomy (RP) can be safely delayed for at least 3 months from diagnosis in any risk category.	Weak
Inform patients that no surgical approach (open-, laparoscopic- or robotic RP) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary based on a nomogram, perform an extended LND template for optimal staging.	Strong
Consider avoiding nerve-sparing surgery when there is a risk of ipsilateral extra-capsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined in a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease (60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks).	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low-risk or NCCN favourable intermediate-risk disease.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Offer whole-gland cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2   Treatment by disease stages
6.2.1   Treatment of low-risk disease
6.2.1.1   Active surveillance
The main risk for men with low-risk disease is over-treatment (see Sections 6.1.1.2 and 6.1.1.4); AS should therefore be considered as first treatment for all such patients.

6.2.1.1.1   Active surveillance - inclusion criteria
Guidance regarding selection criteria for AS is limited by the lack of data from prospective RCTs. As a consequence, the Panel undertook an international collaborative study involving healthcare practitioners and patients to develop consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS (DETECTIVE Study) [273], as well as a formal systematic review on the various AS protocols [805]. The criteria most often published include: ISUP grade 1, clinical stage cT1c or cT2a, PSA < 10 ng/mL and PSA-D < 0.15 ng/mL/cc, as based on systematic biopsy schemes [483, 806]. The latter threshold remains controversial [806, 807]. These criteria were supported by the DETECTIVE study consensus.

There was no agreement on the maximum number of systematic cores that can be involved with cancer or the maximum percentage core involvement (CI), although there was recognition that extensive disease on MRI should exclude men from AS, even though there is no firm definition on this, especially when targeted biopsies confirm ISUP grade 1 [273]. A systematic review and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, high PSA-D, > 2 positive cores (on systematic biopsies) and African-American descent [808]. In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), cribriform histology, sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [809] and perineural invasion [810].

Recently, a multidisciplinary consensus conference on germline testing attempted to develop a genetic implementation framework for the management of PCa [178]. Based on consensus, *BRCA2*-gene testing was recommended for AS discussions and could be performed in men with family history of prostate, breast or ovarian cancers. However, the nature of such discussions and how a positive result influences management were beyond the scope of the project. Currently, *BRCA2* mutation does not exclude a patient from AS if tumour factors are otherwise favourable. Furthermore, if included in AS programmes, patients with a known *BRCA2* mutation should be cautiously monitored until such time that more robust data are available.

6.2.1.1.2   Tissue-based prognostic biomarker testing for selection for active surveillance

Biomarkers, including Oncotype Dx®, Prolaris®, Decipher®, PORTOS and ProMark® are promising (see Section 5.2.8.3). However, further data will be needed before such markers can be used in standard clinical practice [221].

6.2.1.1.3   Magnetic resonance imaging for selection for active surveillance

In men eligible for AS based upon systematic biopsy findings alone who did not have a pre-biopsy MRI, a re-biopsy within 6–12 months (usually referred to as 'confirmatory biopsy') seems mandatory to exclude sampling error. A large body of literature including two RCTs showed that adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved detection of ISUP grade ≥ 2 cancers and thus, patient selection for AS [123, 811-815]. Adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved upgrade detection by increments of 0-7.9 per 100 men depending on the series [813]. In a meta-analysis of 6 studies, the rate of upgrading to ISUP grade ≥ 2 cancer increased from 20% (95% CI: 16–25%) to 27% (95% CI: 22–34%) when MRI-targeted biopsy was added to systematic biopsy [811]. The Active Surveillance Magnetic Resonance Imaging Study (ASIST) randomised men on AS scheduled for confirmatory biopsy to either 12-core systematic biopsy or to MRI with targeted biopsy (when indicated), combined with systematic biopsy (up to 12 cores in total). After 2 years of follow-up, use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%, p = 0.017) and in fewer patients progressing to ISUP grade ≥ 2 cancer (9.9% vs. 23%, p = 0.048) [812]. However, systematic biopsy retains its additional value, which argues for a combined biopsy approach [811, 813]. The DETECTIVE study agreed that men eligible for AS after combined systematic- and MRI-targeted biopsy do not require a confirmatory biopsy [273].

If the PCa diagnosis is made on MRI-targeted biopsy alone (recommended in some countries national guidelines, e.g., the Nordic countries [816] in order to lower the risk of over-detection of insignificant tumours) a confirmative systematic biopsy should be performed before definite decision of AS to rule out more widespread cancer growth in the prostate.

6.2.1.1.4   Follow-up during active surveillance

Based on the DETECTIVE consensus study, the follow-up strategy should be based on serial DRE (at least once yearly), PSA (at least once, every 6 months) and repeated biopsy. It was also agreed that PSA progression or change in PSA kinetics alone should lead to reclassification only if accompanied by changes in histology on repeat biopsy [273].

Yerram *et al.*, analysed a prospectively-maintained AS cohort of 369 patients (272 with ISUP grade 1 cancer and 97 with ISUP grade 2 cancer) who had been selected for AS after combined systematic and MRI-targeted sampling during confirmatory biopy. At two years, systematic biopsy, MRI-targeted biopsy and combined biopsy detected grade progression in 44 patients (15.9%), 73 patients (26.4%) and 90 patients (32.5%), respectively. This suggests that both biopsy approaches retain added value, not only for confirmatory biopsy, but also during AS [817].

In 2016, the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria were established to standardise the assessment of tumour progression on serial MRI [818]. Progression on MRI, or not, as defined by PRECISE criteria, is a strong predictor of histological upgrading [819, 820]. Two independent meta-analyses assessed the value of MRI progression criteria for predicting histological progression (mostly defined as progression to ISUP grade ≥ 2). The pooled histological progression rate was

27% in both reviews. If biopsies were triggered only by MRI progression findings, approximately two thirds of the biopsies would be avoided, at the cost of missing 40% of men with histological progression. In addition, at least half of biopsied men would have had negative findings for histological progression and thus would have undergone unnecessary biopsies. If histological progression was restricted to progression to ISUP grade > 3, approximately 30% of histological progression would be missed and approximately 80% of the biopsies performed would be unnecessary. The use of the PRECISE criteria did not seem to change these results [821, 822]. This supports maintaining protocol-mandated follow-up biopsies during the course of AS.

However, several factors have been found to be associated with low re-classification rates and long PFS: negative baseline or follow-up MRI [823-830], low PSA-D [825, 826, 828, 829], low PSA velocity [831, 832] or negative biopsy (i.e., no cancer at all) at confirmatory or follow-up biopsy [833]. In patients with stable (PRECISE 3) follow-up MRI, a low PSA-D may be associated with a low rate of progression [834]. Using these criteria, it might be possible, in the future, to create risk-based personalised AS biopsy schedules.

A Panel systematic review incorporating 263 surveillance protocols showed that 78.7% of protocols mandated per-protocol confirmatory biopsies within the first 2 years and that 57.7% of the protocols performed repeat biopsy at least every 3 years for 10 years after the start of AS [805]. In another recent review it was concluded that a negative follow-up biopsy was associated with a 50% decrease in the risk of future reclassification and upgrading [835]. In a single-centre AS cohort of 514 patients who underwent at least three protocol-mandated biopsies after diagnosis (the confirmatory biopsy and at least two additional surveillance biopsies), men with one negative biopsy (i.e., no cancer at all) at confirmatory or second biopsy, or men with two consecutive negative biopsies had a lower likelihood of a positive third biopsy and significantly better 10-year treatment-free survival [833]. This suggests that men with repetitive negative biopsies may pursue AS with at least less frequent untriggered biopsies.

6.2.1.1.5   Active Surveillance - change in treatment
Men may remain on AS whilst they continue to consent, have a life expectancy of > 10 years and the disease remains indolent. Patient anxiety about continued surveillance occurs in around 10% of patients on AS [836] and was recognised as a valid reason for active treatment [273]. A thorough discussion on pros/cons of AS vs. active treatment already at the time of diagnosis is therefore of outmost importance. More common is the development of other co-morbidities which may result in a decision to transfer to a WW strategy.

A PSA change alone (including PSA-DT < 3 years) should not change management based on its weak link with grade progression [837, 838] but rather trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting that a change in PSA should lead to repeat-MRI and repeat-biopsy. It was also agreed that changes on follow-up MRI needed a confirmatory biopsy before considering active treatment [273].

However, the histopathology criteria required to trigger a change in management in the targeted biopsy era remain debated. Magnetic resonance imaging-targeted biopsy induces a grade shift and ISUP 2–3 cancers detected by MRI-targeted biopsy have, on average, a better prognosis than those detected by systematic sampling (see Section 5.2.4.2.6.4). As an increasing number of men with favourable intermediate-risk disease are managed with AS (see section 6.2.2.1), it seems illogical to use progression to ISUP grade 2 based on targeted biopsies as the sole criterion for reclassification. In addition, as acknowledged in the DETECTIVE consensus meeting, the number of positive cores is not an indicator of tumour volume anymore if targeted biopsies are performed [273, 839]. No agreement could be reached on the pathological criteria required to trigger a change in management during the DETECTIVE consensus meeting [273]. However, based on the findings of a systematic review incorporating 271 reclassification protocols, patients with low-volume ISUP 2 disease at recruitment, and with increased systematic core positivity (> 3 cores involvement [> 50% per core]) on repeat systematic biopsies not using MRI, should be reclassified [805].

6.2.1.2   Alternatives to active surveillance
In terms of alternatives to AS in the management of patients with low-risk disease there is some data from randomised studies. In the PIVOT trial (Section 6.1.1) which compared surgery vs. observation, only 42% of patients had low-risk disease [497]. Sub-group analysis revealed that for low-risk disease there was no statistically significant difference in all-cause mortality between surgery vs. observation (RR: 0.93, 95% CI: 0.78–1.11). In the ProtecT study (Section 6.1.1) which compared the far less organised follow-up of active monitoring (PSA follow-up only) vs. surgery vs. EBRT, 56% of patients had low-risk disease [485]. However, no sub-group analysis on disease risk was performed on this population. The study found no difference between the three arms in terms of OS and CSS, but AM had higher metastatic progression compared with surgery or EBRT (6.0% vs. 2.6%). There are no robust data comparing contemporary AS protocols with either surgery or EBRT in patients with low-risk disease. Active surveillance should be considered SOC in patients with low-risk

disease and a life expectancy > 10 years. Surgery and EBRT should only be considered as alternatives to AS in patients suitable for such treatments after thorough information on pros and cons of AS and active treatment, and who after such information refuse or for some other reason are deemed unfit for AS, and who accept a trade-off between toxicity and prevention of disease progression.

Other treatments such as whole-gland ablative therapy (f.i., cryotherapy or HIFU) or focal ablative therapy remain unproven in the setting of localised low-risk disease compared with AS or radical treatment options and should not be used outside a trial setting or well-designed prospective cohort setting. These treatments are discussed in detail in Section 6.1.5.

6.2.1.2.1   Androgen deprivation monotherapy
Data regarding the use of ADT monotherapy in men with low-risk localised disease may be inferred indirectly from the Early Prostate Cancer (EPC) Trial Programme which published its findings in 2006 [840]. The EPC programme comprises three large RCTs including 8,113 men with localised (cT1–2, N0/NxM0) or locally-advanced (cT3–4, any N; or any T, N+, M0) PCa. The intervention was oral bicalutamide 150 mg monotherapy vs. placebo following standard care (defined as RP, radical EBRT or WW). The primary endpoints were PFS and OS. Patients were stratified according to clinical stage only; data regarding PSA and Gleason score were not assessed. The authors found in patients with localised disease, ADT monotherapy did not improve PFS nor OS in any of the subgroups, compared with placebo. Instead, there was a statistically insignificant numerical trend towards worse OS with ADT in the WW sub-group (HR: 1.16, 95% CI: 0.99–1.37; p = 0.07). Although the trial did not directly address men with low-risk disease, it offered some evidence suggesting that otherwise asymptomatic men with localised disease should not receive ADT monotherapy. Currently, there is no evidence supporting the use of ADT monotherapy in asymptomatic men with low-risk disease who are not eligible for any local/radical treatment; these men should simply be offered WW alone.

Other treatments such as whole-gland ablative therapy (f.i., cryotherapy or HIFU) or focal ablative therapy remain unproven in the setting of localised low-risk disease compared with AS or radical treatment options; these have been discussed in detail in Section 6.1.5.

6.2.1.3   Summary of evidence and guidelines for follow-up during active surveillance

Summary of evidence	LE
Serial magnetic resonance imaging can improve the detection of aggressive cancers during follow-up.	3
A progression on MRI mandates a repeat biopsy before a change in treatment strategy.	
A stationary MRI does not make repeat biopsy superfluous.	

Recommendations	Strength rating
Base follow-up during active surveillance (AS) on a strict protocol including digital rectal examination (at least once yearly), prostate-specific antigen (PSA) (at least once every 6 months) and repeated biopsy every 2 to 3 years.	Strong
Perform magnetic resonance imaging (MRI) and repeat biopsy if PSA is rising (PSA-doubling time < 3 years).	Strong
Re-classify 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 2 disease.	Weak
Base change in treatment on biopsy progression, not on progression on MRI and/or PSA.	Weak
Patients with a PI-RADS 1-2 findings on MRI and a low PSA density (< 0.15) may be excepted from repeat biopsy.	Weak

6.2.1.4   Summary of evidence and guidelines for the management of low-risk disease*

Summary of evidence	LE
Active surveillance or WW is SOC, based on life expectancy.	2a
All active treatment options present a risk of over-treatment.	1a

Recommendations	Strength rating
Watchful Waiting	
Manage patients with a life expectancy < 10 years by watchful waiting.	Strong
Active surveillance (AS)	
Manage patients with a life expectancy > 10 years and low-risk disease by AS.	Strong
Selection of patients	
Patients with intraductal histology on biopsy should be excluded from AS.	Strong
Perform magnetic resonance imaging (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
Follow-up of patients	
Repeat biopsies should be performed at least once every 3 years for 10 years.	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

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2.2 Treatment of intermediate-risk disease

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13.0% and 19.6%, respectively [841]. These estimates are based on systematic biopsies and may be overestimated in the era of MRI-targeted biopsies.

6.2.2.1 Active Surveillance

In the ProtecT trial, where 34% of the randomised patients had intermediate- or high-risk disease, there was no statistically significant difference in CSS at 10 years [485]. In the comprehensive characterisation of the patients in the ProtecT trial, treatment received, PSA, ISUP grade at diagnosis, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs. 3.0 mm), aggregate length of tumour (median 8.0 vs. 4.0 mm), and presence of perineural invasion were each associated with increased risk of disease progression (p < 0.001 for each). However, these factors could not reliably predict progression in individuals [483].

The outcomes of AS in intermediate-risk PCa has also been analysed in two recent systematic reviews and meta-analyses, summarising available data on its oncological outcomes and comparing patients with intermediate-risk PCa to patients with low-risk disease [842, 843]. The definition of AS was not strictly defined in either of the reviews: instead the search strategies included 'active surveillance' as a search term, and no *a priori* study protocol was available. The primary outcome was the proportion of patients who remained on AS, whilst secondary outcomes included CSS, OS, and metastasis-free survival in both studies.

In the first review 17 studies were included, incorporating 6,591 patients with intermediate-risk disease. Sixteen studies included patients with low- and intermediate-risk disease, hence enabling comparative outcome assessment via pooled analysis. Only one study performed MRI at recruitment and follow-up. There was significant clinical heterogeneity in terms of inclusion criteria for intermediate-risk disease. The results showed the proportion of patients who remained on AS was comparable between the low- and intermediate-risk groups after 10 and 15 years' follow-up (OR: 0.97, 95% CI: 0.83–1.14; and OR: 0.86, 95% CI: 0.65–1.13, respectively). Cancer-specific survival was worse in the intermediate-risk group after 10 years (OR: 0.47, 95% CI: 0.31–0.69) and 15 years (OR: 0.34, 95% CI: 0.2–0.58). Overall survival was not statistically significantly different at 5 years' follow-up (OR: 0.84, 95% CI: 0.45–1.57) but was significantly worse in the intermediate-risk group after 10 years (OR: 0.43, 95% CI: 0.35–0.53). Metastases-free survival did not significantly differ after 5 years (OR: 0.55, 95% CI: 0.2–1.53) but was worse in the intermediate-risk group after 10 years (OR: 0.46, 95% CI: 0.28–0.77).

The slightly more recent review, including 25 studies and a total of 29,673 low- or intermediate-risk patients, showed similar results in terms of treatment-free survival at 10 years (RR: 1.16, 95% CI: 0.99-1.36), risk of developing metastases (RR: 5.79, 95% CI: 4.61-7.29), risk of dying from PCa (RR: 3.93, 95% CI: 2.93-5.27) and risk of dying from any cause (RR: 1.44, 95% CI: 1.11-1.86).

In a subgroup analyses of four studies comparing outcomes of patients with intermediate- and low-risk PCa of ISUP ≤ 2 (n = 1,900) no statistically significant difference could be found in terms of treatment-free survival or risk of developing metastases (RR: 1.03, 95% CI: 0.62-1.71 and RR: 2.09, 95% CI: 0.75-5.82, respectively). Both reviews indicate that AS in unselected intermediate-risk patients implies a higher risk of progression over time. It remains unclear whether this difference only reflects the inborne difference in outcome, that can also be seen when comparing immediate treatment of low- and intermediate-risk PCa, or

if the delay in treatment caused any worsenening of the outcomes in the intermediate-risk group in any way. Both reviews conclude that AS could be offered to patients with intermediate-risk disease, but they should be informed of a higher risk of progression and the latter study suggests limiting the inclusion of intermediate-risk patients to those with low-volume ISUP 2 disease.

A Canadian consensus group proposes that low volume ISUP grade 2 (< 10% Gleason pattern 4 on systematic biopsies) may also be considered for AS. These recommendations have been endorsed by the American Society of Clinical Oncology (ASCO) [338] and the DETECTIVE study consensus [273] for those patients with a PSA < 10 ng/mL and low core positivity. The DETECTIVE Study concluded that men with favourable ISUP 2 cancer (PSA < 10 ng/mL, low density, clinical stage ≤ cT2a and a low number of positive systematic cores) should also be considered for deferred treatment [273]. In this setting, re-biopsy within 6 to 12 months to exclude sampling error is even more relevant than in low-risk disease [806, 844]. The DETECTIVE Study-related qualitative systematic review aimed to determine appropriate criteria for inclusion of intermediate-risk disease into AS protocols [805]. Out of 371 AS protocols included in the review, more than 50% included patients with intermediate-risk disease on the basis of PSA up to 20 ng/mL (25.3%), ISUP 2 or 3 (27.7%), clinical stage cT2b/c (41.6%) and/or direct use of D'Amico risk grouping of intermediate risk or above (51.1%). The DETECTIVE study reached consensus that patients with ISUP 3, or patients with intraductal or cribriform histology, should not be considered for AS. The presence of any grade 4 pattern is associated with a 3-fold increased risk of metastases compared to ISUP grade 1, while a PSA up to 20 ng/mL might be an acceptable threshold [844-846], especially in the context of low PSA-D. In addition, it is likely that MRI and targeted biopsies will detect small foci of Gleason grade 4 cancer that might have been missed with systematic biopsy. Therefore, care must be taken when explaining this treatment strategy, especially to patients with the longest life expectancy.

There are no clear concensus on how to interpret MRI and targeted biopsies for AS but the DETECTIVE study concensus was that if targeted biopsies based upon mpMRI images are performed, the number of positive cores of the targeted biopsies are not an indicator of the extent of disease or tumour volume. Indicator of the tumour volume may be either the number of positive cores, and the length of cancer in each core, based on systematic biopsies, or the volume of the dominant lesion seen on mpMRI [273].

In summary, AS can be considered in patients with low-volume ISUP 2 (defined as ≤ 3 positive systematic cores and ≤ 50% core involvement) or another single element of intermediate-risk disease (i.e. favourable intermediate-risk disease). Patients with ISUP 3 disease, or patients with intraductal or cribriform histology, should be excluded. The monitoring schedule should be diligent, given the potential higher risk of progression, development of regional or distant metastases and death of this group compared with patients with low-risk disease. During monitoring, if repeat non-MRI-based systematic biopsies reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease, patients should be reclassified (i.e., actively treated).

6.2.2.2   Radical prostatectomy

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71, 95% CI: 0.53–0.95), death from PCa (RR: 0.38, 95% CI: 0.23–0.62) and distant metastases (RR: 0.49, 95% CI: 0.32–0.74) were significantly reduced in intermediate-risk PCa at 18 years. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69, 95% CI: 0.49–0.98), but not death from PCa (0.50, 95% CI: 0.21–1.21) at 10 years. A meta-analysis based on the findings of SPCG-4, PIVOT and ProtecT demonstrated a benefit from RP over observation with a significantly decreased risk of death of 9% and of disease progression of 43% [847]. However, no stratification by disease stages was performed. The risk of having positive LNs in intermediate-risk PCa is between 3.7–20.1% [848]. An ePLND should be considered in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [400] or 7% if using the nomogram by Gandaglia *et al*., which incorporates MRI-guided biopsies [364]. However, preliminary data show a high NPV (96%) for LN-positivity when using PSMA PET for staging (See Section 6.1.2.3.2). In all other cases ePLND can be omitted, which means accepting a low risk of missing positive nodes. Nerve sparing surgery is discussed in Section 6.1.2.3.5.

6.2.2.3   Radiation therapy
6.2.2.3.1   Recommended IMRT/VMAT for intermediate-risk PCa
Patients suitable for ADT can be given combined IMRT/VMAT with short-term ADT (4–6 months) [849-851]. For adjuvant RT of the pelvic lymphatics (45-50 Gy) for NCCN unfavourable intermediate risk (cN0) see Section 6.2.3.2.1 - Radiotherapy for localised high-risk PCa. For patients unsuitable (e.g., due to co-morbidities) or unwilling to accept ADT (e.g., to preserve their sexual health) the recommended treatment is IMRT/VMAT (76–78 Gy or equivalent moderate HFX) or a combination of IMRT/VMAT and brachytherapy as described below (see Section 6.2.2.3.2). A secondary analysis of the PCS III trial has suggested that patients with NCCN favourable intermediate-risk disease (see Section 4.4) can safely omit ADT if their RT dose is 76 Gy, but this is based on an unplanned subgroup analysis and only 138 patients had favourable intermediate-risk disease. An

individual discussion between the physician and the patient of the possible benefits and harms of omitting ADT in this group is essential [852]. In the absence of higher quality data, SOC will remain short-term ADT + IMRT/VMAT.

6.2.2.3.2   Brachytherapy for intermediate-risk PCa

Systematic review recommends LDR brachytherapy monotherapy can be offered to patients with NCCN favourable intermediate-risk disease and good urinary function (see Section 4.4) [853]. Fractionated HDR brachytherapy as monotherapy can be offered to selected patients with intermediate-risk PCa although they should be informed that results are only available from small series in very experienced centres. Five-year PSA control rates over 90% are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [723]. There are no direct data to inform on the use of ADT in this setting. Trimodality therapy with IMRT plus brachytherapy boost and short-term ADT can be considered for NCCN unfavourable intermediate-risk PCa (see Section 4.4) but patients should be made aware that the potential improvements in biochemical control are accompanied with an increased risk of long-term urinary problems [714, 715, 719].

6.2.2.4   Other options for the primary treatment of intermediate-risk PCa (experimental therapies)

6.2.2.4.1   Focal therapy

A prospective study on focal therapy using HIFU in patients with localised intermediate-risk disease was published but the data was derived from an uncontrolled single-arm case series [789]. There is a paucity of high-certainty data for either whole-gland or focal ablative therapy in the setting of intermediate-risk disease. Consequently, neither whole-gland ablative treatment nor focal treatment can be considered as standard therapy for intermediate-risk patients and, if offered, it should only be in the setting of clinical trials or prospective registries [778].

6.2.2.4.2   Androgen deprivation therapy monotherapy

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from the EORTC 30891 trial, which was a RCT comparing deferred ADT vs. immediate ADT in 985 patients with T0–4 N0–2 M0 disease [848]. The trial showed a small, but statistically significant, difference in OS in favour of immediate ADT monotherapy but there was no significant difference in CSS, predominantly because the risk of cancer-specific mortality was low in patients with PSA < 8 ng/mL. Consequently, the use of ADT monotherapy for this group of patients is not considered as standard, even if they are not eligible for radical treatment.

*6.2.2.5   Guidelines for the treatment of intermediate-risk disease**

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW in asymptomatic patients with life expectancy < 10 years.	Strong
Active surveillance (AS)	
Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per 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 ISUP grade group 3 disease should be excluded from AS protocols.	Strong
Re-classify 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 2 disease.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with a life expectancy of > 10 years.	Strong
Radical prostatectomy can be safely delayed for at least 3 months.	Weak
Offer nerve-sparing surgery to patients with a low risk of extra-capsular disease on that side.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2.)	Weak
Radiotherapeutic treatment	
Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Strong

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 months).	Weak
Offer high-dose rate (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 months).	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
Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Weak

*All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2.3 *Treatment of high-risk localised disease*

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP [854]. When managed with non-curative intent, high-risk PCa is associated with 10-year and 15-year PCSM rates of 28.8 and 35.5%, respectively [855]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

Some evidence suggests that radical treatment for high-risk PCa can be delayed up to 3 months after the diagnosis without any oncological consequences [516, 856]. Systematic reviews suggest that there is a higher risk of biochemical recurrence and worse pathological outcomes when definitive treatment is given beyond a 6 to 9 months delay. However, there is no conclusive data regarding stronger endpoints (CSS or OS).

6.2.3.1 *Radical prostatectomy*

Provided that the tumour is not fixed to the pelvic wall or there is no invasion of the urethral sphincter, RP is a standard option in selected patients with a low tumour volume. Extended PLND should be performed in all high-risk PCa cases [400, 401]. Patients should be aware pre-operatively that surgery may be part of multi-modal treatment, with adjuvant or SRT or ADT. Neoadjuvant therapy using ADT with or without new generation HT or docetaxel is not indicated. (See Section 6.1.2.2.4) [511, 513]. Nerve sparing management is discussed in Section 6.1.2.3.5.

6.2.3.1.1 ISUP grade 4–5

The incidence of organ-confined disease is 26–31% in men with an ISUP grade ≥ 4 on systematic biopsy. A high rate of downgrading exists between the biopsy ISUP grade and the ISUP grade of the resected specimen [855]. Several retrospective case series have demonstrated CSS rates over 60% at 15 years after RP in the context of a multi-modal approach (adjuvant or salvage ADT and/or RT) in patients with a biopsy ISUP grade 5 [441, 519, 857, 858].

6.2.3.1.2 Prostate-specific antigen > 20 ng/mL

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multi-modal approach demonstrated a CSS at 15 years of over 70% [441, 519, 525, 859-861].

6.2.3.1.3 Radical prostatectomy in cN0 patients with pathologically confirmed LN invasion (pN1)

At 15 years follow-up cN0 patients who undergo RP but who were found to have pN1 were reported to have an overall CSS and OS of 45% and 42%, respectively [862-867]. A systematic review has reported 10-year BCR-free, CSS, and OS rates ranging from 28% to 56%, 72% to 98%, and 60% to 87.6%, respectively, in pN1 patients [868]. These findings highlight that pN1 patients represent a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Sections 6.2.5.2 and 6.2.5.6).

6.2.3.2 *External beam radiation therapy*

For high-risk localised PCa, a combined modality approach should be used consisting of IMRT/VMAT plus long-term ADT. The duration of ADT has to take into account PS, co-morbidities and the number of poor prognostic factors. It is important to recognise that in several studies EBRT plus short-term ADT did not improve OS in high-risk localised PCa and long-term ADT (at least 2 to 3 years) is currently recommended for these patients [676, 677, 687]. Moderate HFX is an option in selected high-risk patients with localised disease. The CHHiP study included 12% high-risk patients (n = 386) but limited entry to those with a PSA < 30 ng/mL and a Roach formula risk of SV involvement < 30% [661]. Patients were ineligible if they had both T3a tumours and ISUP grade 4 or higher.

6.2.3.2.1   Lymph node irradiation in cN0

There is no clear evidence for prophylactic irradiation of the pelvic LNs in intermediate- and high-risk disease. The long-term results of the NRG/RTOG 9413-trial which randomised intermediate-risk and high-risk localised PCa patients (1,322 cN0 patients were enrolled), showed that neoadjuvant HT plus whole pelvic RT improved PFS only compared with neoadjuvant ADT plus prostate RT and whole pelvic RT plus adjuvant ADT [869]. However, at the increased risk of ≥ grade 3 GI-toxicity.

A well-conducted single-centre RCT randomised 224 patients comparing prostate-only RT (PORT) vs. whole pelvic RT (WPRT) in localised high-risk- and locally-advanced tumours (cN0) with a risk of > 20% of positive nodes (Roach formula). With a median follow-up of 68 months there was a significant improvement of distant metastasis-free survival (95.9% vs. 89.2%, HR: 0.35, p = 0.01) and DFS (89.5% vs.77.2%, p = 0.02). However, there was a significant higher rate of late GU ≥ 2 effects (17.7% vs. 7.5%, p = 0.02), the trial was relatively small in size with additional limitations and these findings are therefore insufficient to define a change in practice [870, 871]. The benefits of pelvic nodal irradiation using IMRT/VMAT merit further investigation in large scale RCTs as conducted by the RTOG or the UK National Cancer Research Institute (NCRI).

6.2.3.2.2   Brachytherapy boost

In men with NCCN unfavourable intermediate- or high-risk PCa, brachytherapy boost with supplemental EBRT and HT may be considered. See Sections 6.1.3.4.1 and 6.1.3.4.2 for details on RCTs comparing EBRT alone and EBRT with LDR or HDR boost, respectively.

6.2.3.3   *Options other than surgery or radiotherapy for the primary treatment of localised PCa*

Currently there is a lack of evidence supporting any other treatment option apart from RP and radical RT in localised high-risk PCa. The use of ADT monotherapy was addressed by the EORTC 30891 trial [848] (see Section 6.2.4.4.2). Immediate ADT may only benefit patients with a PSA-DT < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour [848, 872].

6.2.3.4   *Guidelines for radical and palliative treatment of high-risk localised disease**

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Radical prostatectomy can be safely delayed for at least 3 months.	Weak
Offer RP to selected patients as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong
Radiotherapeutic treatment	
Offer patients intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2.4   ***Treatment of locally-advanced PCa***

In the absence of high-level evidence, a recent systematic review could not define the most optimal treatment option [873]. Randomised controlled trials are only available for EBRT. A local treatment combined with a systemic treatment provides the best outcome, provided the patient is fit enough to receive both. The initial results of the SCPG-15 trials suggested that randomisation between surgery and EBRT is feasible, but oncologic outcomes are awaited [874].

6.2.4.1 Radical prostatectomy

Surgery for locally-advanced disease as part of a multi-modal therapy has been reported [855, 875, 876]. However, the comparative oncological effectiveness of RP as part of a multi-modal treatment strategy vs. upfront EBRT with ADT for locally-advanced PCa remains unknown, although a prospective phase III RCT (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally-advanced (T3) disease is currently recruiting [877]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at 10 years [855, 875, 876, 878-881]. For cT3b–T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [882, 883]. The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement (cN0), based on conventional imaging. In case of suspected positive LNs during RP (initially considered cN0) the procedure should not be abandoned since RP may have a survival benefit in these patients. Intra-operative frozen section analysis is not justified in this case [580]. An ePLND is considered standard if a RP is planned.

6.2.4.2 Radiotherapy for locally-advanced PCa

In locally-advanced disease RCTs have clearly established that the additional use of long-term ADT combined with RT produces better OS than ADT or RT alone (see Section 6.1.3.1.4 and Tables 6.1.9 and 6.1.10) [873]. See Sections 6.1.3.4.1 and 6.1.3.4.2 for LDR and HDR brachytherapy boost in T3N0M0 PCa.

6.2.4.3 Treatment of cN1 M0 PCa

Lymph-node metastasised PCa is where options for local therapy and systemic therapies overlap. Approximately 5% to 10% of newly diagnosed PCa patients have synchronous suspected pelvic nodal metastases on conventional imaging (CT/bone scan) without bone or visceral metastases (cN1 M0 stage). Meta-analyses have shown that PSMA-PET/CT prior to primary treatment in advanced PCa detected disease outside the prostate in 32% of cases despite prior negative conventional imaging using bone scan and pelvic CT/MRI [416]. A RCT assessing PSMA-PET/CT as staging tool in high-risk PCa confirmed these findings and showed a 32% increase in accuracy compared with conventional imaging for the detection of pelvic nodal metastases [433]. Notably, more sensitive imaging also causes a stage shift with more cases classified as cN1, but with, on average, lower nodal disease burden.

The management of cN1M0 PCa is historically based on long-term ADT combined with a local treatment. The benefit of adding local treatment has been assessed in various retrospective studies, summarised in one systematic review [884] including 5 studies only [885-889]. The findings suggested an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT as compared to ADT alone. The main limitations of this analysis were the lack of randomisation, of comparisons between RP and RT, as well as the value of the extent of PLND and of RT fields. Only limited evidence exists supporting RP for cN1 patients. Moschini *et al*., compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at pre-operative staging. cN+ was not a significant predictor of CSS [890].

Based on the consistent benefit seen in retrospective studies including cN1 patients, local therapy is recommended in patients with cN1 disease at diagnosis in addition to long-term ADT (see Table 6.2.4.1).

The addition of a brachytherapy boost to ADT plus EBRT was not associated with improved OS in a retrospective study of 1,650 cN1 patients after multivariable adjustment and propensity score matching [891].

The intensification of systemic treatment (abiraterone acetate, docetaxel, zoledronic acid) has been assessed in unplanned sub-group analyses from the STAMPEDE multi-arm RCT by stratifying for cN1 and M1 status [888, 892]. The analyses were balanced for nodal involvement and for planned RT use in STAMPEDE at randomisation and at analysis. Abiraterone acetate was associated with a non-significant OS improvement (HR: 0.75, 95% CI: 0.48–1.18) in non-metastatic patients (N0/N+M0), but OS data were still immature with a low number of events. Furthermore, this was an underpowered subgroup analysis and hypothesis generating at best. Moreover, subgroup analyses were performed according to the metastatic/non-metastatic status and to the nodal status (any M) without specific data for the N1M0 population (n = 369; 20% of the overall cohort). The same would apply for the docetaxel arm in the STAMPEDE trial for which no specific subgroup analysis of newly diagnosed N1M0 PCa (n = 171, 14% of the overall cohort) was performed. However, the addition of docetaxel, zoledronic acid, or their combination, did not provide any OS benefit when stratifying by M0 and N+ status.

In the AFU-GETUG 12 trial comparing the impact of docetaxel plus estramustine in addition to ADT, 29% of included high-risk non-metastatic PCa patients had a nodal involvement (pN1) at randomisation [893]. A non-significant trend towards better relapse-free survival rates was reported in the treatment arm (HR 0.66;

0.43–1.01) without OS benefit. A meta-analysis of docetaxel trials in N0/N1-M0 patients concluded to an 8% 4-year survival advantage for docetaxel compared with ADT alone in terms of failure-free survival without OS benefit [894].

Two RCTs from the STAMPEDE platform protocol reported on men with *de novo* high-risk/locally-advanced M0 disease, or relapse after primary curative therapy with high-risk features. Thirty-nine percent of patients (n = 774) were N1 on conventional imaging [895]. Radiotherapy in addition to long-term ADT was administered in 71% of these patients. Given the MFS and OS benefits observed in the overall population (see Section 6.2.4.2), combined ADT (for 3 years) and additional abiraterone (for 2 years) should be a SOC in cN1 patients in addition to prostate- and whole pelvic RT.

Table 6.2.4.1: Selected studies assessing local treatment in (any cT) cN1 M0 prostate cancer patients

Study	n	Design	Study period/ follow-up	Treatment arms	Effect on survival
Bryant, *et al*. 2018 [896]	648	Retrospective (National Veterans Affairs)	2000-2015 61 mo.	ADT ± EBRT	Significant benefit for combined treatment only if PSA levels less than the median (26 ng/mL) All-cause mortality HR: 0.50 CSS, HR: 0.38
Sarkar, *et al*. 2019 [897]	741	Retrospective (National Veterans Affairs)	2000-2015 51 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for RP All cause mortality HR 0.36 CSS, HR: 0.32 No statistical difference for RP vs. RT (p ≥ 0.1) All-cause mortality HR: 047 CSS, HR: 0.88
Lin, *et al*. 2015 [886]	983 before propensity score matching	Retrospective (NCDB)	2004-2006 48 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 73% vs. 52% HR: 0.5
Tward, *et al*. 2013 [885]	1,100	Retrospective (SEER)	1988-2006 64 mo.	EBRT (n = 397) vs. no EBRT (n = 703) No information on ADT)	Significant benefit for EBRT 5-yr CSS 78% vs. 71% HR: 0.66 5-yr. OS: 68% vs. 56%, HR: 0.70
Rusthoven, *et al*. 2014 [889]	796	Retrospective (SEER)	1995-2005 61 mo.	EBRT vs. no EBRT (no information on ADT)	Significant benefit for EBRT 10-yr OS: 45% vs. 29% HR: 0.58
Seisen, *et al*. 2018 [887]	1,987	Retrospective (NCDB)	2003-2011 50 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for combined treatment 5-yr OS: 78.8% vs. 49.2% HR: 0.31 No difference between RP and RT
James, *et al*. 2016 [888]	177	Unplanned sub-group analysis RCT	2005-2014 17 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 93% vs. 71% 2-yr FFS: 81% vs 53% FFS, HR: 0.48

ADT = androgen deprivation therapy; CSS = cancer-specific survival; EBRT = external beam radiotherapy; FFS = failure-free survival; HR = hazard ratio; mo = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; yr = year.

6.2.4.4 Options other than surgery or radiotherapy for primary treatment
6.2.4.4.1 Investigational therapies
Currently cryotherapy, HIFU or focal therapies have no place in the management of locally-advanced PCa.

6.2.4.4.2 Androgen deprivation therapy monotherapy
The deferred use of ADT as single treatment modality has been answered by the EORTC 30891 trial [848]. Nine hundred and eighty-five patients with T0–4 N0–2 M0 PCa received ADT alone, either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS favoured immediate treatment (HR: 1.21, 95% CI: 1.05–1.39). Surprisingly, no different disease-free or symptom-free survival was observed, raising the question of survival benefit. In locally-advanced T3–T4 M0 HSPC unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50 ng/mL and a PSA-DT < 12 months or those that are symptomatic [848, 872]. The median time to start deferred treatment was 7 years. In the deferred treatment arm 25.6% of patients died without needing treatment.

6.2.4.5 Guidelines for radical- and palliative treatment of locally-advanced disease*

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND.	Strong
Radiotherapeutic treatments	
Offer patients with cN0 disease intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guide radiation therapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer patients with cN0 disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Offer long-term ADT for at least 2 years.	Strong
Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 years 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 years of abiraterone to cN1M0 patients.	Strong
Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Strong
Therapeutic options outside surgery or radiotherapy	
Do not offer whole gland treatment or focal treatment.	Strong

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.2.5 Adjuvant treatment after radical prostatectomy
6.2.5.1 Introduction
Adjuvant treatment is by definition additional to the primary or initial therapy with the aim of decreasing the risk of relapse, despite the apparent full control following surgery. A post-operative detectable PSA is an indication of persistent prostate cells (see Section 6.2.6). All information listed below refers to patients with a post-operative undetectable PSA.

6.2.5.2 Risk factors for relapse
Patients with ISUP grade > 2 in combination with EPE (pT3a) and particularly those with SV invasion (pT3b) and/or positive surgical margins are at high risk of progression, which can be as high as 50% after 5 years [898]. Irrespective of the pT stage, the number of removed nodes [899-906], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [907]. A LN density (defined as 'the percentage of positive LNs in relation to the total number of analysed/removed LNs') of over 20% was found to be associated with poor prognosis [908]. The number of involved nodes seems to be a major factor for predicting relapse [901, 902, 909]; the threshold considered is less than 3 positive nodes from an ePLND [536, 901, 909]. However, prospective data are needed before defining a definitive threshold value.

6.2.5.2.1   Biomarker-based risk stratification after radical prostatectomy

The Decipher® gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment. A meta-analysis of five studies analysed the performance of the Decipher® Genomic Classifier (GC) test on men post-RP. The authors showed in multivariable analysis that Decipher® GC remained a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47, $p < 0.001$) per 0.1 unit increase in score and concluded that it can independently improve prognostication of patients post-RP within nearly all clinicopathologic, demographic, and treatment subgroups [910]. A systematic review of the evidence for the Decipher® GC has confirmed the clinical utility of this test in post-RP decision-making [911]. Further studies are needed to establish how to best incorporate Decipher® GC in clinical decision-making.

6.2.5.3   *Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0)*

Four prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]) (undetectable PSA mostly defined as PSA < 0.1 ng/mL), demonstrating an advantage (endpoint, development of BCR) in high-risk patients (e.g., pT2 with positive surgical margins and ISUP 3–5 or pT3/4 with- or without positive surgical margins and ISUP 3–5) post-RP (Table 6.2.5.1). In the ARO 96-02 trial, 80% of the pT3/R1/GS 8–10 patients randomised to observation developed BCR within 10 years [912]. It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial which presents a major limitation interpreting these findings as patients with a detectable PSA would now be considered for salvage therapy rather than ART [912].

Table 6.2.5.1: Overview of all four randomised trials for adjuvant surgical bed radiation therapy after RP*
(without ADT)

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [913]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr.: 53% vs. 30% (p < 0.05)	**10 yr.: 74% vs. 66%** Median time: 15.2 vs. 13.3 yr., p = 0.023
EORTC 22911 2012 [914]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr.: 60.6% vs. 41% (p < 0.001)	**81% vs. 77% n.s.**
ARO 96-02 2014 [912]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr.: 56% vs. 35% (p = 0.0001)	**10 yr.: 82% vs. 86% n.s.**
FinnProstate Group 2019 [915]	250	pT2,R1/ pT3a	66.6 Gy vs. observation (+ SRT)	> 0.4 (in 2 successive measurements)	112 vs. 103 (patients alive)	10 yr.: 82% vs. 61% p < 0.001	**10 yr.: 92% vs. 87% n.s.**

*See Section 6.3.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.
BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; n.s. = not significant;
OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin;
SRT = salvage radiotherapy.

6.2.5.4   *Comparison of adjuvant- and salvage radiotherapy*

Two retrospective matched studies (510 and 149 patients receiving ART) failed to show an advantage for metastasis-free survival [916, 917]. However, both studies were underpowered for high-risk patients (pT3b/R1/ISUP grade 4–5 PCa). In contrast to these studies, a propensity score-matched retrospective analysis of two cohorts of 366 pT3 and/or R1 patients found that compared to SRT at a PSA between 0.1 and 0.5 ng/mL, ART given at an undetectable PSA (< 0.1 ng/mL) improved all three endpoints; BCR, metastasis-free survival, and OS [918].

Both approaches (ART and early SRT) together with the efficacy of adjuvant ADT are compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial [919], the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial [920], and the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG-AFU 17) trial [921]. In addition, a pre-planned meta-analysis of all three trials has been published (Table 6.2.5.2) [922].

Two trials closed early after randomising 333/470 patients (RAVES) and 424/718 (GETUG-AFU-17) patients. RADICALS-RT included 1,396 patients with the option of subsequent inclusion in RADICALS-HT; 154/649 (24%) of patients starting in the adjuvant RT group also received neoadjuvant or adjuvant HT; 90 patients for 6 months/45 for 2 years/19 patients outside RADICALS-HT. From the SRT group, 61/228 (27%) received neoadjuvant or adjuvant HT for 6 months (n = 33) and 2 years (n = 13). Fifteen of these patients were treated outside the trial [919]. All men in the GETUG-AFU-17 trial (n = 424) received 6 months of HT. All together, 684 out of 2,153 patients received additional ADT for at least 6 months across both trials [922]. Radiotherapy to the pelvic lymphatics was allowed in the GETUG-AFU and in the RADICALS-RT trials.

The primary endpoint for RAVES and GETUG-AFU 17 was biochemical PFS, and for RADICALS-RT metastasis-free survival. So far only PFS data has been reported, and not metastasis-free survival- or OS data. With a median follow-up between 4.9 years and 6.25 years there was no statistically significant difference for biochemical PFS for both treatments in all three trials (see Table 6.2.5.2) indicating that in the majority of patients adjuvant irradiation should be avoided. Additionally, there was a significant lower rate of grade ≥ 2 GU late side effects and grade 3–4 urethral strictures in favour of early SRT; which may also be caused by the low number of patients with PSA-progression and subsequent need for early SRT at the time of analysis (40% of patients).

It is important to note that the indication for ART changed over the last ten years with the introduction of ultra-sensitive PSA-tests, favouring early SRT. Therefore many patients, randomised in these 3 trials (accruing 2006–2008) are not likely to benefit from ART as there is a low risk of biochemical progression (~20–30%) in, for example, pT3R0 or pT2R1-tumours. The median pre-SRT PSA in all 3 trials was 0.24 ng/mL. Therefore, patients with 'low-risk factors' of biochemical progression after RP should be closely followed up with ultra-sensitive assays and SRT should be discussed, if needed, as soon as PSA starts to rise, which has to be confirmed by a second PSA measurement (see Section 6.3). The proportion of patients with adverse pathology at RP (ISUP grade group 4–5 and pT3 with or without positive margins) in all 3 trials was low (between 10–20%) and therefore even the meta-analysis may be underpowered to show an outcome in favour of SRT [922]. In addition, the side-effect profile may have been impacted with a larger proportion of ART patients receiving treatment with older 3D-treatment planning techniques as compared to SRT patients (GETUG-AFU 17: ART, 69% 3D vs. 46% SRT) and patients treated more recently were more likely to undergo IMRT techniques with a proven lower rate of late side effects [634].

For these reasons, 10-year OS and metastasis-free survival endpoints results should be awaited before drawing final conclusions. Due to the small number of patients with adverse pathology (ISUP grade group 4–5 and pT3) included in these 3 trials (between 10–20%), ART remains a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients') i.e. ISUP grade group 4–5 and pT3 with or without positive margins [923, 924]. This recommendation was supported by a published retrospective multi-centre study comparing ART and SRT in patients with high-risk features (pN1 or ISUP 4–5 and pT3/4-tumours) after RP [925]. After a median follow-up of 8.2 years of the 26,118 men included in the study, 2,104 patients died, 25.62% from PCa (n = 539) and 2,424 patients had adverse pathology compared with 23,694 who did not. After excluding men with persistent PSA after RP, ART when compared with early SRT showed a significantly lower acute mortality risk (p = 0.02, HR: 0.33).

Table 6.2.5.2: Overview of all three randomised trials and one meta-analysis for patients treated with adjuvant vs. early salvage RT after RP

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (yr)	BPFS	OS or MFS	Side effects
RAVES TROG 08.03/ ANZUP 2020 [920]	333 target was 470 early closed	pT3a/pT3b any T - SM+ PSA post-RP: < 0.1 ng/mL	64 Gy ART PSA: < 0.1 ng/mL vs. 64 Gy early SRT at PSA > 0.2 ng/mL med. pre-SRT: n.r.	> 0.4 post RT	6.1	**5 yr.: 86% vs. 87%** (p > 0.05)	n.r.	LT grade ≥ GU: 70% vs. 54% (p = 0.002)
RADICALS-RT 2020 [919]	1,396	pT3a/ pT3b/pT4 PSA > 10 ng/mL pre-RP any T, SM+ Gleason 7-10 PSA post-RP: < 0.2 ng/mL	52.5 Gy (20 Fx) or 66 Gy (33 Fx) ART early SRT identical at PSA > 0.1 med.pre-SRT: 0.2 ng/mL	> 0.4 or 2 at any time	4.9	**5 yr.: 85% vs. 88%** (p = 0.56)	n.r.	SR urinary incontinence 1 yr: 4.8 vs. 4 (p = 0.023) urethral stricture grade 3/4 2 yr: 6% vs. 4% (p = 0.02)
GETUG-AFU 17 2020 [921]	424 target was 718 early closed	pT3a/pT3b/ pT4a and SM + PSA post-RP: < 0.1 ng/mL	66 Gy (ART) vs. 66 Gy early SRT at PSA 0.1 both groups: 6 mo. LHRH-A med. pre-SRT 0.24	> 0.4	6.25	**5 yr: 92% vs. 90%** (p = 0.42)	n.r.	LT grade ≥ 2 GU 27% vs. 7% (p < 0.001) ED: 28% vs. 8% (p < 0.001)
ARTISTIC-Meta-analysis 2020 [922]	2,153	see above	see above	see above	4.5	**5 yr.: 89% vs. 88%** p = 0.7	n.r.	n.r.

ART = adjuvant radiotherapy; BCR = biochemical recurrence; BPFS = biochemical progression-free survival; ED = erectile dysfunction; FU = follow-up; Fx = fraction; GU = genito-urinary; LHRH = luteinising hormone-releasing hormone; LT = late toxicity; mo = months; med = median; MFS = metastasis-free survival; n.r. = not reported; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SR = self reported; SRT = salvage radiotherapy; + = positive; yr = year.

6.2.5.5   Adjuvant systemic therapy in N0 disease
Adjuvant androgen ablation with bicalutamide 150 mg daily did not improve PFS in localised disease while it did for locally-advanced disease after RT. However, this never translated to an OS benefit [926]. A systematic review showed a possible benefit for PFS but not OS for adjuvant androgen ablation [511].

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (6 cycles) ended prematurely due to poor accrual. A phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally-advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [927]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [928].

6.2.5.6   Adjuvant treatment in pN1 disease
6.2.5.6.1   Adjuvant androgen ablation alone
The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% and has been shown to significantly improve CSS and OS in prospective RCTs [929, 930]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and these findings may not apply to men with less extensive nodal metastases.

6.2.5.6.2   Adjuvant radiotherapy combined with ADT in pN1 disease
In a retrospective multi-centre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated 'adjuvantly' with continuous ADT (within 6 months after

surgery irrespective of PSA). The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), ISUP grade 2–5 and pT3–4 or R1, as well as men with 3 to 4 positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [931]. In contrast, a recent retrospective multi-centre study including 1,614 patients and a median follow-up of 7,02 years assessed ART + ADT. Adjuvant RT compared to SRT was associated with a decreased all-cause mortality and this reduction increased with each additional positive pelvic LN, from the first one on and the highest effect was for more than 3 positive nodes [932]. These data are in agreement with a US National Cancer Database analysis based on 5,498 patients [933]. Another US National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT plus EBRT (including pelvic LNs) vs. observation and vs. ADT alone in all men with single or multiple adverse pathological features. Men without any adverse pathological features did not benefit from immediate adjuvant therapy [934].

In a systematic review of the literature, RT with or without ADT was associated with improved survival in men with locally-advanced disease and a higher number of positive nodes [868]. Radiotherapy to the pelvic lymphatics and the prostate fossa plus long-term ADT can be offered to patients with pN1 disease [931, 935]. However, the optimal duration of ADT is still unkown.

6.2.5.6.3   Observation of pN1 patients after radical prostatectomy and extended lymph node dissection
Several retrospective studies and a systematic review addressed the management of patients with pN1 PCa at RP [868, 909, 931, 935, 936]. A subset of patients with limited nodal disease (1–2 positive LNs) showed favourable oncological outcomes and did not require additional treatment.

An analysis of 209 pN1 patients with one or two positive LNs at RP showed that 37% remained metastasis-free without need of salvage treatment at a median follow-up of 60.2 months [936]. Touijer *et al*., reported their results of 369 pN1-positive patients (40 with and 329 without adjuvant treatment) and showed that higher pathologic grade group and > 3 positive LNs were significantly associated with an increased risk of BCR on multivariable analysis [909]. Biochemical-free survival rates in pN1 patients without adjuvant treatment ranged from 43% at 4 years to 28% at 10 years [868]. Reported CSS rates were 78% at 5 years and 72% at 10 years. The majority of these patients were managed with initial observation after surgery, had favourable disease characteristics, and 63% had only one positive node [868]. Initial observation followed by early salvage treatment at the time of recurrence may represent a safe option in selected patients with a low disease burden [868].

6.2.5.7   Guidelines for adjuvant treatment for pN0 and pN1 disease after radical prostatectomy*

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) to pN0 patients.	Strong
In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT).	Strong
In pN1 patients, after an extended lymph node dissection, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak

*All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

*6.2.6   **Persistent PSA after radical prostatectomy***
Between 5 and 20% of men continue to have detectable or persistent PSA after RP (when defined in the majority of studies as detectable post-RP PSA of ≥ 0.1 ng/mL within 4 to 8 weeks of surgery) [937, 938]. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue.

6.2.6.1   Natural history of persistently elevated PSA after RP
Several studies have shown that persistent PSA after RP is associated with more advanced disease (such as positive surgical margins, pathologic stage ≥ T3a, positive nodal status and/or pathologic ISUP grade > 3) and poor prognosis. Initially defined as ≥ 0.1 ng/mL, improvements in the sensitivity of PSA assays now allow for the detection of PSA at much lower levels.

Moreira *et al.*, demonstrated that failure to achieve a PSA of less than 0.03 ng/mL within 6 months of surgery was associated with an increased risk of BCR and overall mortality [939, 940]. However, since the

majority of the published literature is based on the 0.1 ng/mL PSA cut-off, there is significantly more long-term data for this definition. Predictors of PSA persistence were higher BMI, higher pre-operative PSA and ISUP grade ≥ 3 [940]. In patients with PSA persistence, one and 5-year BCR-free survival were 68% and 36%, compared to 95% and 72%, respectively, in men without PSA persistence [939]. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively.

Spratt *et al.*, confirmed that a persistently detectable PSA after RP represents one of the worst prognostic factors associated with oncological outcome [941]. Of 150 patients with a persistent PSA, 95% received RT before detectable metastasis. In a multivariable analysis the presence of a persistently detectable PSA post-RP was associated with a 4-fold increase in the risk of developing metastasis. This was confirmed by data from Preisser *et al.*, who showed that persistent PSA is prognostic of an increased risk of metastasis and death [942]. At 15 years after RP, metastasis-free survival rates, OS and CSS rates were 53.0 vs. 93.2% ($p < 0.001$), 64.7 vs. 81.2% ($p < 0.001$) and 75.5 vs. 96.2% ($p < 0.001$) for persistent vs. undetectable PSA, respectively. The median follow-up was 61.8 months for patients with undetectable PSA vs. 46.4 months for patients with persistent PSA. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR: 3.59, $p < 0.001$), death (HR: 1.86, $p < 0.001$) and cancer-specific death (HR: 3.15, $p < 0.001$).

However, not all patients with persistent PSA after RP experience disease recurrence. Xiang *et al.*, showed a 50% 5-year BCR-free survival in men who had a persistent PSA level > 0.1 but ≤ 0.2 ng/mL at 6–8 weeks after RP [943].

Rogers *et al.*, assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [944]. No patient received adjuvant therapy before documented metastasis. In their study, 38% of patients had no evidence of metastases for ≥ 7 years while 32% of the patients were reported to develop metastases within 3 years. Noteworthy is that a significant proportion of patients had low-risk disease. In multivariable analysis the PSA slope after RP (as calculated using PSA levels 3 to 12 months after surgery) and pathological ISUP grade were significantly associated with the development of distant metastases.

6.2.6.2 Imaging in patients with persistently elevated PSA after RP
Standard imaging with bone scan and MRI has a low detection rate in men with a PSA below 2 ng/mL. However, PSMA PET/CT has been shown to identify residual cancer with positivity rates of 33%, 46%, 57%, 82%, and 97%, in men with post-RP PSA ranges of 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and ≥ 2 ng/mL, respectively [945-950] which can guide SRT planning [951]. Based on these post-RP PSA ranges, Schmidt-Hegemann *et al.*, studied 129 patients who had either persistent PSA (52%) or BCR (48%) after RP, showing that men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those developing a detectable PSA [952]. In a multi-centre retrospective study including 191 patients, ^{68}Ga-PSM localised biochemical persistence after RP in more than two-thirds of patients with high-risk PCa features. The obturator and presacral/mesorectal nodes were identified as high risk for residual disease [953]. Another retrospective study included 150 patients with persistent PSA after RARP who were re-staged with both ^{68}Ga-PSMA and ^{18}F-DCFPyL PSMA. The authors found that in the presence of persistent PSA the majority of patients already had metastatic pelvic LNs or distant metastases which would support a role of PSMA PET/CT imaging in guiding (salvage) treatment strategies [954]. At present there is uncertainty regarding the best treatment if PSMA PET/CT shows metastatic disease outside the pelvis.

6.2.6.3 Impact of post-operative RT and/or ADT in patients with persistent PSA
The benefit of SRT in patients with persistent PSA remains unclear due to a lack of RCTs, however, it would appear that men with a persistent PSA do less well than men with BCR undergoing RT.

Preisser *et al.*, compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not [942]. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with SRT vs. no RT, OS rates at 10 years after RP were 86.6 vs. 72.6% in the entire cohort ($p < 0.01$), 86.3 vs. 60.0% in patients with positive surgical margin ($p = 0.02$), 77.8 vs. 49.0% in pT3b disease ($p < 0.001$), 79.3 vs. 55.8% in ISUP grade 1 disease ($p < 0.01$) and 87.4 vs. 50.5% in pN1 disease ($p < 0.01$), respectively. Moreover, CSS rates at 10 years after RP were 93.7 vs. 81.6% in the entire cohort ($p < 0.01$), 90.8 vs. 69.7% in patients with positive surgical margin ($p = 0.04$), 82.7 vs. 55.3% in pT3b disease ($p < 0.01$), 85.4 vs. 69.7% in ISUP grade 1 disease ($p < 0.01$) and 96.2 vs. 55.8% in pN1 disease ($p < 0.01$), for SRT vs. no RT, respectively. In multivariable models, after 1:1 propensity score matching, SRT was associated with lower risk of death (HR: 0.42, $p = 0.02$) and lower cancer-specific death (HR: 0.29, $p = 0.03$). These survival outcomes in patients with persistent PSA who underwent SRT suggest they benefit but outcomes are worse than for men experiencing BCR [955].

It is clear from a number of studies that poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade ≥ 4 in the RP histology and pT3b disease [956-961]. Fossati *et al.*, suggested that only men with a persistent PSA after RP and ISUP grade ≤ 3 benefit significantly [962], although this is not supported by Preisser *et al*. [942]. The current data do not allow making any clear treatment decisions.

Addition of ADT may improve PFS [957]. Choo *et al.*, studied the addition of 2-year ADT to immediate RT to the prostate bed in patients with pT3 and/or positive surgical margins after RP [957]. Twenty-nine of the 78 included patients had persistently detectable post-operative PSA. The relapse-free rate was 85% at 5 years and 68% at 7 years, which was superior to the 5-year progression-free estimates of 74% and 61% in the post-operative RT arms of the EORTC and the SWOG studies, respectively, which included patients with undetectable PSA after RP [913, 914]. Patients with persistently detectable post-operative PSA comprised approximately 50% and 12%, respectively, of the study cohorts in the EORTC and the SWOG studies.

In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only (66 Gy per protocol [arm C]). The 10-year clinical relapse-free survival was 63% [956]. The GETUG-22 trial comparing RT with RT plus short-term ADT for post-RP PSA persistence (0.2–2.0 ng/mL) reported good tolerability of the combined treatment. The oncological endpoints are yet to be published [963].

Two systematic reviews addressing persistent PSA confirmed a strong correlation of PSA persistence with poor oncologic outcomes [937, 938]. Ploussard *et al.*, also reported that SRT was associated with improved survival outcomes, although the available evidence is of low quality [938].

6.2.6.4   Conclusion
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.

6.2.6.5   Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT scan to men with a persistent prostate-specific antigen > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.3   Management of PSA-only recurrence after treatment with curative intent
Follow-up will be addressed in Chapter 7 and is not discussed in this section.

6.3.1   *Background*
Between 27% and 53% of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.3.1.1   PSA velocity and doubling time
Various PSA kinetics definitions have been proposed with different methods of calculation (log transformed or not) and eligible PSAs:
•   PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year);
•   PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time.

Prostate-specific antigen velocity is more simple to calculate by subtracting the initial value from the final value, dividing by time. However, by ignoring middle values, not all PSA values are accurately taken into account.

Prostate-specific antigen-DT is calculated assuming an exponential rise in serum PSA. The formula takes into account the natural logarithm of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA over time [964]. However, many different PSA-DT calculations have been assessed according to the mathematical formula used and to the included PSA values (number, time period, intervals) [965]. For example,

the 'MSKCC' method calculates a regression slope integrating all PSA values. Other methods transform PSA before calculating the slope and do not include all PSA values (different time frames and minimal intervals) [966]. O'Brien and colleagues identified more than 20 different definitions of PSAV and PSA-DT and demonstrated that obtained values could vary widely between definitions [966].

However, some rules can be considered for PSA-DT calculation [964]:
• At least 3 PSA measurements are required;
• A minimum time period between measurements (4 weeks) is preferable due to potential statistical 'noise' when PSA values are obtained too close together (this statement can be reconsidered in case of very active disease);
• All included PSA values should be obtained within the past 12 months at most, to reflect the current disease activity;
• PSA-DT is often mentioned in months, or in weeks in very active disease.

These measurements do not provide additional information compared with PSA alone [966-969]. In the post-local therapy relapse setting, PSA-DT has been correlated with distant progression and with poorer outcomes after salvage treatments [970, 971]. Prostate-specific antigen-DT has been linked with metastasis-free- and OS in non-metastatic CRPC (nmCRPC) and identifies patients with high-risk nmCRPC who benefit from intensified therapy (PSA-DT threshold < 10 months) [972].

6.3.2 Controversies in the definitions of clinically relevant PSA relapse
The PSA level that defines treatment failure depends on the primary treatment. Patients with rising PSA after RP or primary RT have different risks of subsequent symptomatic metastatic disease based on various parameters, including the PSA level. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments. Clinicians should interpret a PSA rise in light of the EAU BCR risk groups (see Section 6.3.3).

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [973-975]. However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients.
 After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is 'any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir' [976].
 After HIFU or cryotherapy no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments [977].

6.3.3 Natural history of biochemical recurrence
Once a PSA recurrence has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. A systematic review and meta-analysis investigated the impact of BCR on hard endpoints and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, PCa-specific and overall mortality [977]. However, the effect size of BCR as a risk factor for mortality is highly variable. After primary RP its impact ranges from HR 1.03 (95% CI: 1.004–1.06) to HR 2.32 (95% CI: 1.45–3.71) [978, 979]. After primary RT, OS rates are approximately 20% lower at 8 to 10 years follow-up even in men with minimal co-morbidity [980, 981]. Still, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality.
 The risk of subsequent metastases, PCa-specific- and overall mortality may be predicted by the initial clinical and pathologic factors (e.g., T-category, PSA, ISUP grade) and PSA kinetics (PSA-DT and interval to PSA failure), which was further investigated by the systematic review [977].

For patients with BCR after RP, the following outcomes were found to be associated with significant prognostic factors:
• distant metastatic recurrence: positive surgical margins, high RP specimen pathological ISUP grade, high pT category, short PSA-DT, high pre-SRT PSA;
• prostate-cancer-specific mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure as defined by investigators, short PSA-DT;
• overall mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure, high PSA-DT.

For patients with BCR after RT, the corresponding outcomes are:
- distant metastatic recurrence: high biopsy ISUP grade, high cT category, short interval to biochemical failure;
- prostate-cancer-specific mortality: short interval to biochemical failure;
- overall mortality: high age, high biopsy ISUP grade, short interval to biochemical failure, high initial (pre-treatment) PSA.

Based on this meta-analysis, proposal is to stratify patients into two risk categories since not all patients with BCR will have similar outcomes (see Table 6.3.1). The stratification into 'EAU Low-Risk' or 'EAU High-Risk' BCR has recently been validated in a European cohort [982].

Table 6.3.1: EAU risk categories for biochemical recurrence

	EAU Low Risk	EAU High Risk
After RP	PSA-DT > 1 year AND pathological ISUP grade < 4	PSA-DT < 1 year OR pathological ISUP grade 4–5
After RT	interval to biochemical failure > 18 months AND biopsy ISUP grade < 4	interval to biochemical failure < 18 months OR biopsy ISUP grade 4–5

6.3.4 *The role of imaging in PSA-only recurrence*
Imaging is only of value if it leads to a treatment change which results in an improved outcome. In practice, however, there are very limited data available regarding the outcomes consequent on imaging at recurrence.

6.3.4.1 *Assessment of metastases (including nodal)*
6.3.4.1.1 Bone scan and abdominopelvic CT
Because BCR after RP or RT precedes clinical metastases by 7 to 8 years on average [903, 983], the diagnostic yield of conventional imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [984]. In men with PSA-only recurrence after RP the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [985, 986]. Only 11–14% of patients with BCR after RP have a positive CT [985]. In a series of 132 men with BCR after RP the mean PSA level and PSA velocity associated with a positive CT were 27.4 ng/mL and 1.8 ng/mL/month, respectively [987].

6.3.4.1.2 Choline PET/CT
In two different meta-analyses the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86–89% and 89–93%, respectively [988, 989].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [990] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [991]. The specificity of choline PET/CT is also higher than bone scan, with fewer false-positive and indeterminate findings [420]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.3). Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [429, 992, 993]. In patients with BCR after RP, PET/CT detection rates are only 5–24% when the PSA level is < 1 ng/mL but rises to 67–100% when the PSA level is > 5 ng/mL. Despite its limitations, choline PET/CT may change medical management in 18–48% of patients with BCR after primary treatment [994-996].

Choline PET/CT should only be recommended in patients fit enough for curative loco-regional salvage treatment.

6.3.4.1.3 Fluoride PET/CT
^{18}F-NaF PET/CT has a higher sensitivity than bone scan in detecting bone metastases [997]. However, ^{18}F -NaF PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [998].

6.3.4.1.4 Fluciclovine PET/CT
^{18}F-Fluciclovine PET/CT has been approved in the U.S. and Europe and it is therefore one of the PCa-specific radiotracers widely commercially available [999-1001].

^{18}F-Fluciclovine PET/CT has a slightly higher sensitivity than choline PET/CT in detecting the site of relapse in BCR [1002]. In a multi-centre trial evaluating 596 patients with BCR in a mixed population fluciclovine

PET/CT showed an overall detection rate of 67.7%; lesions could be visualised either at local level (38.7%) or in LNs and bones (9%) [1003]. As for choline PET/CT, fluciclovine PET/CT sensitivity is dependent on the PSA level, with a sensitivity likely inferior to 50% at PSA < 1 ng/mL.

In a prospective RCT evaluating the impact of ^{18}F-fluciclovine PET/CT on SRT management decisions in patients with recurrence post-prostatectomy, in 28 of 79 (35.4%) patients overall radiotherapeutic management changed following ^{18}F-fluciclovine PET/CT [1004]. ^{18}F-Fluciclovine PET/CT had a significantly higher positivity rate than conventional imaging (abdominopelvic CT or MRI plus bone scan) for whole body (79.7% vs. 13.9%, p < 0.001), prostate bed (69.6% vs. 5.1%, p < 0.001), and pelvic LNs (38.0% vs. 10.1%, p < 0.001) [1004]. However, as yet, no data demonstrating that these changes translate into a survival benefit are available.

6.3.4.1.5   Prostate-specific membrane antigen based PET/CT
PSMA PET/CT has shown good potential in patients with BCR, although most studies are limited by their retrospective design. Reported predictors of ^{68}Ga-PSMA PET in the recurrence setting were recently updated based on a high-volume series (see Table 6.3.2) [945]. High sensitivity (75%) and specificity (99%) were observed on per-lesion analysis.

Table 6.3.2: PSMA-positivity separated by PSA level category [945]

PSA (ng/mL)	^{68}Ga-PMSA PET positivity
< 0.2	33% (CI: 16–51)
02–0.49	45% (CI: 39–52)
0.5–0.99	59% (CI: 50–68)
1.0–1.99	75% (CI: 66–84)
2.0+	95% (CI: 92–97)

PSA = prostate-specific antigen; ^{68}Ga-PSMA PET = Gallium-68 prostate-specific membrane antigen positron emission tomography.

PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL [1005, 1006]. In a study of 314 patients with BCR after treatment and a median PSA level of 0.83 ng/mL, ^{68}Ga-PSMA PET/CT was positive in 197 patients (67%) [1007]. In another prospective multi-centre trial including 635 patients with BCR after RP (41%), RT (27%), or both (32%), PPV for ^{68}Ga-PSMA PET/CT was 0.84 (95% CI: 0.75–0.90) by histopathologic validation (primary endpoint, n = 87) and 0.92 (95% CI: 0.75–0.90) by a composite reference standard. Detection rates significantly increased with PSA value [1008].

A prospective multi-centre, multi-reader, open-label, phase II/III trial (OSPREY) evaluated the diagnostic performance of ^{18}F-DCFPyL in patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging [415]. Median sensitivity and median PPV were 95.8% (95% CI: 87.8%–99.0%) and 81.9% (95% CI: 73.7%–90.2%), respectively.

Another prospective study evaluated the diagnostic performance of ^{18}F-DCFPyL in 208 men with BCR after RP or RT. The primary endpoint, the correct localisation rate was achieved, demonstrating positive findings on ^{18}F-DCFPyL PET/CT in the setting of negative standard imaging [1009]. At present there are no conclusive data about comparison of such tracers [1010].

6.3.4.1.6   Whole-body and axial MRI
Whole body MRI has not been widely evaluated in BCR because of its limited value in the detection of early metastatic involvement in normal-sized LNs [418, 431, 1011]. In a prospective series of 68 patients with BCR, the diagnostic performance of DW-MRI was significantly lower than that of ^{68}Ga-PSMA PET/CT and [18]NaF PET/CT for diagnosing bone metastases [1012].

6.3.4.2   Assessment of local recurrences
6.3.4.2.1   Local recurrence after radical prostatectomy
Because the sensitivity of anastomotic biopsies is low, especially for PSA levels < 1 ng/mL [984], SRT is usually decided on the basis of BCR without histological proof of local recurrence. The dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Therefore, most patients undergo SRT without local imaging.

Magnetic resonance imaging can detect local recurrences in the prostatic bed. The PSA threshold for MRI positivity seems between 0.3 and 0.5 ng/mL; PSA kinetics also influence the MRI positivity, even at low PSA

values [1013]. Two single-centre studies found that a negative MRI was an independent predictor of failure of SRT [1014, 1015].

Choline PET/CT is less sensitive for local relapse than MRI but detects more regional and distant metastases [1016].

The detection rates of ^{68}Ga-PSMA PET/CT in patients with BCR after RP increase with the PSA level [1017]. PSMA PET/CT studies showed that a substantial part of recurrences after RP were located outside the prostatic fossa, even at low PSA levels [946, 1018]. Combining ^{68}Ga-PSMA PET and MRI may improve the detection of local recurrences, as compared to ^{68}Ga-PSMA PET/CT alone [1019-1021].

The EMPIRE-1, a single-centre, open-label, phase II/III RCT included 365 patients with detectable PSA after RP, but negative results on conventional imaging. They were randomised to RT directed by conventional imaging alone or to conventional imaging plus ^{18}F-fluciclovine-PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. After a median follow-up of 3.5 years, the PET/CT group was significantly associated with longer event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1022].

6.3.4.2.2   Local recurrence after radiation therapy
In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained 18–24 months after initial treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [984].

MRI has yielded excellent results in identifying local recurrence and can be used for biopsy targeting and guiding local salvage treatment [984, 1023-1026], even if it slightly underestimates the volume of the local recurrence [1027]. Prostate-specific membrane antigen PET/CT can also detect local recurrences after RT [945] and concordance between PSMA PET/CT and MRI is highly suggestive of cancer recurrence [1028].

6.3.4.3   Summary of evidence of imaging in case of biochemical recurrence
In patients with BCR imaging can detect both local recurrences and distant metastases, however, the sensitivity of detection depends on the PSA level. After RP, PSMA PET/CT seems to be the imaging modality with the highest sensitivity at low PSA levels (< 0.5 ng/mL) and may help distinguishing patients with recurrences confined to the prostatic fossa from those with distant metastases which may impact the design and use of post-RP SRT. After RT, MRI has shown excellent results at detecting local recurrences and guiding prostate biopsy. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences and who are fit for these salvage therapies. Choline-, fluciclovine- or PSMA-PET/CT can be used to detect metastases in these patients but for this indication PSMA PET/CT seems the most sensitive technique.

6.3.4.4   Summary of evidence and guidelines for imaging in patients with biochemical recurrence

Recommendations	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

6.3.5   **Treatment of PSA-only recurrences**
The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

6.3.5.1   Treatment of PSA-only recurrences after radical prostatectomy
6.3.5.1.1   Salvage radiotherapy for PSA-only recurrence after radical prostatectomy (cTxcN0M0, without PET/CT)
Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al.*, reported a 75% reduced risk of systemic progression with SRT when comparing 856 SRT patients with 1,801 non-SRT

patients [1029]. The RAVES and RADICAL trials assessing SRT in post-RP patients with PSA levels exceeding 0.1–0.2 ng/mL showed 5-year freedom from BCR and BCR-free survival rates of 88% [919, 1030].

The PSA level at BCR was shown to be prognostic [1029]. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [1031-1034], corresponding to a ~80% chance of being progression-free 5 years later [1035]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or SRT alone (n = 160) within 2 years of BCR showed that SRT was associated with a 3-fold increase in PCa-specific survival relative to those who received no salvage treatment (p < 0.001). Salvage RT has been shown to be effective mainly in patients with a short PSA-DT [1036]. For an overview of SRT see Table 6.3.3.

The EAU BCR definitions have been externally validated and may be helpful for individualised treatment decisions [977, 982]. Despite the indication for SRT, a 'wait and see' strategy remains an option for the EAU BCR 'Low-Risk' group [977, 982].

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence; metastatic disease, disease-specific and OS are more meaningful endpoints to support clinical decision-making. A systematic review and meta-analysis on the impact of BCR after RP reports SRT to be favourable for OS and PCSM. In particular SRT should be initiated in patients with rapid PSA kinetics after RP and with a PSA cut-off of 0.4 ng/mL [977]. An international multi-institutional analysis of pooled data from RCTs has suggested that metastasis-free survival is the most valid surrogate endpoint with respect to impact on OS [1037, 1038]. Table 6.3.4 summarises results of recent studies on clinical endpoints after SRT.

Table 6.3.3: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy PSA level* (cTxcN0M0, without PET/CT)

Study	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, et al. 2018 [1039]	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Soto, et al. 2012 [1040]	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16
Stish, et al. 2016 [1031]	1,106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Tendulkar, et al. 2016 [1041]	2,460	60	0.5	66 Gy 16% ADT	56% (5)	Pre-SRT PSA 71% 0.01–0.2 ng/mL 63% 0.21–0.5 ng/mL 54% 0.51–1.0 ng/mL 43% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

*Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival'. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.
ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up;
mo = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen;
SRT = salvage radiotherapy; yr = year.

Table 6.3.4: Recent studies reporting clinical endpoints after SRT (cTxcN0M0, without PET/CT) (the majority of included patients did not receive ADT)

Study	n	Median FU (mo)	Regimen	Outcome
Bartkowiak, et al. 2018 [1039]	464	71	66.6 (59.4-72) Gy no ADT	5.9 yr. OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p = 0.005

Jackson, et al. 2014 [1042]	448	64	68.4 Gy no ADT	5 yr. DM post-SRT PSA < 0.1 ng/mL 5% post-SRT PSA ≥ 0.1 ng/mL 29% p < 0.0001 5 yr. DSM post-SRT PSA < 0.1 ng/mL 2% post-SRT PSA ≥ 0.1 ng/mL 7% p < 0.0001 OS post-SRT PSA < 0.1 ng/mL 97% post-SRT PSA ≥ 0.1 ng/mL 90% p < 0.0001
Stish, et al. 2016 [1031]	1,106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr. DM SRT: PSA ≤ 0.5 ng/mL 7% and 12% SRT: PSA > 0.5 ng/mL 14% and 23% p < 0.001 5 and 8.9 yr. DSM SRT: PSA ≤ 0.5 ng/mL < 1% and 6% SRT: PSA > 0.5 ng/mL 5% and 10% p = 0.02 5 and 8.9 yr. OS SRT: PSA ≤ 0.5 ng/mL 94% and 86% SRT: PSA > 0.5 ng/mL 91% and 78% p = 0.14
Tendulkar, et al. 2016 [1041]	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10-yr. DM (19% all patients) Pre-SRT PSA 9% 0.01–0.2 ng/mL 15% 0.21–0.5 ng/mL 19% 0.51–1.0 ng/mL 20% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality;
FU = follow up; mo. = month; n = number of patients; OS = overall survival; PSA = prostate specific antigen;
SRT = salvage radiotherapy.

6.3.5.1.2   Salvage radiotherapy combined with androgen deprivation therapy (cTxcN0, without PET/CT)
Data from RTOG 9601 suggest both CSS and OS benefit when adding 2 years of bicalutamide (150 mg o.d.) to SRT [1043]. According to GETUG-AFU 16 also 6-months treatment with a LHRH-analogue can significantly improve 10-year BCR, biochemical PFS and, modestly, metastasis-free survival. However, SRT combined with either goserelin or placebo showed similar DSS and OS rates [1044]. In addition, Pollack *et al*., reported on the results of a randomised 3-arm phase III trial (NRG Oncology/RTOG 0534 SPPORT) adding six months treatment with a LHRH-analogue to SRT of the prostate bed (PBRT) (group 2) compared with PBRT alone (group 1) or the former combination with PBRT-RT and pelvic LN RT (PLNRT) (group 3) [1045]). The primary endpoint was freedom from progression (FFP) after 5 years. However, using the phoenix-definition of biochemical progression (nadir + 2 ng/mL used for definitive RT), and not the criterion of nadir + 0.2, as is used commonly (but without clear evidence) will have resulted in a later diagnosis of progression in the SPPORT trial.

With a median follow-up of 8.2 years of the surviving patients FFP increased significant for group 3 (87.4%) compared with group 2 (81.3%) (p = 0.0027) and group 1 (70.9%) (p < 0.0001) The difference between group 2 and group 1 was also significant (p < 0.0001). Distant metastasis incidence rates were lowest in group 3 and were lower compared with group 1 (PBRT only, HR: 0.52) similar to the rate of PCa deaths (HR: 0.51). No significant difference was seen for OS. There was a significantly higher risk of both acute- and late side effects in group 3. In conclusion, the role of additional PLNRT remains unclear and should be further proven in RCTs including PSMA PET-CT [1046]. Table 6.3.5 provides an overview of these three RCTs.

These RCTs support adding ADT to SRT. However, when interpreting these data it has to be kept in mind that RTOG 9601 used outdated radiation dosages (< 66 Gy) and technique. The question with respect to the patient risk profile, whether to offer combination treatment or not, and the optimal combination (LHRH or bicalutamide) remains, as yet, unsolved. The EAU BCR risk classification may offer guidance in this respect [977].

One of these RCTs reports improved OS (RTOG 96-01) and the other (GETUG-AFU 16) improved metastasis-free survival but due to methodological discrepancies and also related to follow-up and risk

patterns, it is, as yet, not evident which patients should receive ADT, which type of ADT, and for how long. Men at high risk of further progression (e.g., with a PSA ≥ 0.7 ng/mL and GS ≥ 8) may benefit from SRT combined with two years of ADT; for those at lower risk (e.g., PSA < 0.7 ng/mL and GS = 8) SRT combined with 6 months of ADT may be sufficient. Men with a low-risk profile (PSA < 0.5 ng/mL and GS < 8) may receive SRT alone. In a sub-analysis of men with a PSA of 0.61 to 1.5 (n = 253) there was an OS benefit associated with anti-androgen assignment (HR: 0.61, 95% CI: 0.39–0.94) [1047]. In those receiving early SRT (PSA 0.6 ng/mL, n = 389), there was no improvement in OS (HR: 1.16, 95% CI: 0.79–1.70), with increased other-cause mortality (sub-distribution HR: 1.94, 95% CI: 1.17–3.20, p = 0.01) and increased odds of late grades 3–5 cardiac and neurologic toxic side effects (OR: 3.57, 95% CI: 1.09–15.97, p = 0.05). These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of anti-androgen treatment with SRT. In patients receiving late SRT (PSA > 0.6 ng/mL), HT was associated with improved outcomes. In men receiving early SRT (PSA < 0.6 ng/mL), long-term anti-androgen treatment was not associated with improved OS [1047].

A systematic review addressing the benefit from combining HT with SRT suggested risk stratification of patients based on the pre-SRT PSA (< 0.5, 0.6–1, > 1 ng/mL), margin status and ISUP grade as a framework to individualise treatment [1048].

Table 6.3.5: Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone

Study	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 2019 [1044]	369 RT + ADT 374 RT	ISUP grade ≤ 2/3 89% ISUP grade ≥ 4 11% cN0	112	66 Gy PBRT + 6 mo. LHRH analogue 66 Gy BPRT	**10-yr.** **PFS: RT + ADT, 64%** **PFS: RT, 49%** p < 0.0001 **MFS: RT + ADT, 75%** **MFS: RT, 69%** p = 0.034
RTOG 9601 2017 [1043]	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy PBRT + bicalutamide 24 mo. 64.8 Gy PBRT + placebo	**12-yr.** **cumulative DM** **RT + ADT: 14%** **RT + placebo: 23%** p = 0.005 **OS** **RT + ADT: 76%** **RT + placebo: 71%** p = 0.04 **DSM** **RT + ADT: 5.8%** **RT + placebo: 13.4%** p < 0.001
NRG Oncology/ RTOG 0534 SPPORT [1045]	574 SRT + PBRT + ADT 578 SRT + ADT 564 SRT	pT2 or pT3 ISUP < 5 Pre SRT PSA: 0.1-2.0	survivors: 8.2 years	64.8–0.2 Gy PBRT 64.8–70.2 Gy PBRT 6 mo. LHRH analogue 64.8–70.2 Gy PBRT + 45 Gy PLNRT 6 mo. LHRH analogue	**5-yr. FFP (primary endpoint)** **70.9% Group 1** **81.3% Group 2** **87.4% Group 3** **Comparisons :** **G 3 vs. G 1:** p < 0.0001 **G 2 vs. G 1** p < 0.0001 **G 3 vs. G 2** p < 0.0027

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; PFS = progression free survival; FFP = Freedom From Progression; FU = follow-up; LHRH = luteinising hormone-releasing hormone; MFS = metastasis-free survival; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = radiotherapy; yr = year, PBRT = prostate bed radiotherapy; PLNRT = pelvic lymph node radiotherapy.

6.3.5.1.2.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for 'clinical target volumes' for pN0 PCa [1049-1051] and for organs at risk of normal tissue complications [1050, 1051]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS but not metastasis-free survival has been reported in patients receiving whole pelvis SRT (± ADT) but the advantages must be weighed against possible side effects [1046]. This is supported by data from the SPPORT-Trial (NRG Oncology/RTOG 0534 SPPORT) but it remains controversial [1045].

The optimal SRT dose has not been well defined. It should be at least 64 Gy to the prostatic fossa (± the base of the SVs, depending on the pathological stage after RP) [924, 1032, 1052]. In a systematic review, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that the treatment dose above 70 Gy should be administered at the lowest possible PSA level [1053]. The combination of pT stage, margin status and ISUP grade and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [916, 1054, 1055]. In a study on 894 node-negative PCa patients, doses ranging from 64 to > 74 Gy were assigned to twelve risk groups defined by their pre-SRT PSA classes < 0.1, 0.1–0.2, 0.2–0.4, and > 0.4 ng/mL and ISUP grade, < 1 vs. 2/3 vs. > 4 [1056]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [1041].

Two RCT's were recently published (Table 6.3.6). Intensity-modulated radiation therapy plus IGRT was used in 57% of the patients in the SAKK-trial [924] and in all patients of a Chinese trial [1057]. No patient had a PSMA PET/CT before randomisation. The primary endpoint in both trials was 'freedom from biochemical progression', which was not significantly improved with higher doses. However, in the Chinese trial a subgroup analysis showed a significant improvement of this endpoint for patients with Gleason 8-10 tumours (79.7% vs. 55%, p = 0.049). In this trial, patients were treated with ART or SRT and the number of patients was relatively small (n = 144). At this time it seems difficult to draw final conclusions about the optimal total RT-dose and longer follow-up should be awaited.

Table 6.3.6: Randomized trials investigating dose escalation for SRT without ADT and without PET-CT

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
SAKK 09/10 trial, 2021 [924]	350	pT2a-3b R0 – R1 pN0 or cN0 PSA post-op undetectable (< 0.1 ng/mL) or persistent (> 0.1 ng/mL < 0.4 ng/mL)	64 Gy vs. 70 Gy No ADT allowed VMAT + IGRT: 57% 3-D planning: 43%	6.2 yr.	Primary endpoint: FFBP	**6 yr. FFBP: 62% vs. 61% OS: no difference** **Late side effects: GI grade 2: 7.3% vs. 20% GI grade 3: 4.2% vs. 2.3%** p for ≥ grade 2/3: 0.009
Phase-III-Trial Qi X, *et al.*, 2020 [1057]	144 ART: 33% SRT: 67%	pT2-4 R0-R1 pN0 or cN0 Med. PSA pre-RT: 0.2 ng/mL	66 Gy vs. 72 Gy All patients VMAT + IGRT No ADT allowed High risk (pT3–4, GS: 8–10, PSA > 20 ng/mL): whole pelvis RT: 126 (87.5%)	49 mo.	Primary endpoint: FFBP	**4 yr. FFBP: 75.9% vs. 82.6%** (p > 0.05) **High risk (GS: 8–10): 55.7% vs. 79.7%** p < 0.049) **Late side effects: GI + GU grade 2 p > 0.05 No grade 3**

ADT = androgen deprivation therapy; ART = adjuvant radiotherapy; FFBP = freedom from biochemical failure; GI = gastro-intestinal; GU = genito-urinary; Gy = Gray; IGRT = image guided radiotherapy; mo = month; n = number of patients; PSA = prostate-specific antigen; RT = radiotherapy; SRT = y = year; vs. = versus; VMAT = volumetric arc radiation therapy.

Salvage RT is associated with toxicity. In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late grade 3 reactions of the GI tract, but overall, severe GU tract toxicity was not observed. Late grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [1039].

In a RCT on dose escalation for SRT (n = 350), acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastro-intestinal tract grades 2 and 3 toxicity occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy. Late effects have yet to be reported [1058, 1059]. Late grade 2 and 3 GI toxicity was significantly increased with higher doses but without significant differences in QoL. In this study, however, the rectal wall dose constraints were rather permissive and in 44% of the patients outdated 3-D-techniques were used [924].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side effects, especially GU symptoms, clearly increases, even with newer planning and treatment techniques [1060, 1061]. In particular, when compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02) but no effect on the relatively high level of GU toxicity was shown (5-year, 3D-CRT 15.8% vs. IMRT 16.8%) [1060]. However, in a RCT comparing 66 Gy and 72 Gy with all patients having IMRT plus IGRT (n = 144), no significant differences for GI and GU-toxicity was demonstrated [1057]. After a median salvage IMRT dose of 76 Gy, however, the 5-year risk of grade 2–3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [1061]. Doses of at least 64 Gy and up to 72 Gy in patients without PET/CT can be recommended [1039, 1058].

6.3.5.1.2.2 Salvage radiotherapy with or without ADT (cTx cN0/1) with PET/CT
In a prospective multi-centre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [1062].

A prospective study in a subgroup of 119 BCR patients with low PSA (< 0.5 ng/mL) reported a change in the intended treatment in 30.2% of patients [946]; however, no data exist on the impact on final outcome.

Another prospective study in 272 patients with early biochemical recurrent PCa after RP showed that ^{68}Ga-PSMA PET/CT may tailor further therapy decisions (e.g., local vs. systemic treatment) at low PSA values (0.2–1 ng/mL) [948].

A single-centre study retrospectively assessed 164 men who underwent imaging with PSMA PET/CT for a rising PSA after RP with PSA levels < 0.5 ng/mL. In men with a negative PSMA PET/CT who received SRT, 85% (23 out of 27) demonstrated a treatment response compared to a further PSA increase in 65% of those not treated (22 out of 34). In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (29 out of 36) responded to SRT [1063]. Thus, PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to the prostate) and poor response (positive nodes or distant disease) to SRT.

A recent multi-centre retrospective study evaluated patients who underwent SRT for BCR after RP, without any signs of distant metastatic disease on PET/CT. After case-controle matching, 2 cohorts (n = 108 patients each), with and without PSMA PET/CT prior to SRT were analysed. In the cohort without PSMA PET/CT, 23 patients (21%) had BCR at 1 year after SRT vs. 9 patients (8%) who underwent restaging with PSMA PET/C prior to SRT (p = 0.007). PSMA-PET/CT was found to be associated with an improved oncological outcome in patients with BCR after RP, receiving SRT to the prostatic fossa [1064]. It is worth mentioning that in this study the median biologically effective radiation dose administered in the PSMA-cohort was significantly higher than in the historical cohort (70 Gy vs. 66 Gy, respectively, p < 0.001). However, another publication showed that the biochemical progression rate after SRT between patients who underwent 64 Gy or 70 Gy to the prostate bed, without HT for BCR, did not differ significantly [1065]. Therefore, it is questionable whether this difference in administered radiation dose influenced the outcome in both cohorts. As there are no prospective phase III data (in particular not for PCa-specific survival or OS) these results have to be confirmed before a recommendation can be provided.

A single-centre open-label, phase II/III RCT (EMPIRE-1) evaluated the role of ^{18}F-fluciclovine-PET/CT compared with conventional imaging for SRT. Three hundred and sixty five patients with detectable PSA after RP but negative results on conventional imaging, were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow-

up was 3.5 years. In adjusted analyses, the study group was significantly associated with event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1022].

6.3.5.1.2.3 Nodal-directed therapy for rcN1 (with PET/CT)
Radiolabelled PSMA PET/CT is increasingly used as a diagnostic tool to assess metastatic disease burden in patients with BCR following prior definitive therapy. A review including 30 studies and 4,476 patients showed overall estimates of positivity in a restaging setting of 38% in pelvic LNs and 13% in extra-pelvic LN metastases [945]. The percentage positivity of PSMA PET/CT was proven to increase with higher PSA values [945]. Results of this review demonstrated a high sensitivity and specificity of ^{68}Ga-PSMA in advanced PCa, with a per-lesion-analysed sensitivity and specificity of 75% and 99%, respectively.

A large retrospective international study included patients with LN-recurrent PCa (cN1 and M1a) and PSA progression following multi-modality treatment (surgery and post-operative RT) [1066]. The aim of the study was to compare standard of care (SOC) with nodal metastasis-directed therapy (MDT). The nodal MDT-group showed significantly better CSS than the SOC control group (5-year survival 98.6% vs. 95.7%, p < 0.01, respectively) [1066].
        Another retrospective study compared SABR with elective nodal irradiation (ENRT) in nodal oligo-recurrent PCa (n = 506 patients, 365 of which with N1 pelvic recurrence). With a median follow-up of 36 months, ENRT (n = 197) was associated with a significant reduction of nodal recurrences (p < 0.001), compared with SABR (n = 309) of 2% vs. 18%, respectively. In a a multi-variable analysis, patients with one LN at recurrence had longer adjusted MFS after ENRT (HR: 0.50, 95% CI: 0.30–0.85, p = 0.009). The tendency to relapse was higher for pelvic- than extra-pelvic nodes (p < 0.001) [1067]. For patients presenting with two or more (extra)pelvic LNs, adjusted MFS was not significantly different (HR: 0.92, 95% CI: 0.54– 1.59, p = 0.8). In these situations, SABR should be used in highly selected patients in prospective cohorts or clinical trials only, before any recommendations can be made. For MDT in M1 patients see Section 6.4.7.

6.3.5.1.3   Salvage lymph node dissection
The surgical management of recurrent nodal metastases in the pelvis has been the topic of several retrospective analyses [1068-1070] and a systematic review [1071]. The reported 5-year BCR-free survival rates ranged from 6% to 31%. Five-year OS was approximately 84% [1071]. Biochemical recurrence rates were found to be dependent on PSA at salvage surgery and location and number of positive nodes [1072]. Addition of RT to the lymphatic template after salvage LN dissection may improve the BCR rate [1073]. In a multi-centre retrospective study long-term outcomes of 189 patients who underwent salvage LN dissection were reported to be worse than previously described in studies with shorter follow-up [1074]. Biochemical recurrence (BCR)-free survival at 10 years was 11%. Patients with a PSA response after salvage LN dissection and patients receiving ADT within 6 months from salvage LN dissection had a lower risk of death from PCa [1074]. The majority of the patients (81%) had received a choline PET and median PSA at salvage LN dissection was 2.5 ng/mL. In a cohort study including patients treated with salvage LN dissection via PSMA-radio-guided surgery (PSMA-RGS), 2-year BCR-free survival rate was 32% [1075]. In multi-variable analyses, higher pre-operative PSA, higher number of PSMA-avid lesions, multiple (pelvic plus retroperitoneal), and retroperitoneal localisation of lesions at pre-operative imaging were independent predictors of BCR after PSMA-RGS. High-level evidence for the oncological value of salvage LN dissection (including adjuvant RT of the LNs) is still lacking [1071].

6.3.5.2   Management of PSA failures after radiation therapy
Therapeutic options in these patients are ADT or salvage local procedures, as well as a 'wait and see' approach, based on EAU BCR risk categories at relapse. A systematic review and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage HIFU, salvage cryotherapy, SBRT, salvage LDR brachytherapy, and salvage HDR brachytherapy in the management of locally recurrent PCa after primary radical EBRT [1076]. The outcomes were BCR-free survival at 2 and 5 years. No significant differences with regards to recurrence-free survival (RFS) between these modalities was found. Five-year RFS ranged from 50% after cryotherapy to 60% after HDR brachytherapy and SBRT. The authors reported that severe GU toxicity exceeded 21% for HIFU and RP, whereas it ranged from 4.2% to 8.1% with re-irradiation. Differences in severe GI toxicity also appeared to favour re-irradiation, particularly HDR brachytherapy [1076]. Due to the methodological limitations of this review (the majority of the included studies were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes) the available evidence for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made. The following is an overview of the most important findings for each of these techniques.

6.3.5.2.1   Salvage radical prostatectomy
Salvage RP after RT is associated with a higher likelihood of AEs compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation [1077].

6.3.5.2.1.1 Oncological outcomes
In a systematic review of the literature, Chade, *et al*., showed that SRP provided 5- and 10-year BCR-free survival estimates ranging from 47–82% and from 28–53%, respectively. The 10-year CSS and OS rates ranged from 70–83% and from 54–89%, respectively. The pre-SRP PSA value and prostate biopsy ISUP grade were the strongest predictors of the presence of organ-confined disease, progression, and CSS [1078]. In a multi-centre analysis including 414 patients, 5-year BCR-free survival, CSS and OS were 56.7%, 97.7% and 92.1%, respectively [1079]. Pathological T stage ≥ T3b (OR: 2.348) and GS (up to OR 7.183 for GS > 8) were independent predictors for BCR (see Table 6.3.7).

Table 6.3.7: Oncological results of selected salvage radical prostatectomy case series

Study	n	Median FU (mo)	Pathologic Organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability
Chade, *et al*. 2011 [1080]	404	55	55	25	16	37	83	10 yr.
Mandel, *et al*. 2016 [1081]	55	36	50	27	22	49	89	5 yr.
Ogaya-Pinies, *et al*. 2018 [1082]	96	14	50	17	8	85*	-	14 mo.
Marra, *et al*. 2021 [1079]	414	36	46	30	16	57	98	5 yr.

Percentage of patients without BCR.
BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin; yr. = year.

6.3.5.2.1.2 Morbidity
Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [1083]. In more recent series, these complications appear to be less common [1077, 1078, 1081].
Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [1078, 1081].

6.3.5.2.1.3 Summary of salvage radical prostatectomy
In general, SRP should be considered only in patients with low co-morbidity, a life expectancy of at least 10 years, a pre-SRP PSA < 10 ng/mL and initial biopsy ISUP grade ≤ 2/3, no LN involvement or evidence of distant metastatic disease pre-SRP, and those whose initial clinical staging was T1 or T2 [1078].

6.3.5.2.2   Salvage cryoablation of the prostate
6.3.5.2.2.1 Oncological outcomes
Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to salvage RP, as it has a potentially lower risk of morbidity and equal efficacy.
In a systematic review a total of 32 studies assessed SCAP, recruiting a total of 5,513 patients. The overwhelming majority of patients (93%) received whole-gland SCAP. The adjusted pooled analysis for 2-year BCR-free survival for SCAP was 67.49% (95% CI: 61.68–72.81%), and for 5-year BCR-free survival was 50.25% (95% CI: 44.10–56.40%). However, the certainty of the evidence was low. Table 6.3.8 summarises the results of a selection of the largest series on SCAP to date in relation to oncological outcomes (BCR only) [1076].

Table 6.3.8: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Ginsburg, *et al*. 2017 [1084]	898	19.0	5	71.3%	Phoenix criteria
Spiess, *et al*. 2010 [1085]	450	40.8	3.4	39.6%	PSA > 0.5 ng/mL
Li, *et al*. 2015 [1086]	486	18.2	5	63.8%	Phoenix criteria
Kovac, *et al*. 2016 [1087]	486	18.2	5	75.5% (nadir PSA < 0.4 ng/mL); 22.1% (nadir PSA ≥ 0.4 ng/mL)	Phoenix criteria
Ahmad, *et al*. 2013 [1088]	283	23.9	3	67.0% (nadir PSA ≤ 1 ng/mL); 14.0% (nadir PSA > 1 ng/mL)	Phoenix criteria
Pisters, *et al*. 2008 [1089]	279	21.6	5	58.9% (ASTRO) 54.5% (Phoenix)	ASTRO and Phoenix criteria

ASTRO = American Society for Therapeutic Radiology and Oncology; BCR = biochemical recurrence; FU = follow-up; mo. = months; n = number of patients; PSA = prostate-specific antigen; yr. = year.

6.3.5.2.3   Salvage re-irradiation
6.3.5.2.3.1 Salvage brachytherapy for radiotherapy failure
Carefully selected patients with a good PS, primary localised PCa, good urinary function and histologically proven local recurrence are candidates for salvage brachytherapy using either HDR or LDR.

In a systematic review a total of 16 studies (4 prospective) and 32 studies (2 prospective) assessed salvage HDR and LDR brachytherapy, respectively, with the majority (> 85%) receiving whole-gland brachytherapy rather than focal treatment [1076]. The adjusted pooled analysis for 2-year BCR-free survival for HDR was 77% (95% CI: 70–83%) and for LDR was 81% (95% CI:74–86%). The 5-year BCR-free survival for HDR was 60% (95% CI: 52–67%) and for LDR was 56% (95% CI: 48–63%). As noted above, brachytherapy techniques are associated with lower rates of severe GU toxicity when compared to RP or HIFU, at 8% for HDR (95% CI: 5.1–11%) and 8.1% for LDR (95% CI: 4.3–13%). Rates of severe GI toxicity are reported to be very low at 0% for HDR (95% CI: 0–0.2%) and 1.5% for LDR (95% CI: 0.2–3.4%). High-dose-rate or LDR brachytherapy are effective treatment options with an acceptable toxicity profile. However, the published series are small and likely under-report toxicity. Consequently, this treatment should be offered in experienced centres ideally within randomised clinical trials or prospective registry studies (see Table 6.3.9).

Table 6.3.9: Treatment-related toxicity and BCR-free probability in selected salvage brachytherapy studies including at least 100 patients.

Study	Study design	n and BT type	Median FU (mo)	Treatment toxicity	BCR-free probability
Lopez, *et al*. 2019 [1090]	multi-centre retrospective	75 HDR 44 LDR	52	23.5% late G3+ GU	5 yr 71% (95% CI: 65.9-75.9%)
Crook, *et al*. 2019 [1091]	multi-centre prospective	100 LDR	54	14% late G3 combined GI/GU	n.r.
Smith, *et al*. 2020 [1092]	single-centre retrospective	108 LDR	76	15.7%/2.8% late G3 GU/GI	5 yr. 63.1% 10 yr. 52%
Lyczek, *et al*. 2009 [1093]	single-centre retrospective	115 HDR	n.r.	12.2%/0.9% late G3+ GU/GI	60% at 40 mo.

BT = brachytherapy; CI = confidence interval; G = grade; GI = gastro-intestinal; GU = genito-urinary; HDR = high-dose rate; LDR = low-dose rate; mo = months; n = number of patients; n.r. = not reported; yr = year.

6.3.5.2.3.2 Salvage stereotactic ablative body radiotherapy for radiotherapy failure

6.3.5.2.3.2.1 Oncological outcomes and morbidity

Stereotactic ablative body radiotherapy (CyberKnife® or linac-based treatment) is a potentially viable new option to treat local recurrence after RT. Carefully selected patients with good IPSS-score, without obstruction, good PS and histologically proven localised local recurrence are potential candidates for SABR. In a meta-analysis and systematic review five mostly retrospective studies including 206 patients were treated with CyberKnife® or linac-based treatment showing 2-year RFS estimates (61.6%, 95% CI: 52.6–69.9%) [1076]. In a retrospective multi-centre study (n = 100) the median pre-salvage PSA was 4.3 ng/mL with 34% of patients having received ADT for twelve months (median). All recurrences were biopsy proven. Patients were treated with the CyberKnife® with a single dose of 6 Gy in six daily fractions (total dose 36 Gy). With a median follow-up of 30 months the estimated 3-year second BCR-free survival was 55% [1094].

In a smaller retrospective series including 50 men with histologically proven local recurrence with a median pre-salvage PSA of 3.9 ng/mL only 15% had received additional ADT. The estimated 5-year second BCR-free survival was 60% (median follow-up of 44 months) which is an outcome comparable to series treating patients with RP, HIFU or brachytherapy [1095]. Table 6.3.10 summarises the results of the two larger SABR series addressing oncological outcomes and morbidity.

Table 6.3.10: Treatment-related toxicity and BCR-free survival in selected SABR studies

Study	Study design	n and RT-type	Median FU (mo)	Fractionation (SD/TD)	ADT	Treatment toxicity	BCR-free survival
Bergamin, *et al.* 2020 [1096]	single-centre prospective	25 LINAC based	25	SD 6-6.2 TD 36-38 Gy	0/25	2 yr. late G1 GI 8% G2 GU 4%	2 yr. 80%
Fuller, *et al.* 2020 [1095]	single-centre retrospective	50 Cyber Knife	44	SD 6.8 Gy TD 34 Gy	7/50	5 yr: 8% late G3+ GU	5 yr. 60%
Pasquier, *et al.* 2020 [1094]	multi-centre retrospective	100 Cyber Knife	30	SD 6 Gy TD 36 Gy	34/100 median 12 mo.	3 yr. grade 2+ GU 20.8% GI 1%	3 yr. 55%

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; RT-type = type of radio-therapy; SD = single dose; TD = total dose; yr = year.

6.3.5.2.3.2.2 Morbidity

In a retrospective single-centre study with 50 consecutive patients chronic significant toxicity was only seen for the GU domain with 5-year grade 2+ and grade 3+ GU rates of 17% and 8%, respectively. No GI toxicity > grade 1 was seen. Of note, of the fifteen patients who were sexually potent pre-salvage SBRT, twelve subsequently lost potency [1095]. In a retrospective French (GETUG) multi-centre series (n = 100) the 3-year late grade 2+ GU and GI toxicity was 20.8% (95% CI: 13–29%) and 1% (95% CI: 0.1–5.1%), respectively [1094].

6.3.5.2.3.2.3 Summary of salvage stereotactic ablative body radiotherapy

Despite the encouraging results so far the number of patients treated with SABR is relatively limited. In view of the rates of higher grade 2+ GU side effects, SABR should only be offered to selected patients, in experienced centres as part of a clinical trial or well-designed prospective study.

6.3.5.2.4 Salvage high-intensity focused ultrasound

6.3.5.2.4.1 Oncological outcomes

Salvage HIFU has emerged as an alternative thermal ablation option for radiation-recurrent PCa. Being relatively newer than SCAP the data for salvage HIFU are even more limited. A systematic review and meta-analysis included 20 studies (n = 1,783) assessing salvage HIFU [1076]. The overwhelming majority of patients (86%) received whole-gland salvage HIFU. The adjusted pooled analysis for 2-year BCR-free survival for salvage HIFU was 54.14% (95% CI: 47.77–60.38%) and for 5-year BCR-free survival 52.72% (95% CI: 42.66–62.56%). However, the certainty of the evidence was low. Table 6.3.11 summarises the results of a selection of the largest series on salvage HIFU to date in relation to oncological outcomes (BCR only).

Table 6.3.11: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Crouzet, *et al*. 2017 [1097]	418	39.6	5	49.0%	Phoenix criteria
Murat, *et al*. 2009 [1098]	167	Mean 18.1	3	25.0% (high-risk) 53.0% (low-risk)*	Phoenix criteria or positive biopsy or initiation of post-HIFU salvage therapy
Kanthabalan, *et al*. 2017 [1099]	150	35.0	3	48.0%	Phoenix criteria
Jones, *et al*. 2018 [1100]	100	12.0	1	50.0%	Nadir PSA > 0.5 ng/mL or positive biopsy

Results stratified by pre-EBRT D'Amico risk groups.
BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; yr = year.

6.3.5.2.4.2 Morbidity
The main adverse effects and complications relating to salvage HIFU include urinary incontinence, urinary retention due to bladder outflow obstruction, rectourethral fistula and ED. The systematic review and meta-analysis showed an adjusted pooled analysis for severe GU toxicity for salvage HIFU of 22.66% (95% CI: 16.98–28.85%) [1076]. The certainty of the evidence was low. Table 6.3.12 summarises the results of a selection of the largest series on salvage HIFU to date in relation to GU outcomes.

Table 6.3.12: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage HIFU case series, including at least 100 patients

Study	n	Time point of outcome measurement (yr)	Incontinence* (%)	Obstruction/ retention (%)	Rectourethral fistula (%)	ED (%)
Crouzet, *et al*. 2017 [1097]	418	Median 39.6	42.3	18.0	2.3	n.r.
Murat, *et al*. 2009 [1098]	167	Median 18.1	49.5	7.8	3.0	n.r.
Kanthabalan, *et al*. 2017 [1099]	150	24	12.5	8.0	2.0	41.7
Jones, *et al*. 2018 [1100]	100	12	42.0	49.0	5.0	74.0

Incontinence was heterogeneously defined; figures represent at least 1 pad usage.
ED = erectile dysfunction; n.r. = not reported; n = number of patients.

6.3.5.2.4.3 Summary of salvage high-intensity focused ultrasound
There is a lack of high-certainty data which prohibits any recommendations regarding the indications for salvage HIFU in routine clinical practice. There is also a risk of significant morbidity associated with its use in the salvage setting. Consequently, salvage HIFU should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study.

6.3.6 *Hormonal therapy for relapsing patients*
The Panel conducted a systematic review including studies published from 2000 onwards [1101]. Conflicting results were found on the clinical effectiveness of HT after previous curative therapy of the primary tumour. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [1102]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [1103]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic workup and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. Predictive factors for poor outcomes were; CRPC, distant metastases, CSS, OS, short PSA-DT, high ISUP grade, high PSA, increased age and co-morbidities. In some studies, such as the Boorjian, *et al*., study [1104], high-risk patients, mainly defined by a high ISUP grade and a short PSA-DT (most often less than 6 months) seem to benefit most from (early) HT, especially men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [1036]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [1105]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors. Based on the lack of definitive efficacy and the undoubtedly associated significant side effects, patients with recurrence after primary curative therapy should not receive standard HT since only a minority of them will progress to metastases or PCa-related death. The objective of HT should be to improve OS, postpone distant metastases, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with co-morbidities the side effects of HT may even decrease life expectancy; in particular cardiovascular risk factors need to be considered [1106, 1107]. Early HT should be reserved for those at the highest risk of disease progression defined mainly by a short PSA-DT at relapse (< 6–12 months) or a high initial ISUP grade (> 2/3) and a long life expectancy.

6.3.7   ***Observation***
In unselected relapsing patients the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [903]. For patients with EAU Low-Risk BCR features (see Section 6.3.3), unfit patients with a life expectancy of less than 10 years or patients unwilling to undergo salvage treatment, active follow-up may represent a viable option.

6.3.8   ***Guidelines for second-line therapy after treatment with curative intent***

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence (BCR) after radical prostatectomy	
Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises.	Strong
A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with BCR.	Weak
Recommendations for BCR after radiotherapy	
Offer monitoring, including PSA to EAU Low-Risk BCR patients.	Weak
Only offer salvage radical prostatectomy (RP), brachytherapy, stereotactic body radiotherapy, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling time > 12 months.	Strong
Recommendations for follow-up after radical prostatectomy or radiotherapy	
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

6.4   Treatment: Metastatic prostate cancer
6.4.1   ***Introduction***
All prospective data available rely on the definition of M1 disease based on CT scan or MRI and bone scintigraphy. The influence on treatment and outcome of newer, more accurate, imaging has not been assessed yet.

6.4.2 Prognostic factors

Median survival of patients with newly diagnosed metastases (synchronous mHSPC) is approximately 42 months with ADT alone, however, it is highly variable since the M1 population is heterogeneous [1108]. Several prognostic factors for survival have been suggested including the number and location of bone metastases, presence of visceral metastases, ISUP grade, PS status and initial PSA and alkaline phosphatase level, but only few have been validated [1109-1112].

'Volume' of disease as a potential predictor was introduced by CHAARTED (Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) [1112-1114] (see table 6.4.1) and subsequently, in STAMPEDE, was shown to be predictive in an adequately powered subgroup analysis for benefit of addition of prostate RT to ADT in the subgroup of patients with low volume/ burden disease [1115] (See table 6.4.1).

'Metachronous' metastatic disease (after radical local treament of the primary tumour) vs. synchronous (or *de novo*) metastatic disease has also been shown to have generally a better prognosis [1116].

Based on a large SWOG 9346 cohort, the PSA level after 7 months of ADT was used to create 3 prognostic groups (see Table 6.4.2) [1117]. A PSA ≤ 0.2 ng/mL at 7 months has been confirmed as a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study independent of the addition of docetaxel [1118].

Table 6.4.1 Definition of high- and low-volume in CHAARTED [1112-1114] **and high- and low-risk in LATITUDE** [765]

	High	Low
CHAARTED (volume)	≥ 4 Bone metastases including ≥ 1 outside vertebral column or pelvis **AND/OR** Visceral metastasis*	Not high
LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high

Lymph nodes are not considered as visceral metastases.

Table 6.4.2: Prognostic factors based on the SWOG 9346 study [1117]

PSA after 7 months after start of ADT	Median survival on ADT monotherapy
< 0.2 ng/mL	75 months
0.2 ≤ 4 ng/mL	44 months
> 4 ng/mL	13 months

6.4.3 First-line hormonal treatment

Primary ADT has been the SOC for over 50 years [728]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, neither for orchiectomy nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist, therefore patients with impending spinal cord compression or other potential impending complications from the cancer should be treated with either a bilateral orchidectomy or LHRH antagonists as the preferred options.

There is a suggestion in some studies that cardiovascular side effects are less frequent in patients treated with LHRH antagonists than patients treated with LHRH agonists [747, 1119, 1120]; therefore, patients with pre-existing cardiovascular disease or other cardio-vascular risk factors might be considered to be treated with antagonists if a chemical castration is chosen.

6.4.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to ADT (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to AEs [1121] and is generally not recommended also because ADT-based combination treatments have become SOC.

6.4.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [1122-1124] and two meta-analyses [1125, 1126] looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included 8 RCTs of which only 3 were

conducted in patients with exclusively M1 disease.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [1127]. Of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that only about 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1, CI: 0.99–1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out even in this highly selected subgroup. The use of intermittent ADT has been superseeded as continuous ADT has become SOC.

6.4.3.3 Early versus deferred androgen deprivation therapy
Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease despite lack of randomised phase III data in this specific setting and specifically not with the combination therapies that are standard nowadays.

A Cochrane analysis from 2019 about the topic concluded that early ADT probably extends time to death of any cause and time to death from PCa [1128]. Since the analysis included only a very limited number of biochemical recurrence patients, the benefit of early ADT in this setting remains unproven. All of the trials testing the combination therapies in the metastatic hormone-sensitive setting also included asymptomatic patients.

The only candidates with metastatic disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side effects. The risk of developing symptoms, and even dying from PCa, without receiving the benefit from HT with deferred treatment has been highlighted [841, 1129], but in the era before next generation imaging was used.

Patients with deferred treatment for advanced PCa must be amenable to close follow-up. Another potential exception are patients with recurrent oligometastatic disease who have a strong wish to postpone the start of ADT (see Section 6.4.7).

6.4.4 **Combination therapies**
All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.4.4.1 'Combined' androgen blockade with older generation NSAA (bicalutamide, flutamide, nilutamide)
Systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [1130, 1131] but this minimal survival advantage must be balanced against the increased side effects. In addition, the newer combination therapies (see Tables 6.4.3, 6.4.4, 6.4.5) are more effective as shown specifically for enzalutamide which was tested against. NSAA in a phase III trial [1132]. More recently another trial has demonstrated a significant OS benefit for the addition of rezvilutamide vs. addition of bicalutamide to ADT in patients with high-volume mHSPC [1133]. Therefore, combination with NSAAs should only be considered if other combination therapies are not available.

6.4.4.2 Androgen deprivation combined with other agents
6.4.4.2.1 Androgen deprivation therapy combined with chemotherapy
Three large RCTs were conducted [849, 1112, 1134]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within 3 months of ADT initiation). The primary objective in all three studies was to assess OS. The key findings are summarised in Table 6.4.3.

Table 6.4.3: Key findings - Hormonal treatment combined with chemotherapy

	STAMPEDE [849, 1135]		**GETUG-AFU 15** [1134]		**CHAARTED** [1112,1113]	
	ADT	ADT + Docetaxel (6 cycles) + P	ADT	ADT + Docetaxel (9 cycles)	ADT	ADT + Docetaxel (6 cycles)
N	1,184	592	193	192	393	397
Newly diagnosed M+	58%	59%	75%	67%	73%	73%

Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL, or nodal or metastatic relapse	Metastatic disease Karnofsky score ≥ 70%	Metastatic disease ECOG PS 0, 1 or 2
Primary objective	OS	OS	OS
Median follow up (mo)	43; 78.2 (update M1)	50	54 (update)
HR (95% CI)	0.78 (0.66-0.93)	1.01 (0.75-1.36)	0.72 (0.59-0.89)
M1 only			
N	1,086	-	-
HR (95% CI)	0.81 (0.69-0.95)	-	-

ADT = androgen deprivation therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ISUP = International Society for Urological Pathology; mo = month; n = number of patients; OS = overall survival; P = prednisone; PSA-DT = prostate-specific antigen-doubling time.

In the GETUG 15 trial, all patients had M1 PCa, either *de novo* or after a primary treatment [1134]. They were stratified based on previous treatment and Glass risk factors [1109]. In the CHAARTED trial the same inclusion criteria applied, and patients were stratified according to disease volume (see Table 6.4.1) [1112].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1 or N1 or having two of the following 3 criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade 4–5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA > 4 ng/mL with a PSA-DT < 6 months or a PSA > 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [849]. In all 3 trials toxicity was mainly haematological with around 12–15% grade 3–4 neutropenia, and 6–12% grade 3–4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [1136, 1137].

Docetaxel in all three trials was used at the standard dose of 75 mg/sqm every 3 weeks, 6 cycles in CHAARTED and STAMPEDE and up to 9 cycles in GETUG-AFU-15.

In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT was most evident in men with *de novo* metastatic high-volume disease [1113, 1114], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [1135]. The effect of adding docetaxel was less apparent in men who had prior local radical treatment although the numbers were small and the event rates lower. A systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to SOC improved survival [1137]. The HR of 0.77 (95% CI: 0.68–0.87, $p < 0.0001$) translates into an absolute improvement in 4-year survival of 9% (95% CI: 5–14).

Based on these data, upfront docetaxel combined with ADT was considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive docetaxel [1137]. More recently two large Phase 3 studies have now shown an OS benefit by adding an ARPI to ADT and docetaxel. Therefore adding docetaxel alone to ADT should only be considered if no ARPI is available or all available ones are contra-indicated (see Section 6.4.4.2.3).

6.4.4.2.2   Combination with an ARPI alone (abiraterone, apalutamide, enzalutamide)

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC was studied [765, 892, 1138] (see table 6.4.4). The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only *de novo* high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [765]. The HR in STAMPEDE was very similar with 0.63 (0.52–0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [892]. While only high-risk patients were included in the LATITUDE trial a *post-hoc* analysis from STAMPEDE showed the same benefit whatever the risk or the volume stratification [1139].

All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were positive and in favour of the combination. No difference in treatment-related deaths was observed with the combination of ADT plus AAP compared to ADT monotherapy (HR: 1.37 [0.82–2.29]). However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%) [1138]. Based on these data upfront AAP combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug.

In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with mHSPC was tested [763, 764, 1132]. In ARCHES the primary endpoint was radiographic PFS (rPFS). In the primary analysis rPFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3–0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In the final prespecified analysis the key secondary enpoint OS was significantly improved with a HR of 0.66 (0.53-0.81) and a significant benefit for rPFS was maintained with a HR of 0.63 (0,52–0.76) [1140]. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT in the first analysis improved OS with a HR of 0.67 (0.52–0.86) compared to ADT plus a non-steroidal antiandrogen. Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [764]. In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. In the primary analysis rPFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39–0.6); OS at 24 months was improved for the combination with a HR of 0.67 (0.51–0.89). In the final analysis the HR for OS was 0.65 (0.53–0.79) without adjustment for cross-over. In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [763, 1141]. In the more recently published CHART trial, ADT plus rezvilutamide was tested vs. ADT plus bicalutamide in patients with high-volume *de novo* metastatic disease. Ninety percent of the patients were recruited in China. Overall survival and rPFS were co-primary endpoints. At the pre-planned interim analysis rezvilutamide significantly improved rPFS compared with bicalutamide with a HR of 0.44 (0.33–0.58) and OS with a HR of 0.58 (0.44–0.77) [1133].

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients had *de novo* metastatic disease and the evidence is most compelling in this situation. In the trials with the new AR antagonists, a proportion of patients had metachronous disease (see Table 6.4.5); in the subgroup analyses the effect seemed to be consistent and therefore, a combination should also be offered for men progressing after radical local therapy [1142].

Table 6.4.4: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [892]		**LATITUDE** [765]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
N	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: ISUP grade ≥ 4, ≥ 3 bone lesions, measurable visceral metastasis	

Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	40		30.4	
3-yr. OS	83% (ADT + AA + P) 76% (ADT)		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52-0.76)		0.62 (0.51-0.76)	
M1 only				
N	1,002		1,199	
3-yr. OS	NA		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.61 (0.49-0.75)		0.62 (0.51-0.76)	
HR	FFS (biological, radiological, clinical or death): 0.29 (0.25-0.34)		rPFS: 0.49 (0.39-0.53)	

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo = month; n = number of patients; NA = not available; OS = overall survival; P = prednisone; rPFS = radiographic progression-free survival; PSA = prostate-specific antigen; yr. = year.

Table 6.4.5: Results from the ENZAMET and TITAN studies with OS as primary endpoint

	ENZAMET [1132]		**TITAN** [763, 1141]	
	ADT+ older antagonist ± docetaxel (SOC)	ADT + enzalutamide ± docetaxel	ADT + placebo	ADT + apalutamide
N	562	563	527	525
Newly diagnosed M+	72.1%	72.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS rPFS	
Median follow up (mo)	34		30.4	
3-yr. OS	3-yr survival: 80% (ADT + enzalutamide) 72% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.67 (0.52-0.86)		0.67 (0.51-0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = month; n = number of patients; OS = overall survival; SOC = standard of care; rPFS = radiographic progression-free survival; yr = year.

Table 6.4.6: Results from the ARCHES and CHART studies [764, 1133, 1140]

	ARCHES [764, 1140]		**CHART** [1133]	
	ADT ± docetaxel	ADT + enzalutamide ± docetaxel	ADT + bicalutamide	ADT + rezvilutamide
N	576	574	328	326
Newly diagnosed M+	63%	70%	100%	100%
Low volume	35%	38%	0%	0%
Use of early docetaxel	18% (previous)	18% (previous)	0%	0%
Primary objective	rPFS		OS rPFS	
Median follow up (mo)	44.6		29.3	
Median rPFS (mo.)	38.9	49.8	23.5	Not reached
HR (95% CI) for rPFS	HR: 0.63 (0.52–0.76)		HR: 0.46 (0.36–0.60)	
Median OS	Not reached	Not reached	Not reached	Not reached
HR (95% CI) for OS	0.66 (0.53–0.81): Main secondary endpoint		0.58 (0.44–0.77)	

HR = hazard ratio; mo = month; n = number of patients; OS = overall survival; rPFS = radiographic progression-free survival; yr = year.

6.4.4.2.3   Combination with docetaxel and an ARPI

The addition of abiraterone to ADT and docetaxel has been reported to have a benefit in rPFS and in OS in the PEACE-1 trial [1143, 1144]. The trial has a 2x2 factorial design and participants with *de novo* (synchronous) metastatic PCa were randomised to SOC; at the beginning of the trial ADT, later ADT plus docetaxel for 6 cycles if chemotherapy-fit) vs. SOC plus radiotherapy vs. SOC plus abiraterone vs. SOC plus radiotherapy plus abiraterone. Co-primary endpoints were rPFS and OS, both were statistically significantly improved in the total population. Also in the group of patients who received ADT plus docetaxel as SOC (n = 710) both rPFS and OS were increased with a HR: 0.5 (0.34–0.71) and 0.75 (0.59–0.95), respectively. Of note; in this population about 35% had low-volume disease. Toxicity was modestly increased, mostly hypertension.

In the ARASENS Phase 3 trial all patients received ADT and docetaxel for 6 cycles as SOC plus darolutamide or placebo [1145]. 1,306 metastatic patients were included, 14 % of them with relapsed disease after radical local treatment (metachronous). Primary endpoint was OS and this was statistically significanty increased by the addition of darolutamide with a HR of 0.68 (0.57–0.8).

Until now no subgroup analysis for high- and low-volume disease was reported. Interestingly, in this trial the occurrence of AEs was similar in both arms. In both trials docetaxel and the ARPI have been given concomitantly.

Also in ENZAMET, TITAN and ARCHES there were patients who received docetaxel as a part of SOC, thus not all concommitantly, but the percentage of patients receiving docetaxel in these trials was much lower [763, 764, 1132].

6.4.5   Treatment selection and patient selection

There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the combination therapies has been clearly proven to be superior over another [1146, 1147]. As a consequence, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on non-cancer co-morbidities).

Since the data of the above mentioned Phase III trials of the triplet therapies have been reported, docetaxel as sole addition to ADT is not longer a valid option in the majority of patients if an androgen receptor pathway inhibitor (ARPI) is available and there are no contra-indiactions to use one. From subgroup analysis of all the above-mentioned RCTs we know that probably all subgroups (high vs. low volume and synchronous vs. metachronous) can profit from the addition of an ARPI to ADT. Therefore, in view of the current data the recommendation is using ADT plus ARPI as the sole additional therapy or the triplet with an ARPI plus docetaxel. Formally the question what the added value of adding docetaxel to ADT plus an ARPI has not been evaluated, but since triplet therapy seems not to add a lot of unexpected overlapping toxicities, the data should be discussed with patients who are fit for chemotherapy and an ARPI, realising that most of the toxicity is caused by adding the chemotherapy. There is more evidence for using the triplet in synchronous disease and the OS benefit in PEACE-1 seemed to be driven mostly by the high volume patients at the time point of the analysis for the publication. In summary, the choice will most likely be driven by fitness for docetaxel, the nature of the disease (low/high volume; synchronous/metachronous), patient preference, the specific side effects, availability, logistics and cost.

6.4.6   Treatment of the primary tumour in newly diagnosed metastatic disease

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [1148]. The STAMPEDE trial evaluated 2,061 men with metastatic castration-sensitive PCa (mCSPC) who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1115]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved, and patients categorised as low- or high volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT. This was confirmed by the latest analysis of long-term follow-up (median follow-up of 61 months [HR: 0.64 for OS benefit in the low-volume group]) [1149].

A secondary, not pre-planned, analysis of the STAMPEDE trial confirmed the benefit of prostate RT in patients with ≤ 3 bone metastases, but also showed a benefit in patients with M1a disease [1150]. No evidence of difference in time to symptomatic local events was found with median follow-up of over 5 years [1149]. The dose used in these indications should be equivalent of up to 72 Gy in 2 Gy fractions.

Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel and no patients had additional AAP,

so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment as results of ongoing trials are awaited.

In a systematic review and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04, p = 0.195) [1151]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases.

6.4.7 Metastasis-directed therapy in M1-patients

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There are two randomised phase II trials testing metastasis-directed therapy (MDT) using surgery ± SABR vs. surveillance [1152] or SABR vs. surveillance in men with oligo-recurrent PCa [1153]. Oligo-recurrence was defined as < 3 lesions on choline-PET/CT only [1152] or conventional imaging with MRI/CT and/or bone scan [1153]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1152]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1152]. The primary endpoint in the ORIOLE trial was progression after 6 months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1153].

Recently the combined results of STOMP and ORIOLE confirmed the significant improvement in PFS in favour of MDT (HR: 0.44, p < 0.001) [1154].

A phase II trial assessed the biochemical response after ^{18}F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1155].

Currently there are no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as investigational until the results of the ongoing RCT are available [1156, 1157]. Thus far, the toxicity of MDT appears to be low, but this also needs to be confirmed [1158, 1159].

6.4.8 Guidelines for the first-line treatment of hormone-sensitive metastatic disease*

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease and who are fit for the regimen.	Strong
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with non-curative prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria/M1a disease.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

*All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.

6.5 Treatment: Castration-resistant PCa (CRPC)

6.5.1 Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

   or

b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [1160]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

6.5.2 Management of mCRPC - general aspects

Selection of treatment for mCRPC is multifactorial and in general dependent on:

- previous treatment for mHSPC and for non-mHSPC;
- previous treatment for nmCRPC and mCRPC;
- quality of response and pace of progression on previous treatment;
- known cross resistance between androgen receptor pathway inhibitor (ARPI);
- co-medication and known drug interactions (see approved summary of product characteristics);
- known genetic alterations and microsatellite instability–high (MSI-H)/mismatch repair–deficient (*dMMR*) status;
- known histological variants and DNA repair deficiency (to consider platinum or targeted therapy like PARPi);
- local approval status of drugs and reimbursement situation;
- available clinical trials;
- The patient and his co-morbidities.

6.5.2.1 Molecular diagnostics

All metastatic patients should be offered somatic genomic testing for homologous repair and MMR defects, preferably on metastatic carcinoma tissue but testing on primary tumour may also be performed. Alternatively, but still less common, genetic testing on circulating tumour DNA (ctDNA) is an option and has been used in some trials. One test, the FoundationOne® Liquid CDx, has been FDA approved [1161]. Defective *MMR* assessment can be performed by IHC for *MMR* proteins (*MSH2, MSH6, MLH1* and *PMS2*) and/or by next-generation sequencing (NGS) assays [1162]. Germline testing for *BRCA1/2, ATM* and *MMR* is recommended for high-risk- and particularly for metastatic PCa if clinically indicated.

Molecular diagnostics should be performed by a certified (accredited) institution using a standard NGS multiplication procedure (minimum depth of coverage of 200 X). The genes and respective exons should be listed; not only DNA for mutations but RNA needs to be examined for fusions and protein expression to obtain all clinically relevant information. A critical asset is the decision support helping to rate the mutations according to their clinical relevance [1163, 1164].

Level 1 evidence for the use of PARP-inhibitors has been reported [1165-1167]. Microsatellite instability (MSI)-high (or *MMR* deficiency) is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA and could be a valuable additional treatment option [770, 1168]. Germline molecular testing is discussed in Section 5.1.3 - Genetic testing for inherited PCa. Recommendations for germline testing are provided in Section 5.1.4.

6.5.3 Treatment decisions and sequence of available options

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel, olaparib and radium-223. In general, sequencing of ARPIs like abiraterone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARPI was short (≤ 12 months) and high-risk features of rapid progression are present (see detailed discussion in Section 6.5.7) [1169, 1170].

The use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence is recommended and should be applied early enough when the patient is still fit for chemotherapy. This is supported by high-level evidence [1169].

6.5.4 Non-metastatic CRPC

Frequent PSA testing in men treated with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases within two years, detected by conventional imaging [972].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline

PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free survival and OS [972, 1171]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1172]. Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC [1173]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

Three large phase III RCTs, PROSPER [1174], SPARTAN [1175] and ARAMIS [1176], evaluated metastasis-free survival as the primary endpoint in patients with nmCRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide vs. placebo (ARAMIS), respectively (see Table 6.5.1). The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ 10 months were included. Patient characteristics in trials revealed that about two-thirds of participants had a PSA-DT of < 6 months. All trials showed a significant metastasis-free survival benefit. All three trials showed a survival benefit after a follow-up of more than 30 months. In view of the long-term treatment with these AR targeting agents in asymptomatic patients, potential AEs need to be taken into consideration and the patient informed accordingly.

Table 6.5.1: Randomised phase III controlled trials – nmCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ARAMIS 2019, 2020 [1176, 1177]	ADT + darolutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**59% reduction of distant progression or death Median MFS: darolutamide 40.4 vs placebo 18.4 mo; 31% reduction in risk of death** HR = 0.69 (95% CI: 0.53–0.88) p = 0.003
PROSPER 2018, 2020 [1174, 1178]	ADT + enzalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**71% reduction of distant progression or death Median MFS: enzalutamide 36.6 vs placebo 14.7 months; 27% reduction in risk of death** HR = 0.73 (95% CI: 0.61–0.89) p = 0.001
SPARTAN 2018, 2021 [1175, 1179]	ADT + apalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**72% reduction of distant progression or death Median MFS: apalutamide 40.5 vs placebo 16.2 months; 22% reduction in risk of death** HR = 0.78 (95% CI: 0.64–0.96) p = 0.0161

ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; nmCRPC = non-metastatic castrate-resistant prostate cancer; PSA-DT = prostate-specific antigen doubling time.

6.5.5 *Metastatic CRPC*
The remainder of this section focuses on the management of men with proven mCRPC on conventional imaging.

6.5.5.1 *Conventional androgen deprivation in CRPC*
Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [1180, 1181]. However, in the absence of prospective data, the modest potential benefits of continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression, therefore, it should be continued in these patients.

6.5.6   First-line treatment of metastatic CRPC

6.5.6.1   Abiraterone

Abiraterone was evaluated in 1,088 chemo-naive, asymptomatic or mildly symptomatic mCRPC patients in the phase III COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [1182]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and rPFS were the co-primary endpoints. After a median follow-up of 22.2 months there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93, p = 0.0033) [1183]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1–2. Subset analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [1184].

6.5.6.2   Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [1185]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naive mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186, CI: 0.15–0.23, p < 0.0001), and OS (HR: 0.706, CI: 0.6–0.84, p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men > 75 years [1186] as well as in those with or without visceral metastases [1187]. However, for men with liver metastases, there seemed to be no discernible benefit [1187, 1188].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double-blind phase II study (TERRAIN) showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44, p < 0.0001) in favour of enzalutamide [1188]. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [1189].

6.5.6.3   Docetaxel

A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxel-based chemotherapy compared to mitoxantrone plus prednisone [1190, 1191]. The standard first-line chemotherapy is docetaxel 75 mg/m^2, 3-weekly doses combined with prednisone 5 mg twice a day (BID), up to 10 cycles. Prednisone can be omitted if there are contra-indications or no major symptoms. The following independent prognostic factors: visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help stratify the response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), and show three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [1192].

Age by itself is not a contra-indication to docetaxel [1193] but attention must be paid to careful monitoring and co-morbidities as discussed in Section 5.4 - Estimating life expectancy and health status [1194]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m^2 every two weeks seems to be well tolerated with less grade 3–4 AEs and a prolonged time to treatment failure [1195].

6.5.6.4   Sipuleucel-T

In 2010 a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [1196]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related AEs grade 1–2 in the sipuleucel-T group, but the same grade 3–4 AEs in both arms. Sipuleucel-T is not available in Europe.

6.5.6.5   Ipatasertib

The AKT inhibitor ipatasertib in combination with AAP was studied in asymptomatic or mildly symptomatic patients with and without PTEN loss by IHC and previously untreated for mCRPC. The randomised phase III trial (IPAtential) showed a significant benefit for the first endpoint rPFS in the PTEN loss (IHC) 18.5 vs. 16.5 mo; p = 0.0335, HR: 0.77, 95% CI: 0.61–0,98) but not in the intention to treat (ITT) population. The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhoea [771]. Grade 3 or higher AEs occurred nearly double as often in the combination group and the discontinuation rate due to AEs was 4 times higher. This combination is still investigational [1197].

6.5.6.6 Combinations

Based on the suggestion that there is a synergistic antitumour effect when combining abiraterone with a PARP inhibitor, several such combination trials were conducted with conflicting results.

Abiraterone/prednisone plus olaparib

A randomised double-blind, phase 3 trial (PROpel) of abiraterone (1000 mg once daily) plus prednisone 5 mg/twice daily (AAP) and olaparib (300 mg twice/daily) or placebo in patients with mCRPC in the first-line setting was conducted [1198]. Of note, 796 patients met the eligibility criteria and were randomly assigned 1:1 to study treatment regardless of homologous recombination repair gene mutation (HRRm) status which was retrospectively evaluated and determined by tumour tissue and circulating tumour DNA tests. The primary end point was imaging-based PFS (ibPFS) by investigator assessment. The result was significantly positive in favour of the combination with ibPFS of 24.8 vs. 16.6 mo (HR 0.66; 95% CI: 0.54 to 0.81; p = 0.001). The subgroup of patients with positive HRRm status showed a HR of 0.50 (CI: 0.34 to 0.73) which seems to be a major driver of the overall result. Survival data are still immature. The most common side effects with the combination were anaemia, fatigue/asthenia, and nausea.

Abiraterone/prednisone plus niraparib

At ASCO 2022, a randomised, double-blind, phase 3 trial (MAGNITUDE) evaluating abiraterone (1,000 mg once daily) plus prednisone 5 mg twice/daily plus niraparib 200 mg once/daily or placebo, was presented [1199]. The final paper has not yet been published.

Table 6.5.2: Randomised phase III controlled trials - first-line treatment of mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [1200]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		**OS: 17.52 vs. 15.6 mo.** (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) **PFS: 6.3 vs. 3.2 mo.** (p < 0.001)
TAX 327 2004, 2008 [1190,1201]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, Prednisone 5 mg BID		**OS: 19.2 for 3 weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.** (p = 0.004, HR: 0.79, 95% CI: 0.67-0.93)
ABIRATERONE				
COU-AA-302 2013, 2014, 2015 [1182, 1183, 1202]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	**OS: 34.7 vs. 30.3 mo.** (HR: 0.81, p = 0.0033). **FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.** (p < 0.0001)
ENZALUTAMIDE				
PREVAIL 2014 [1185]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	**OS: 32.4 vs. 30.2 mo.** (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) **rPFS: 20.0 mo. vs. 5.4 mo.** HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001

SIPULEUCEL-T				
IMPACT2010 [1196]	sipuleucel-T	placebo	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	**OS: 25.8 vs. 21.7 mo.** (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). **FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo.** (no difference)
2006 [1203]	sipuleucel-T	placebo	- ECOG 0-1. - No visceral met. - No corticosteroids.	**OS: 25.9 vs. 21.4 mo.** (p = 0.1). FU: 36 mo. **PFS: 11.7 vs. 10.0 wk.**
IPATASERTIB				
IPAtential150 2021 [1197]	ipatasertib (400 mg/d) + abiraterone (1000 mg/d) + prednisone (5 mg bid)	abiraterone + prednisolone + placebo	Previously untreated for mCRPC, asymptomatic/ mildly symptomatic, with and without PTEN loss by IHC	**rPFS in PTEN loss (IHC) population: 18.5 vs. 16.5 mo.** (p = 0.0335, HR: 0.77 95% CI: 0.61-0.98)
PROpel [1198]	olaparib (300mg BID) + abiraterone (1000 mg/d) + prednisone (5 mg BID)	placebo + abiraterone + prednisone	- ECOG 0-1. - regardless of HRRm (retrospective testing). - prior taxane for mHSPC allowed.	HR: 0.66; 95% CI: 0.54–0.81; (p = 0.001)

BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mets. = metastases; mo = month; ib (imaging based); (r)PFS = (radiographic) progression-free survival; OS = overall survival; IHC = immunohistochemistry ; HRRm = homologour recombination repair genes mutation; ITT = intention to treat; BICR = blinded independent central review.

6.5.7 *Second-line treatment for mCRPC and sequence*
All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.3. High-level evidence exists for second-line treatments after first-line treatment with docetaxel and for third-line therapy.

6.5.7.1 *Cabazitaxel*
Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [1204]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/day). Overall survival was the primary endpoint which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months, p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3–4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) but also non-haematological (57.4 vs. 39.8%, p < 0.0002) toxicity. In two post-marketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m^2 cabazitaxel was not inferior to 25 mg/m^2, but less toxic. Therefore, the lower dose should be preferred [1205, 1206]. Cabazitaxel should preferably be given with prophylactic granulocyte colony-stimulating factor (G-CSF) and should be administered by physicians with expertise in handling neutropenia and sepsis [1207].

6.5.7.2 *Abiraterone acetate after docetaxel*
Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [1208] and confirmed by the final analysis [1209]. A total of 1,195 patients with mCRPC were randomised 2:1 to AAP or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary endpoint was OS, with a planned HR of 0.8 in favour of AAP. After a median follow-up of 20.2 months, the median survival in the AAP group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, p < 0.0001). The benefit was observed in all subgroups and all the secondary objectives were in favour of AAP (PSA, radiologic tissue response, time to PSA or objective

progression). The incidence of the most common grade 3–4 AEs did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the AAP group, mainly grade 1–2 (fluid retention, oedema and hypokalaemia).

6.5.7.3 Enzalutamide after docetaxel

The planned interim analysis of the AFFIRM study was published in 2012 [1210]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary endpoint was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, p < 0.001). This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [1189]. Enzalutamide was active also in patients with visceral metastases.

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA, or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.5.7.4 Radium-223

The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA) 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo plus SOC. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70, p < 0.001) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [1211]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, which did not differ significantly from that in the placebo arm [1211]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [1212]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent [1213]. In particular, the use of radium-223 in combination with AAP showed significant safety risks related to fractures and more deaths. This was most striking in patients without the concurrent use of bone health agents [1214].

6.5.8 Treatment after docetaxel and one line of hormonal treatment for mCRPC

6.5.8.1 Hormonal treatment

For men progressing quickly on AR targeted therapy (< 12 months) it is now clear that cabazitaxel is the treatment supported by the best data. The CARD trial, an open label randomised phase III trial, evaluated cabazitaxel after docetaxel and one line of ARPI (either AAP or enzalutamide) [1169]. It included patients progressing in less than 12 months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARPI and reduced the risk of death by 36% vs. ARPI. The rPFS with cabazitaxel remained superior regardless of the ARPI sequence and if docetaxel was given before, or after, the first ARPI.

The choice of further treatment after docetaxel and one line of HT for mCRPC is open for patients who have a > 12 months response to first-line abiraterone or enzalutamide for mCRPC [1215]. Either radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [1216, 1217] and there is evidence of cross-resistance between enzalutamide and abiraterone [1218, 1219].

In this context, radioligand therapy has been discussed for many years. In pre-treated and highly selected patients, based on PSMA- and FDG PET scan results, [117]Lu-PSMA-617 was compared with cabazitaxel in a randomised phase II trial. The primary endpoint PSA reduction $\geq$ 50% was in favour of the radioligand therapy [1220]. Pivotal phase III data for [117]Lu-PSMA-617 are discussed in Section 6.5.8.2.2.

Poly (ADP-ribose) polymerase inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one ARPI and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate to olaparib [1221] and in another confirmatory trial a confirmed composite response of 54.3% (95% CI: 39.0–69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1–54.6) evaluable patients in the 300 mg cohort [1222]. See also section 'Second-line management').

6.5.8.2   Radiopharmaceuticals

6.5.8.2.1   Introduction

Historically, several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 were developed for the treatment of bone pain secondary to metastasis from PCa [1223]. They proved effective in a palliation setting, by relieving pain and improving QoL, especially in the setting of diffuse bone metastases. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223 (see Section 6.5.7.4).

6.5.8.2.2   PSMA-based therapy

The increasing use of PSMA PET as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope which accumulates where the tumour is demonstrated (theranostics) [1224]. Therefore, after identification of the target, usually with diagnostic [68]Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with β(lutetium-177 or yttrium-90) or α(actinium-225)-emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported by the most robust data is ^{177}Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of ^{177}Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [1225]. The early data were based on single-centre experience [1226]. Data from uncontrolled prospective phase II trials reported high response rates with low toxic effects [1227, 1228]. Positive signals are also coming from a randomised trial (TheraP) [1220].

In TheraP, a randomised phase II trial, patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by ^{68}Ga-PSMA-11 and [18]FDG PET-CT scans, were randomised to receive ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously every 6 weeks for up to 6 cycles) or cabazitaxel (20 mg/m^2 for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for ^{177}Lu–PSMA-617 vs. cabazitaxel, respectively, by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016) [1220].

An open-label phase III trial (VISION) compared ^{177}Lu–PSMA-617 radioligand therapy with protocol-permitted SOC (i.e., excluded chemotherapy, immunotherapy, radium-223 and investigational drugs) in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARPI and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. More than 800 patients were randomised. ^{177}Lu-PSMA-617 plus SOC significantly prolonged both imaging-based PFS and OS, as compared with SOC alone (see Table 6.5.3). Grade 3 or above AEs were higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. ^{177}Lu–PSMA-617 has shown to be a valuable additional treatment option in this mCRPC population [1229].

Recently, a systematic review and meta-analysis was updated, investigating the proportion of patients with any or more than 50% PSA decrease, and OS. The review, including 69 articles and a total of 4,157 patients, showed that patients treated with ^{177}Lu–PSMA 617 had a significantly higher response to therapy compared to controls, based on ≥ 50% PSA decrease (OR = 5.33, 95% CI: 1.24–22.90, p < 0.05). Meta-analysis revealed an OS of 0.26 according to pooled HRs for any PSA decline, which was significant after ^{177}Lu–PSMA-617 therapy (95% CI: 0.18–0.37, p < 0.00001) and an OS of 0.52 for ≥ 50% PSA decrease, also significant after radioligand (RLT) (95% CI: 0.40–0.67, p < 0.00001) [1230].

Currently, an increased interest for PSMA-targeted alpha therapy ([225]Ac-PSMA) is observed, due to the ability to deliver potent higher local radiation more selectively to cancer cells than PSMA-targeted beta therapy, while minimising unwanted damage to the surrounding normal tissues. Additionally, the intensive radiation to cancer cells results in more effective DNA strand breakage and reduces the development of treatment resistance. A meta-analysis, including 9 studies with 263 patients, investigated the therapeutic effects of [225]Ac-PSMA RLT in patients with metastatic CRPC, pre-treated with chemotherapy, ^{177}Lu-PSMA and/or radium-223. The pooled proportions of patients with more than 50% PSA decline and any PSA decline were 60.99% (95% CI: 54.92%–66.83%) and 83.57% (95% CI: 78.62%–87.77%), respectively. The estimated mean PFS and mean OS were 9.15 months (95% CI: 6.69–11.03 months) and 11.77 months (95% CI: 9.51–13.49 months), respectively. These findings suggests that [225]Ac-PSMA RLT may be an effective treatment option for patients with mCRPC [1231]. Despite the encouraging therapeutic response and survival of patients who received [225]Ac-PSMA RLT, major AEs like xerostomia and severe haematotoxicity have to be considered as possible reasons for dose reduction or discontinuation of the therapy.

6.5.8.3 PARP inhibitors for mCRPC

So far, two PARP inhibitors, olaparib and rucaparib, are licenced by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation (e.g., talazoparib, niraparib).

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARPI in mCRPC with alterations in ≥ 1 of any qualifying gene with a role in HRR and progression on an ARPI. Most patients were heavily pre-treated with 1–2 chemotherapies and up to 2 ARPIs [1166, 1167]. Radiographic PFS by blinded independent central review in the *BRCA1/2* or *ATM* mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). The final results for OS demonstrated a significant improvement among men with *BRCA1/2* or *ATM* mutations (Cohort A) (p = 0.0175; HR: 0.69, 95% CI: 0.50– 0.97). This was not significant in men with any (other) HRR alteration (Cohort B) (HR: 0.96, 95% CI: 0.63–1.49). Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 66% (n = 86/131) crossed over to olaparib.

The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary to an AEs, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first trial to show a benefit for genetic testing and precision medicine in mCRPC.

The olaparib approval by the FDA is for patients with deleterious or suspected deleterious germline- or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1* and *BRCA2* alterations [1232]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib has been approved by the FDA for patients with deleterious *BRCA* mutations (germline and/ or somatic) who have been treated with ARPI and a taxane-based chemotherapy [1233]. Approval was not based on OS data but on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious *BRCA* mutations was 43.5% (95% CI: 31–57) [1234].

6.5.8.4 Sequencing treatment

6.5.8.4.1 ARPI -> ARPI (chemotherapy-naive patients)

The use of sequential ARPIs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial [1235-1242]. In particular in patients who had a short response to the first ARPI for mCRPC (< 12 months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present).

In highly selected patients treated for more than 24 weeks with AAP, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1–8.3) and an unconfirmed PSA response rate of 27% [1243]. In case the patient is unfit for chemotherapy and a PARP inhibitor, best supportive care should be considered in case no other appropriate treatment option is available (clinical trial or immunotherapy if MSI-high). An ARPI-ARPI sequence should never be the preferred option but might be considered in such patients if the PS still allows for active treatment and the potential side effects seem manageable.

First prospective cross-over data on an ARPI-ARPI sequence [1235] and a systematic review and meta-analysis suggest that for the endpoints PFS and PSA PFS, but not for OS, abiraterone followed by enzalutamide is the preferred choice [1244].

6.5.8.4.2 ARPI -> PARP inhibitor/olaparib

This sequence in patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial [1167]. A subgroup of patients in this trial was pre-treated with one or two ARPIs and no chemotherapy (35%). The ARPI – docetaxel - PARP inhibitor vs. ARPI – PARP inhibitor - docetaxel sequences are still under investigation.

6.5.8.4.3 Docetaxel for mHSPC -> docetaxel rechallenge

There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mHSPC. Docetaxel seems to be less active than ARPI at progression to mCRPC following docetaxel for mHSPC [1245].

6.5.8.4.4   ARPI -> docetaxel or docetaxel -> ARPI followed by PARP inhibitor
Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARPI and docetaxel in either sequence [1167, 1233].

6.5.8.4.5   ARPI before or after docetaxel
There is level 1 evidence for both sequences (see Table 6.5.3).

6.5.8.4.6   ARPI –> docetaxel -> cabazitaxel or docetaxel –> ARPI -> cabazitaxel
Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high-level evidence favouring cabazitaxel vs. a second ARPI after docetaxel and one ARPI. CARD is the first prospective randomised phase III trial addressing this question (see Table 6.5.3) [1169].

Table 6.5.3: Randomised controlled phase II/III - second-line/third-line trials in mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [1209]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	**OS: 15.8 vs. 11.2 mo.** (p < 0.0001, HR: 0.74, 95% CI: 0.64–0.86; p < 0.0001). FU: 20.2 mo. **rPFS: no change**
COU-AA-301 2011 [1208]				**OS: 14.8 vs. 10.9 mo.** (p < 0.001 HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**
Radium-223				
ALSYMPCA 2013 [1211]	radium-223	placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	**OS: 14.9 vs. 11.3 mo.** (p = 0.002, HR: 0.61; 95% CI: 0.46–0.81). All secondary endpoints show a benefit over best SOC.
CABAZITAXEL				
TROPIC 2013 [1246]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 months OS ≥ 2 yr 27% vs. 16% PFS: -
TROPIC 2010 [1204]				**OS: 15.1 vs. 12.7 mo.** (p < 0.0001, HR: 0.70; 95% CI: 0.59–0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74, 95% CI: 0.64-0.86)
CARD 2019 [1169]	cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	ARTA: abiraterone + prednisone OR enzalutamide	Previous docetaxel. Progression ≤ 12 mo. on prior alternative ARTA (either before or after docetaxel)	**Med OS 13.6 vs. 11.0 mo.** (p = 0.008, HR: 0.64, 95% CI: 0.46–0.89). **rPFS 8.0 vs. 3.7 mo.** (p < 0.001, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.
ENZALUTAMIDE				
AFFIRM 2012 [1210]	enzalutamide	placebo	Previous docetaxel. ECOG 0-2.	**OS: 18.4 vs. 13.6 mo.** (p < 0.001, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35–0.47, p < 0.0001).

PARP inhibitor				
PROfound 2020 [1166, 1167, 1247]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARPI, alterations in HRR mutated genes	**rPFS: 7.39 vs. 3.55 mo.** (p < 0.0001, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). **OS: 19.1 mo vs. 14.7 mo.** (in pts with *BRCA1/2, ATM* alterations) (p = 0.0175; HR 0.69, 95% CI: 0.5–0.97).
Radioligand therapy				
VISION 2021 [1229]	^{177}Lu-PSMA-617 SOC	SOC alone	Previous at least 1 ARPI and one or two taxane regimens; Mandatory: PSMA-positive gallium-68 (^{68}Ga)–labeled PSMA-PET scan	**Imaging-based PFS: 8.7 vs. 3.4 mo.** (p < 0.001; HR 0.40; 99.2% CI: 0.29–0.57) **OS: 15.3 vs. 11.3 mo.** (p < 0.001; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [1220, 1248]	^{177}Lu-PSMA-617 (8.5 GBq i.v.q 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	^{177}Lu-PSMA-617 1:1 randomisation cabazitaxel (20 mg/m^2 i.v.q 3-weekly, up to 10 cycles)	mCRPC post docetaxel, suitable for cabaziaxel	**PSA reduction of > 50%:** 66 vs. 37 PSA responses; 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016).

*Only studies reporting survival outcomes as primary endpoints have been included.
ARPI = androgen receptor pathway inhibitor; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; HR = hazard ratio; Lu = lutetium; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr = year; HRR= homologous recombination repair.*

6.5.8.5 Platinum chemotherapy

Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1249]. More recently, the combination of cabazitaxel and carboplatin was evaluated in pre-treated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5–5.7) to 7.3 months (95% CI: 5.5–8.2; HR: 0.69, 95% CI: 0.50–0.95, p = 0.018) and the combination was well tolerated [1250]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including *TP53, RB1,* and *PTEN* [1251].

Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [1252], also after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients as well as patients without DDR gene alterations also showed a 50% PSA decline in up to 36% of patients [1253]. In view of the excellent tolerability of e.g., carboplatin monotherapy, platinum could be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Prospective controlled trials are ongoing.

6.5.9 Monitoring of treatment

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, total testosterone level, full blood count, renal function, baseline liver function tests, alkaline phosphatase), bone scan and CT of chest, abdomen and pelvis [1254, 1255]. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR or hormone-naive disease. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARPI have been described [1256]. Prostate-specific antigen alone is not reliable enough [1257] for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA [1258]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [1191]. A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating blood

profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [1254]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost and patients with no objective benefit should have their treatment modified. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of no longer 'clinically benefiting' to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [1259]. These recommendations also seem valid for clinical practice outside trials.

6.5.10 When to change treatment

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Preferably, any treatment change should precede development of *de novo* symptoms or worsening of existing symptoms. Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore it is not clear how to select the most appropriate 'second-line' treatment, in particular in patients without HRR alterations or other biomarkers. A positive example, however, is the CARD trial which clearly established cabazitaxel as the better third-line treatment in docetaxel pre-treated patients after one ARPI compared to the use of a second ARPI [1169].

The ECOG PS has been used to stratify patients. Generally men with a PS of 0–1 are likely to tolerate treatments and those with a PS of ≥ 2 are less likely to benefit. However, it is important that treatment decisions are individualised, in particular when symptoms related to disease progression are impacting on PS. In such cases, a trial of active life-prolonging agents to establish if a given treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in a summary paper published following the 2019 APCCC Conference [1260].

6.5.11 Symptomatic management in metastatic CRPC

Castration-resistant PCa is usually a debilitating disease often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [1260, 1261]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

6.5.11.1 Common complications due to bone metastases

Most patients with CRPC have painful bone metastases. External beam RT is highly effective, even as a single fraction [1262, 1263]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [1264]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture whatever its origin, clearly improving both pain and QoL [1265]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1266, 1267]. Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT [1268]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

6.5.11.2 Preventing skeletal-related events
6.5.11.2.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anti-cancer treatments, but for docetaxel, were available. Six hundred and forty three patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for 15 consecutive months, or placebo [1269]. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer SREs compared to the placebo group (44 vs. 33%, p = 0.021) and in particular fewer pathological fractures (13.1 vs. 22.1%, p = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.5.11.2.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ-B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, p = 0.028) [1262]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA or the EMA have approved denosumab for this indication [1270].

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with mCRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR: 0.82, p = 0.008). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p < 0.0001 for both). However, these findings were not associated with any survival benefit and in a *post-hoc* re-evaluation of endpoints, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1271].

The potential toxicity (e.g., osteonecrosis of the jaw, hypocalcaemia) of these drugs must always be kept in mind (5–8.2% in M0 CRPC and mCRPC, respectively) [1272, 1273]]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery or dental infection [1274]. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial [1275] (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1270]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy [1276]. Hypocalcaemia should be identified and prevented during treatment with bone protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively) [1273]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (> 500 mg) and vitamin D (> 400 IU equivalent) are recommended in all patients, unless in case of hypercalcaemia [1273, 1277, 1278].

6.5.12 *Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease*

Summary of evidence	LE
First-line treatment for mCRPC will be influenced by which treatments were used when metastatic cancer was first discovered.	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e., hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist.	3

Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be < 50 ng/dL before diagnosing castrate-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents.	Strong
Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong

6.5.13 *Guidelines for systematic treatments of castrate-resistant disease*

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naiive docetaxel with 75 mg/m^2 every 3 weeks.	Strong

Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

6.5.14   ***Guideline for non-metastatic castrate-resistant disease***

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

6.5.15   ***Guidelines for supportive care of castrate-resistant disease***
These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy/volumetric arc radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

6.6   Summary of guidelines for the treatment of prostate cancer

Table 6.6.1: 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 GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10–20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL Or GS > 7 (ISUP grade 4/5) 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.
* Based on digital rectal examination.
** Based on CT/bone scan.

6.6.1 General guidelines recommendations for the treatment of prostate cancer

Recommendations	Strength rating
No active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all local treatments have side effects.	Strong
Surgical treatment	
Radical prostatectomy can be safely delayed for at least 3 months from diagnosis in any risk category.	Weak
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary based on a nomogram, perform an extended LND template for optimal staging.	Strong
Consider avoiding nerve-sparing surgery when there is a risk of ipsilateral extra-capsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined in a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease (60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks).	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low-risk or NCCN favourable intermediate-risk disease.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Only offer focal therapy with high-intensity focused ultrasound or cryotherapy within a clinical trial or prospective registry.	Strong

6.6.2 Guidelines recommendations for fist-line treatment of various disease stages*

Recommendations		Strength rating
Low-risk disease		
Watchful Waiting (WW)	Offer WW to patients with a life expectancy < 10 years.	Strong
Active surveillance (AS)	Manage patients with a life expectancy > 10 years and low-risk disease by AS.	Strong
	Selection of patients	
	Patients with intraductal histology on biopsy should be excluded from AS.	Strong
	Perform magnetic resonance imaging (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.	Weak
	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

	Follow-up of patients	
	Repeat biopsies should be performed at least once every 3 years for 10 years.	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
Intermediate-risk disease		
WW	Offer WW to asymptomatic patients with a life expectancy < 10 years.	Strong
AS	Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per 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 ISUP grade group 3 disease should be excluded from AS protocols.	Strong
	Re-classify 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 2 disease.	Weak
Radical Prostatectomy (RP)	Offer RP to patients with a life expectancy of > 10 years.	Strong
	Radical prostatectomy can be safely delayed for at least 3 months.	Weak
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease on that side.	Strong
Extended pelvic lymph node dissection (ePLND)	Perform an ePLND based on predicted risk of lymph node (LN) invasion (validated nomogram, see Section 6.1.2.3.2.)	Weak
Radiotherapeutic treatment	Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong
	Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Strong
	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 months).	Weak
	Offer high-dose rate (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 months).	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
	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Weak
High-risk localised disease		
WW	Offer WW to asymptomatic patients with a life expectancy < 10 years.	Strong
RP	Radical prostatectomy can be safely delayed for at least 3 months.	Weak
	Offer RP to selected patients as part of potential multi-modal therapy.	Strong
ePLND	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong

Radiotherapeutic treatments	Offer patients IMRT)/VMAT plus IGRT with 76–78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	Do not offer either whole gland or focal therapy.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong
Locally-advanced disease		
RP	Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
ePLND	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 two years.	Strong
	Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 years 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 years of abiraterone to cN1M0 patients.	Strong
	Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Strong
Therapeutic options outside surgery or radiotherapy	Do not offer whole gland treatment or focal treatment.	Strong
Adjuvant treatment for pN0 and pN1 disease after radical prostatectomy		
pN0 & pN1 disease	Do not prescribe adjuvant ADT to pN0 patients.	Strong
	In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant IMRT/VMAT plus IGRT.	Strong
	In pN1 patients, after an eLND, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak
Non-curative or palliative treatments in a first-line setting		
Persistent PSA after radical prostatectomy		
	Offer a prostate-specific membrane antigen positron-emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL if the results will influence subsequent treatment decisions	Weak
	Treat men with no evidence of metastatic disease with SRT and additional hormonal therapy.	Weak

All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

6.6.3 Guidelines for metastatic disease, second-line and palliative treatments

Recommendations		Strength rating
Metastatic disease in a first-line setting		
M1 patients* *All statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.*	Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
	At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
	Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
	Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
	Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
	Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
	Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease and who are fit for the regimen.	Strong
	Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel.	Strong
	Offer ADT combined with non-curative prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria/M1a disease.	Strong
	Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
	Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
	Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong
Biochemical recurrence after treatment with curative intent		
Biochemical recurrence (BCR) after radical prostatectomy (RP)	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Offer early salvage intensity-modulated radiotherapy (IMRT)/volumetric arc radiation therapy (VMAT) plus image-guided radiotherapy (IGRT) to men with two consecutive PSA rises.	Strong
	A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
	Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with BCR.	Weak
BCR after RT	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Only offer salvage radical prostatectomy (SRP), brachytherapy, stereotactic body RT, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-doubling time (DT) > 12 months.	Strong

Recommendations for follow-up after radical prostatectomy or radiotherapy		
	Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history andserum prostate-specific antigen (PSA) measurement.	Strong
	At recurrence, only perform imaging if the result will affect treatment planning.	Strong
Life-prolonging treatments of castration-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents.	Strong
	Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong
Systemic treatments of castrate-resistant disease		
	Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
	Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
	Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
	Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
	Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
	Avoid sequencing of androgen receptor targeted agents.	Weak
	Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents		
	Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
	Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong
Supportive care of castration-resistant disease		
	Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
	Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as IMRT/VMAT plus IGRT and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong
Non-metastatic castrate-resistant disease		
	Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

Figure 6.1: Treatment non-metastasized (M0) – asymptomatic disease#

* Rule of thumb: Life expectancy 10 years.
** Recommendation based on clinical staging using digital rectal examination, not imaging.
*** Recommendation based on staging using combination of bone scan and CT.
**** See text, dependent on GG and (biopsy) volume.
1EBRT: IMRT/VMAT + IGRT of the prostate.
⌐⌐⌐⌐ = weak recommendation.
ADT = androgen deprivation therapy; EBRT =external beam radiotherapy; ECE = extracapsular extension;
ePLND = extended pelvic lymph node dissection; GG = grade group; HDR = high-dose rate; IDC = intraducal
carcinoma; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; LDR = low-dose rate;
VMAT = volumetric modulated arc therapy.

Figure 6.2: Treatment of metastasized (M1*) – disease, M+HSPC

* Based on staging using combination of bone scan and CT.
** Alphabetical order.
1EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
⌐⌐⌐⌐ = weak recommendation.
EBRT = external beam radiotherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radio-
therapy.

#Note: Please be aware that the various options in the following flowcharts present a generalised approach
only, and cannot take the management of individual patients into account, nor the availability of resources.

7. FOLLOW-UP

The rationale for following up patients is to assess immediate- and long-term oncological results, ensure treatment compliance and allow initiation of further therapy, when appropriate. In addition, follow-up allows monitoring of side effects or complications of therapy, functional outcomes and an opportunity to provide psychological support to PCa survivors, all of which is covered in Chapter 8.

For patients the most critical aspect of PCa is the diagnosis, the ensuing treatment and follow-up. These must be discussed between the patient and the clinician for co-decision on the treatment and the planned follow-up, including modalities, periodicity and how this will be communicated to the patient. The patient must be prepared for different potential outcomes of the follow-up, e.g., PSA levels, and what to expect from these. Otherwise, f.i., even a very small increase in PSA levels can cause unnecessary fear, even panic.

7.1 Follow-up: After local treatment
7.1.1 Definition
Local treatment is defined as RP or RT, either by IMRT plus IGRT or LDR- or HDR-brachytherapy, or any combination of these, including neoadjuvant and adjuvant therapy. Unestablished alternative treatments such as HIFU, cryosurgery and focal therapy options do not have a well-defined, validated, PSA cut-off to define BCR but follow the general principles as presented in this section. In general, a confirmed rising PSA is considered a sign of disease recurrence.

7.1.2 Why follow-up?
The first post-treatment clinic visit focuses on detecting treatment-related complications and assist patients in coping with their new situation apart from providing information on the pathological analysis. Men with PCa are at increased risk of depression and attention for mental health status is required [1279, 1280]. Tumour or patient characteristics may prompt changing the follow-up schedule. Follow-up of men diagnosed with PCa may allow early treatment of disease and treatment-related problems. The use of salvage treatment should be considered in light of the expected life-expectancy, especially when below 10 years in asymptomatic patients.

7.1.3 How to follow-up?
The procedures indicated at follow-up visits vary according to the clinical situation. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications in the post-treatment period is highlighted in Sections 6.1.2.4 and 8.2. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

7.1.3.1 Prostate-specific antigen monitoring
Measurement of PSA is the cornerstone of follow-up after local treatment. While PSA thresholds depend on the local treatment used, PSA recurrence almost always precedes clinical recurrence [975, 1281]. The key question is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value (see Section 6.3) [977]. No prospective studies are available on the optimal timing for PSA testing.

7.1.3.1.1 Active surveillance follow-up
Patients included in an AS programme should be monitored according to the recommendations presented in Section 6.2.1.3.

7.1.3.1.2 Prostate-specific antigen monitoring after radical prostatectomy
Following RP, the PSA level is expected to be undetectable. Biochemical recurrence is any rising PSA after prostatectomy as defined in Section 6.3. Prostate-specific antigen level is expected to be undetectable 2 months after a successful RP [1282]. Prostate-specific antigen is generally determined every 6 months until 3 years and yearly thereafter but the evidence for a specific interval is low [485] and mainly based on the observation that early recurrences are more likely to be associated with more rapid progression [977, 1283, 1284]. A rising PSA may occur after longer intervals up to 20 years after treatment and depends on the initial risk group [898]. A yearly PSA after 3 years is considered adequate considering the fact that a longer interval to BCR is correlated with a lower EAU-BCR risk score but around 50% of recurrence should be expected beyond 3 years. As mentioned in Section 6.3.2 no definitive threshold can be given for relapse after RP. Persistently measurable PSA in patients treated with RP is discussed in Section 6.2.6.

Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with a PSA nadir < 0.01 ng/mL have a high (96%) likelihood of remaining relapse-free within 2 years [1285]. In addition, post-RP PSA levels > 0.01 ng/mL in combination with clinical characteristics such as ISUP grade and surgical margin status may

predict PSA progression and can be useful to establish follow-up intervals [1284]. However, up to 86% of men were reported to have PSA values below 0.2 ng/mL at 5 years after an initial PSA nadir below 0.1 ng/mL within 6 months after surgery [1286]. Lastly, PSA and associated PSA-DT [1287] calculated prior to 0.2 ng/mL may help identify suitable candidates for early intervention [1288]. Prostate-specific antigen monitoring after SRT to the prostatic fossa is done at similar intervals and an early and rapid PSA rise predicts more rapid progression [1283] and is correlated to metastases-free and PCa-specific survival [1289].

7.1.3.1.3   Prostate-specific antigen monitoring after radiotherapy
Following RT, PSA drops more slowly as compared to post RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT although the optimal cut-off value remains controversial [1290]. The interval before reaching the nadir can be up to 3 years, or more. At the 2006 RTOG-ASTRO Consensus Conference the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome (mainly metastases), namely, an increase of 2 ng/mL above the post-treatment PSA nadir [976]. This definition also applies to patients who received HT [976].

7.1.3.2   *Digital rectal examination*
Local recurrence after curative treatment is possible without a concomitant rise in PSA level although very rarely [1291]. This has only been proven in patients with unfavourable undifferentiated tumours. Prostate-specific antigen and DRE comprise the most useful combination for first-line examination in follow-up after RT but the role of DRE was questioned since it failed to detect any local recurrence in the absence of a rising PSA in a series of 899 patients [1292]. In a series of 1,118 prostatectomy patients, no local histologically proven recurrence was found by DRE alone and PSA measurement may be the only test needed after RP [1293, 1294].

7.1.3.3   *Transrectal ultrasound, bone scintigraphy, CT, MRI and PET/CT*
Imaging techniques have no place in routine follow-up of localised PCa as long as the PSA is not rising. Imaging is only justified in patients for whom the findings will affect treatment decisions, either in case of BCR or in patients with symptoms (see Section 6.3.4 for a more detailed discussion).

7.1.3.4   *Functional follow-up*
All local treatments for PCa may cause short- and long-term side effect of various degree that will affect the patients' QoL. For quality control, and in order to help the patient in choosing the optimal treatment for him, it is essential that the functional outcomes of any treatment given is measured and registered by validated and reproducable methods. In order to adress side effects and their impact of QoL specific tools or 'patient-reported outcome measures' (PROMs) have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. For further discussion on this see Section 8.3.

7.1.4   **How long to follow-up?**
Most patients who fail treatment for PCa do so within 7 years after local therapy [503]. Patients should be followed more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE (if considered) are recommended every 6 months until 3 years and then annually. Whether follow-up should be stopped if PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question, but it seems fair that follow-up is only done to the point that if a recurrence is found the patient is fit enough for salvage therapy.

Risk assessment to predict metastases-free and PCa-specific survival after recurrence after primary treatment may guide individual decisions on a need for longer follow-up [903, 977, 1295]. Even in men with a PSA-DT less than 10 months after RP who choose to defer treatment, a median metastasis-free survival of 192 months and OS of 204 months from RP was observed, indicating the relatively long disease-free intervals observed in men with a rising PSA after local treatment [1296].

Symptomatic recurrence without a PSA rise is extremely rare, however, the symptoms typical for recurrent disease may vary and are poorly defined by published data. In case of the following symptoms PSA testing should be performed to exclude a possible cancer recurrence in particular in men not followed up by regular testing of their PSA levels: skeletal pain, haematuria, progressive voiding complaints, progressive lower body oedema, progressive bowel complaints or complaints of fatigue, sarcopenia or unexplained weight loss [1297].

7.1.5 ***Summary of evidence and guidelines for follow-up after treatment with curative intent***

Summary of evidence	LE
A detectable PSA, indicating a relaps of the disease, must be differentiated from a clinically meaningful relapse. The PSA threshold that best predicts further metastases after RP is > 0.4 ng/mL and > NADIR + 2 ng/mL after IMRT/VMAT plus IGRT (± ADT).	3

Recommendations	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and a prostate-specific antigen measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

7.2 Follow-up: During first line hormonal treatment (androgen sensitive period)

7.2.1 ***Introduction***

Androgen deprivation therapy is used in various situations: combined with RT for localised or locally-advanced disease, as monotherapy for a relapse after a local treatment, or in the presence of metastatic disease often in combination with other treatments. All these situations are based on the benefits of testosterone suppression either by drugs (LHRH agonists or antagonists) or orchidectomy. Inevitably, the disease will become castrate-resistant, although ADT will be maintained.

This section addresses the general principles of follow-up of patients on ADT alone. Section 6.5.7 includes further information on other drug treatments. Furthermore the specific follow-up needed for every single drug is outside the scope of this text, as is follow-up after chemotherapy.

To detect disease- and treatment-related complaints, regular clinical follow-up is mandatory and cannot be replaced by imaging or laboratory tests alone. Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs.

7.2.2 ***Purpose of follow-up***

The main objectives of follow-up in patients receiving ADT are to ensure treatment compliance, to monitor treatment response, to detect side effects early, and to guide treatment at the time point of clinical progression. After the initiation of ADT, it is recommended that patients are evaluated every 3 to 6 months. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms. This is even more important for patients who receive a combination of ADT and other potent medication, e.g., ARPI, for their disease.

7.2.3 ***General follow-up of men on ADT***

Patients under ADT require regular follow-up, including monitoring of serum testosterone, creatinine, liver function and metabolic parameters at 3 to 6 month intervals. Men on ADT can experience toxicity independent of their disease stage. Androgen deprivation therapy reduces bone density gradually, increasing the risk of fractures [1298]. It is therefore essential to asses bone density before and during treatment with ADT with or without a combination with other drugs.

As the consequenses of ADT are so varying, a structured follow-up including lab results, radiology and QoL, may be of value both for the patient and for the treating physician [1299].

7.2.3.1 *Testosterone monitoring*

Testosterone monitoring should be considered standard clinical practice in men on ADT. Many men receiving medical castration will achieve a castrate testosterone level (< 20 ng/dL), and most a testosterone level < 50 ng/dL. However, approximately 13–38% of patients fail to achieve these levels and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [1282] referred to as 'acute on-chronic effect' or 'breakthrough response' [1300]. Breakthrough rates for the < 20 ng/dL threshold were found to be more frequent (41.3%) and an association with worse clinical outcomes was suggested [1300].

The timing of measurements is not clearly defined. A 3 to 6-month testosterone level assessment has been suggested to ensure castration is achieved (especially during medical castration) and maintained. In case a castrate testosterone level is not reached, switching to another agonist or antagonist or to an orchiectomy should be considered. In patients with a confirmed rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castration-resistant state. Ideally, suboptimal testosterone castrate levels should be confirmed with an appropriate assay [1301, 1302]. After ADT cessation (intermittent treatment or temporary ADT use as with EBRT) testosterone recovery is dependent on patient' age and the duration of ADT [1303, 1304].

7.2.3.2 Liver function monitoring

Liver function tests will detect treatment toxicity (especially applicable for NSAA), but rarely indicate disease progression. Men on combined ADT should have their transaminase levels checked at least yearly but in particular in the first 6 months of treatment initiation since liver function disorders were observed relatively early in the majority of patients in larger trials [1305]. In view of potential liver toxicity a more frequent check is needed with some drugs (including abiraterone acetate) [1306]. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis, therefore it may be helpful to determine bone-specific isoenzymes as none are directly influenced by ADT [1307].

7.2.3.3 Serum creatinine and haematological parameters

Estimated glomerular filtration rate monitoring is good clinical practice as an increase may be linked to ureteral obstruction or bladder retention. A decline in haemoglobin is a known side effect of ADT. A significant decline after 3 months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue although other causes should be considered [1308]. Anaemia is often multi-factorial and other possible aetiologies should be excluded. An early decrease in haemoglobin 3 months after ADT initiation predicted better survival whereas a decrease beyond 6 months was associated with poor outcome in the SPCG-5 population [1309]. Radiotherapy to more extensive bone metastases locations may result in myelosuppression and haematological toxicity [1310, 1311].

7.2.3.4 Monitoring of metabolic complications

The most severe complications of androgen suppression are metabolic syndrome, cardiovascular morbidity, mental health problems, and bone resorption (see Section 8.2.4.5).

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and routinely) in addition to checking blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Prior to starting ADT a cardiology consultation should be considered in men with a history of cardiovascular disease and in men older than 65 years. Men on ADT are at increased risk of cardiovascular problems and hypertension and regular checks are required [1312]. More profound androgen ablation resulted in a higher cardiovascular toxicity [1313] and cardio-respiratory fitness decreased even after 6 months of ADT [1314]. Although LHRH antagonists have been suggested to provide a more favourable cardiovascular toxicity profile compared to LHRH agonists, the prematurely closed PRONOUNCE study found no difference at 12 months in major adverse cardiovascular events between men receiving degarelix or leuprolide [1315].

7.2.3.5 Monitoring bone problems

Androgen deprivation therapy increases the risk of osteoporosis. A combination of ADT with apalutamide, darolutamide, enzalutamide, abiraterone plus prednisone or docetaxel increases the fracture risk even more [1141, 1316, 1317]. Administration of ADT for more than a year, as compared to less than one year, showed a higher risk of osteoporosis (HR: 1.77 and 1.38, respectively) [1318]. Several scores (e.g., Fracture Risk Assessment Tool [FRAX score], Osteoporosis Self-Assessment Tool [OST], Osteoporosis Risk Assessment Instrument [ORAI], Osteoporosis Index of Risk [OSIRIS], Osteoporosis Risk Estimation [SCORE]) can help identify men at risk of osteoporotic complications but validation of these scores in the ADT setting is required (see Section 8.3.2.2) [1319-1321].

Routine bone monitoring for osteoporosis should be performed using dual emission X-ray absorptiometry (DEXA) scan [1322-1324]. Presence of osteoporosis should prompt the use of bone protective agents. The criteria for initiation of bone protective agents are mentioned in Section 8.3.2.2. If no bone protective agents are given, a DEXA scan should be done regularly, at least every 2 years [1325].

A review summarising the incidence of bone fractures showed an almost doubling of the risk of fractures when using ADT depending on patients' age and duration and type of ADT with the highest incidence in older men and men on additional novel ARPI medication across the entire spectrum of disease [1326]. In case of an osteoporotic fracture a bone protective agent is mandatory. Vitamin D and calcium levels should be regularly monitored when patients receive ADT and patients should be supplemented if needed (see Section 8.3.2.2).

7.2.3.6 Monitoring lifestyle, cognition, fatigue and sexual function

Lifestyle (e.g., diet, exercise, smoking status, etc.) affects QoL and potentially outcome [1307]. During follow-up men should be counselled on the beneficial effects of exercise to avoid ADT-related toxicity [1327]. Androgen deprivation therapy may affect mental and cognitive health and men on ADT are three times more likely to report depression [1328]. Attention to mental health should therefore be an integral part of the follow-up scheme. Men on ADT may experience complaints of fatigue possibly related to systemic inflammation [1329]. Reduced cognitive performance and fatigue may arise within 6 months after initiation of ADT but can

improve over time [1330]. Another apect of starting ADT is that it leads to sexual dysfunction, causing > 80% of couples to cease sexual activity completely. This aspect affects patients as well as their partners and couple counselling should be considered [1331].

7.2.4 Methods of follow-up in men on ADT without metastases

7.2.4.1 Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive non-metastasised PCa. Imaging should be considered when PSA is rising > 2 ng/mL or in case of symptoms suggestive of metastasis.

7.2.4.2 Imaging

In general, asymptomatic patients with a stable PSA level do not require further imaging, although care needs to be taken in patients with aggressive variants when PSA levels may not reflect tumour progression [1332]. New bone pain requires at least targeted imaging and potentially a bone scan. When PSA progression suggests CRPC status and treatment modification is considered, imaging, by means of a bone and CT scan, is recommended for restaging. Detection of metastases greatly depends on imaging (see Section 6.3.4).

7.2.5 Methods of follow-up in men under ADT for hormone-sensitive metastatic PCa

In metastatic patients it is of the utmost importance to counsel about early signs of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk. The intervals for follow-up in M1 patients should be guided by patients' complaints and can vary. Since most men will receive another anti-cancer therapy combined with ADT such as ARPI, chemotherapy or local RT, follow-up frequency should also be dependent on the treatment modality. The specific points related to follow-up during the castrate-resistant situation are detailed in Section 6.5.12.

7.2.5.1 PSA monitoring

In men on ADT alone, a PSA decline to < 4 ng/mL suggests a likely prolonged response and follow-up visits may be scheduled every 3 to 6 months provided the patient is asymptomatic or clinically improving. This applied to men on ADT monotherapy as well as after ADT plus docetaxel [1118]. Depending on symptoms and risk assessment, more frequent visits may be indicated. Treatment response may be evaluated based on a change in serum PSA level [1117, 1118] and bone- and CT scan although there is no consensus about how frequently these should be performed [1260]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. A rising PSA should prompt assessment of testosterone level, which is mandatory to define CRPC status, as well as restaging using imaging. However, it is now recognised that a stable PSA during ADT is not enough to characterise a non-progressive situation [1333].

7.2.5.2 Imaging as a marker of response in metastatic PCa

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [1334, 1335].

When bone scan is used to follow bone metastases, a quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1336]. Nonetheless, bone scan is limited by the so-called 'flare' phenomenon which is defined by the development of new images induced by treatment on a first follow-up scan which, after longer observation, actually represent a favourable response. Flare is observed within 8 to 12 weeks of treatment initiation and can lead to a false-positive diagnosis of disease progression. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. Magnetic resonance imaging can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available [1337]. The ability of PET/CT to assess response has been evaluated in a few studies. Until further data are available, MRI and PET/CT should not be used outside trials for treatment monitoring in metastatic patients [1338].

Men with metastasised PCa on ADT should also in the absence of a PSA rise be followed up with regular imaging since twenty-five percent of men with, or without, docetaxel in the CHAARTED trial developed clinical progression without a PSA rise [1333]. One in eight men with a PSA < 2 ng/mL showed clinical progression [1333]. The addition of docetaxel to ADT in the CHAARTED trial population did not reduce the incidence of clinical progression at low PSA values and this rate was similar for both low- and high-volume disease as per CHAARTED criteria [1333]. However, the optimal timing and image modality to be used remain unclear, as is the real clinical value of any findings.

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3–6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

8.   QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (Section 8.2) will summarise long-term consequences (≥ 12 months) of therapies for PCa. Based on two systematic reviews, the second (Section 8.3) provides evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and also supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1   Introduction
Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as close relations and work or vocation. These multifaceted issues all have a bearing on an individual's perception of QoL [1339, 1340]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others including fellow patients. Attention to the psychosocial concerns of people with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1341]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Psychological distress can be caused by the cancer diagnosis itself, cancer symptoms and/or treatment side effects [1342]. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed. Cross-sectional patient-reported outcomes studies in general PCa populations show the impact of treatment on global and disease-specific QoL is greater than that described in clinical trial populations who often have less co-morbidity and belong to higher socio-economic groups. Individuals undergoing two or more treatments have more symptoms and greater impact on QoL [1343, 1344]. Subgroups of people including those with poor general health, being unmarried, older age and/or pre-exisitng depressive symptoms are more at risk of long-term mental health issues following treatment for PCa [1345].

8.2   Adverse effects of PCa therapies
8.2.1   Surgery
A lack of clear consensus in reporting surgical complications following RP, specifically urinary incontinence and stricture rates, and the introduction of different techniques has resulted in a wide variation in the types of complications reported, as well as variation in the overall incidence of complications [1346-1349]. The most

common post-operative complication is ED but other related issues to consider include dry ejaculation, which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [1350]. The second most commonly occurring complication is long-term incontinence [1346-1349] but voiding difficulties may also occur associated with bladder neck contracture (e.g., 1.1% after RALP) [1351].

For those undergoing minimally-invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar and can occur more rarely with 8 mm and 5 mm trocars [1352]. A key consideration is whether long-term consequences of surgery are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [616-620], and can be compared with contemporaneous reports after RRP [621]. From these reports, the mean continence rates at 12 months were 89–100% for patients treated with RALP and 80–97% for patients treated with RRP. A prospective controlled non-randomised trial of patients undergoing RP in 14 centres using RALP or RRP demonstrated that at 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The unadjusted OR was 1.08 (95% CI: 0.87–1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The unadjusted OR was 0.81 (95% CI: 0.66–0.98) [622, 1353]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1353, 1354]. A single-centre randomised phase III study comparing RALP and RRP (n = 326) also demonstrates similar functional outcomes with both techniques at 24 months [520]. Prostatectomy was found to increase the risk of complaints from an inguinal hernia, in particular after an open procedure when compared to minimally-invasive approaches [1355, 1356].

8.2.2 Radiotherapy
8.2.2.1 Side effects of external beam radiotherapy
Analysis of the toxicity outcomes of the ProtecT trial shows that patients treated with EBRT and 6 months of ADT report bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding (described in detail in Section 8.3.1.1 below) [1357]. Participants in the ProtecT study were treated with 3D-CRT and more recent studies using IMRT demonstrate less bowel toxicity than noted previously with 3D-CRT [1358].

A systematic review 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 bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62) with similar risks over lag times of 5 and 10 years. Absolute excess risks over 10 years are small (1–4%) but should be discussed with younger patients in particular [1359].

8.2.2.2 Side effects from brachytherapy
Some patients experience significant urinary complications following implantation such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0–19%) [1360]. Chronic urinary morbidity is more common with combined EBRT and brachytherapy and can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Urethral strictures account for at least 50% of urinary complications and can be resolved with dilation in the majority [715, 721]. Prevention of morbidity depends on careful patient selection and IPSS score, backed up by urodynamic studies.

8.2.3 Local primary whole-gland treatments other than surgery or radiotherapy
8.2.3.1 Cryosurgery
In a systematic review and meta-analysis there was evidence that the rate of urinary incontinence at one year was lower for cryotherapy than for RP, but the size of the difference decreased with longer follow-up [780]. There was no significant difference between cryotherapy vs. EBRT in terms of urinary incontinence at one year (< 1%); cryotherapy had a similar ED rate (range 0–40%) to RP at one year. There were insufficient data to compare cryotherapy vs. EBRT in terms of ED.

8.2.3.2 High-intensity focused ultrasound
In terms of toxicity there are insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at one year HIFU had lower incontinence rates than RP (OR: 0.06, 95% CI: 0.01–0.48) [780].

8.2.4 Hormonal therapy
A summary of psychological impacts due to the use of ADT such as sexual function, mood, depression, cognitive function and impact on partners can be found in two clinical reviews [1361, 1362].

A small RCT evaluated the QoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. Patients treated by ADT reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue and irritability during treatment [1363]. Conversely, a prospective observational study with follow-up to 3 years

failed to demonstrate an association with cognitive decline in men on ADT when compared to men with PCa not treated with ADT and healthy controls [1364]. A prospective observational study of non-metastatic PCa found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [1365]. Another retrospective non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than patients undergoing orchiectomy. The stage at diagnosis had no effect on health outcomes [1366].

8.2.4.1   Sexual function
Cessation of sexual activity is very common in people undergoing ADT, affecting up to 93% [1367]. Androgen deprivation therapy reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1368].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at 12 months [1369]. A *post-hoc* analysis, including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [1370], preserved libido and erectile function [1371]. Intermittent androgen deprivation has been discussed elsewhere (see Section 6.4.3.2).

8.2.4.2   Hot flushes
Hot flushes are a common side effect of ADT (prevalence estimated between 44–80% of men on ADT) [1367]. They appear 3 months after starting ADT, usually persist long-term and have a significant impact on QoL.

Serotonin re-uptake inhibitors (e.g., venlafaxine or sertraline) also appear to be effective in men but less than hormone therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [1372]. After 6 months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, venlafaxine was inferior -47.2% (interquartile range -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group.

With a placebo effect influencing up to 30% of patients [1373], the efficacy of clonidine, veralipride, gabapentine [1374] and acupuncture [1375] need to be compared in prospective RCTs.

8.2.4.3   Non-metastatic bone fractures
Due to increased bone turnover and decreased BMD in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% RR with long-term ADT) [1376]. Severe fractures in men are associated with a significant risk of death [1377]. A precise evaluation of BMD should be performed by DEXA, ideally before or shortly after starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture and causes should be investigated. Other risk factors include increasing age, BMI of 19 or less, history of previous fracture or parent with fractured hip, current smoking, use of glucocorticoids, rheumatoid arthritis, alcohol consumption > 2 units per day, history of falls and a number of other chronic medical conditions [1378]. Fracture risk algorithms which combine BMD and clinical risk factors such as FRAX score can be used to guide treatment decisions but uncertainty exists regarding the optimal intervention threshold, therefore no specific risk algorithm can be recommended for men on ADT for PCa. Obesity (increase in body fat mass by up to 10% and/or BMI > 30) and sarcopenia (decrease in lean tissue mass by up to 3%) as well as weight loss are common and occur during the first year of ADT [1379]. These changes increase the fracture risk [1380].

Bicalutamide monotherapy may have less impact on BMD but is limited by its suboptimal efficacy for M1 disease [1381, 1382]. The intermittent LHRH-agonist modality might be associated with less bone impact [1383].

8.2.4.4   Metabolic effects
Lipid alterations are common and may occur as early as the first 3 months of treatment [1379]. Androgen deprivation therapy also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [1384], but there is insufficient data to recommend its use in non-diabetic patients.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The definition requires at least three of the following criteria [1385]:
- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure > 130/80 mmHg or use of medication for hypertension;
- high-density lipoprotein (HDL) cholesterol < 1 mmol/L;
- glycaemia > 5.6 mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT [1386]. Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [1387]. Androgen deprivation therapy-induced hypogonadism results in negative effects on skeletal muscle health. A prospective longitudinal study involving 252 men on ADT for a median of 20.4 months reported lean body mass decreases progressively over 3 years; 1.0% at one year, 2.1% at 2 years, and 2.4% at 3 years which appears more pronounced in men at ≥ 70 years of age [1388].

8.2.4.5 Cardiovascular morbidity
Cardiovascular mortality is a common cause of death in PCa patients [1107, 1389, 1390]. Several studies showed that ADT after only 6 months was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1391]. The RTOG 92-02 [1392] and 94-08 [1393] trials confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in both a secondary analysis of PLCO trial, even among subgroups with pre-existing cardiovascular disease [1394] and a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 and EORTC 22863 [1395]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [1396, 1397]. A meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease patients treated for PCa, e.g., the associations between LHRH agonists and nonfatal or fatal myocardial infarction or stroke RR: 1.57 (95% CI: 1.26–1.94) and RR: 1.51 (95% CI: 1.24–1.84), respectively [1398]. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1399] or presenting with a metabolic syndrome [1400]. It has been suggested that antagonists might be associated with less cardiovascular morbidity compared to agonists, but, as yet, there is no definite evidence [1315, 1401]. In a phase III RCT the use of relugolix, an oral LHRH antagonist, was associated with a reduced risk of major adverse cardiovascular events when compared to leuprolide, an injectable LHRH agonists, at 2.9% vs. 6.2%, respectively, over a follow-up time of 48 weeks (HR 0.46, 95% CI: 0.24–0.88) [747].

Concerns about LHRH agonists resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [1106]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, minimising alcohol intake, improved nutrition and smoking cessation [92, 1402].

8.2.4.6 Fatigue
Fatigue often develops as a side effect of ADT. Regular exercise appears to be the best protective measure. Reporting clinically significant fatigue is associated with severe psychological distress and should prompt screening for anxiety and/or depression [1403]. Anaemia may be a cause of fatigue [1367, 1404]. Anaemia requires an aetiological diagnosis (medullar invasion, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Regular blood transfusions may be required in patients with severe anaemia.

8.2.4.7 Neurological side effects
Castration seems also to be associated with an increased risk of stroke [1405], and is suspected to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1406].

8.3 Overall quality of life in men with PCa
Living longer with PCa does not necessarily equate to living well [1339, 1341]. There is clear evidence of unmet needs and ongoing support requirements for some individuals after diagnosis and treatment for PCa [1407]. Fear of cancer recurrence and PSA anxiety has a prevalence of 16% and 22%, respectively, across studies [1408]. Combined cognitive- and education-based psychological interventions improve depression, anxiety and distress [1409]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety and stress in caregivers [1410]. Radical treatment for PCa can negatively impact long-term QoL (e.g., sexual, urinary and bowel dysfunction) as can ADT used in short- or long-term treatment, e.g., sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae and increased cardiovascular and bone fracture risk [1361, 1411]. Direct symptoms from advanced or metastatic cancer, e.g.,

pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1412, 1413]. Patients' QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1414, 1415]. A PCa diagnosis commonly results in financial strain both for the individual and their families. This financial toxicity is associated with younger age at diagnosis, black race, low socio-economic status, low educational attainment and living in a rural area. Clinicians should discuss financial strains and signpost to support services so that quality of life and adherence to treatment can be maintained [1416].

As QoL is subjective and can mean different things to different people it can be difficult to measure and compare. Nevertheless, there are some generally common features across virtually all patients. Drawing from these common features, specific tools or PROMs have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated systematic reviews around cancer-specific QoL outcomes in patients with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

The tools with the best evidence for psychometric properties and feasibility for use in routine practice and research settings to assess PROMs in patients with localised PCa were EORTC QLQ-C30 and QLQ-PR25. Since EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25 module [1417].

Table 8.3.1: PROMs assessing cancer specific quality of life [1417]

Questionnaire	Domains/items
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [1418]	Five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); global health status/QoL scale; and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [1419]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Functional Assessment of Cancer Therapy-General (FACT-G) [1420]	Physical well-being, social/family well-being, emotional well-being, and functional well-being.
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1421]	12 cancer site specific items to assess for prostate-related symptoms. Can be combined with FACT-G or reported separately.
Expanded prostate cancer index composite (EPIC) [1422]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [1423]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1424]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [1425]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [1415]	Urinary, bowel, and sexual domains.

8.3.1 Long-term (> 12 months) quality of life outcomes in men with localised disease

8.3.1.1 Men undergoing local treatments

The results of the ProtecT trial (n = 1,643 men) reported no difference in EORTC QLQ-C30 assessed global QoL, up to 5 years of follow-up in men aged 50–69 years with T1–T2 disease randomised for treatment with AM, RP or RT with 6 months of ADT [1357]. However, EPIC urinary summary scores (at 6 years) were worse in men treated with RP compared to AM or RT (88.7 vs. 89.0 vs. 91.4, respectively) as were urinary incontinence (80.9 vs. 85.8 vs. 89.4, respectively) and sexual summary, function and bother scores (32.3 vs. 40.6 vs. 41.3 for sexual summary, 23.7 vs. 32.5 vs. 32.7 for sexual function and 51.4 vs. 57.9 vs. 60.1 for sexual bother, respectively) at 6 years of follow-up. Minimal clinically important differences for the 50 item EPIC questionnaire are not available. For men receiving RT with 6 months of ADT, EPIC bowel scores were poorer compared to AM and RP in all domains: function (90.8 vs. 92.3 vs. 92.3, respectively), bother (91.7 vs. 94.2 vs. 93.7, respectively)

and summary (91.2 vs. 93.2 vs. 93.0, respectively) at 6 years of follow-up in the ProtecT trial.

The findings regarding RP and RT are supported by other observational studies [503, 668, 1349, 1426-1429]. The Prostate Cancer Outcomes Study (PCOS) studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT [1349]. The study reported that at 5 years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However, despite these differences detected at 5 years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at 15 years. Investigators have reported that although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance 12 months after treatment [1358]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side effects is reduced with IMRT compared to older 3D-CRT techniques. This is supported by 5-year prospective, population-based cohort study where PROMs were compared in men with favourable- and unfavourable-risk localised disease [1426]. In the 1,386 men with favourable risk, comparison between AS and nerve-sparing prostatectomy, EBRT or LDR brachytherapy demonstrates that surgery is associated with worse urinary incontinence at 5 years and sexual dysfunction at 3 years when compared to AS. External beam RT is associated with changes not clinically different from AS, and LDR brachytherapy is associated with worse irritative urinary-, bowel- and sexual symptoms at one year. In 619 men with unfavourable-risk disease, comparison between non-nerve sparing RP and EBRT with ADT demonstrates that surgery is associated with worse urinary incontinence and sexual function through 5 years. Systematic review demonstrates that the risk of post-radiotherapy ED has reduced to a median of 25% at 2 years with utilisation of IMRT and is now similar to that noted after LDR brachytherapy [1430].

A few prospective studies have reported specific long-term urinary functional outcomes after RP and RT even if the studies are not comparative between the two treatment modalities. Considering incontinence and ED after RP the prospective randomised PIVOT trial, comparing RP to observation, reported that 40% of men wore pads, of which 20% wore more than > 1 pad/day, and an increased rate of ED in the RP group as compared to observation from 70% to approximately 87%, after a median follow-up of 12.7 years [503]. The corresponding figures from the prospective non-randomised LAPPRO-trial, comparing open- to robot-assisted RP, were 27–29% of the patients reporting urinary incontinence of some degree after 8 years and 66–70% reporting ED [1427]. Data on urinary, sexual and bowel function after RT has been reported from the HYPO-RT-PC-trial, a prospective randomised non-inferiority trial comparing ultra-HFX to conventional fractionation RT. In this trial 52–55% of the patients reported urinary problems (RTOG toxicity grade $\geq$ 1) at five years, of which 4.2–4.7% reported a RTOG grade $\geq$ 3 urinary morbidity and 7–8% reported moderate-to-severe incontinence at 6 years. Bowel toxicity of any level (RTOG toxicity grade $\geq$ 1) was reported in 53–54% of the patients at five years, of which 1.5–1.9% reported a RTOG grade $\geq$ 3 bowel morbidity, and 66–71% reported to have little or no erection without aids after six years follow-up [668, 1428].

With respect to brachytherapy cancer-specific QoL outcomes, one small RCT (n = 200) evaluated bilateral nerve-sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsening of physical functioning as well as irritative urinary symptomatology in 20% of brachytherapy patients at one year of follow-up. However, there were no significant differences in EORTC QLQ-C30/PR-25 scores at 5 years of follow-up when compared to pre-treatment values [1431]. It should be noted of this trial, within group tests only were reported. In a subsequent study by the same group comparing bilateral nerve-sparing RARP and brachytherapy (n = 165), improved continence was noted with brachytherapy in the first 6 months but lower potency rates up to 2 years [1432]. These data and a synthesis of 18 randomised and non-randomised studies in a systematic review involving 13,604 patients are the foundation of the following recommendations [1433].

8.3.1.2   Guidelines for quality of life in men undergoing local treatments

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

*8.3.2   **Improving quality of life in men who have been diagnosed with PCa***

8.3.2.1   Men undergoing local treatments

In men with localised disease, nurse-led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, relationship issues, depression, managing bowel and urinary function problems) provided positive short-term effects (4 months) on sexual function (effect size 0.45) and long-term (12 months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [1434].

Exercise programs during RT combined with ADT result in consistent benefits for cardiovascular fitness (standardised mean difference [SMD], 0.83; 95% CI: 0.31–1.36; $p < 0.01$) and muscle function (SMD, 1.30; 95% CI: 0.53–2.07; $p < 0.01$) with a reduction in urinary toxicity (SMD, -0.71; 95% CI: -1.25 to -0.18; $p < 0.01$) [1435]. In men undergoing AS, 12 weeks of high-intensity interval training may improve cardiovascular fitness and suppress PSA progression [1436].

Systematic review and meta-analysis of randomised trials show that exercise interventions for patients on ADT result in higher lean body mass (mean difference: 0.88, 95% CI 0.4 to 1.36, $p < 0.01$), a lower body fat mass (mean difference: -0.93, 95% CI: -1.10 to -0.10, $p < 0.05$), and a lower body fat rate (mean difference:-0.93, 95% CI: -1.39 to -0.47, $p < 0.01$). Greater efficacy was noted for exercise duration of $\geq$ 6 months (vs. < 6 months) and exercise immediately after starting ADT (vs. delayed exercise) [1437].

In men with post-surgical urinary incontinence, conservative management options include pelvic floor muscle training with or without biofeedback, electrical stimulation, extra-corporeal magnetic innervation (ExMI), compression devices (penile clamps), lifestyle changes, or a combination of methods. Uncertainty around the effectiveness and value of these conservative interventions remains [1438]. Surgical interventions including sling and artificial urinary sphincter (AUS) significantly decrease the number of pads used per day and increase the QoL compared with before intervention. The overall cure rate is around 60% and results in improvement in incontinence by about 25% [1439]. Other alternatives, such as the he Adjustable Transobturator Male System (ATOMS) and the Adjustable Continence Therapy (proACT) may be an option but seems less efficacious than AUS [1440]. For a more detailed overview of management of urinary incontinence in these men see Chapter 5.6 in the EAU Guidelines for Management of Non-neurogenic Male LUTS [1441].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single-centre, double-blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [1442]. However, a multi-centre double-blind RCT (n = 423) in men aged < 68 years, with normal pre-treatment erectile function undergoing either open, conventional or robot-assisted laparoscopic nerve-sparing RP, tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6, 95% CI: 3.1–16.0) when compared to 20 mg 'on demand' or placebo at 9 months of follow-up, even though the difference vanished after the end of study [1443]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation [1444]. A detailed discussion can be found in the EAU Sexual and Reproductive Health Guidelines [1445].

8.3.2.2   Men undergoing systemic treatments

Similar to men treated with a radical approach (see above), in men with T1-T3 disease undergoing RT and ADT, a combined nurse-led psychological support and physiotherapist-led multi-disciplinary rehabilitation has reported improvements in QoL. Specifically this intervention involved action planning around patients' needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5, 95% CI: 0.6–8.4), irritative (adjusted mean 5.8, 95% CI: 1.4–10.3) and hormonal (adjusted mean 4.8, 95% CI: 0.8–8.8) EPIC domains were found up to 22 weeks of follow-up [1446]. In a 3-year follow-up with 92% response rate from the initial study, fewer participants had moderate-severe bowel problems in the intervention (n = 2; 3%) vs. control group (n = 10; 14%) (p = 0.016) but the benefits in terms of urinary function were maintained only in those participants with moderate-severe urinary problems at baseline [1447].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8, 95% CI: 6.6–24.9) and cognitive domain outcomes (adjusted mean 11.4, 95% CI: 3.3–19.6) as well as symptom scales for fatigue (adjusted mean 11.0, 95% CI: 20.2–1.7), nausea (adjusted mean 4.0, 95% CI: 7.4–0.25), and dyspnoea (adjusted mean 12.4, 95% CI: 22.5–2.3) up to 3 months in men treated with ADT [1448]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9, 95% CI: 3.7–14.2) in men on long-term ADT [1449, 1450]. These findings are supported by a systematic review which reported improvements up to 12 weeks in cancer-specific QoL in a meta-analysis of high quality trials (SMD 0.33, 95%, CI: 0.08–0.58) [1404]. Supervised exercise interventions delivered over 12 months are effective in reducing psychological distress; particularly in those men with highest levels of baseline anxiety and depression [1451]. In untrained older men, systematic review suggests lower

volume exercise programs at moderate-to-high intensity are as effective as higher volume resistance training for enhancing body composition, functional capacity and muscle strength and may reduce barriers to exercise and enhance adherence [1452].

If dietary intake is not adequate, vitamin D and calcium supplementation should be offered, as there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [1442]. Online tools are available to calculate daily calcium intake for individual patients. For vitamin D deficiency a dose of at least 800 IU/day colecalciferol can be recommended. Use of a 25(OH) assay may be helpful to measure vitamin D levels [1453, 1454].

Anti-resorptive therapy is recommended for men on ADT for > 6 months with either a BMD T-score of < -2.5 or with an additional risk factor for osteoporosis or annual bone loss confirmed to exceed 5%, or in cases of severe fracture. Referral to a bone specialist should be considered in complex cases with severe fracture and/or multiple risk factors. Alendronate, risedronate, zoledronate and denosumab have all been shown to prevent bone loss in men with hormone-sensitive locally-advanced and metastatic PCa on ADT [1455-1458]. Patients should be warned about the < 5% risk of osteonecrosis of the jaw and/or atypical femoral fractures associated with these drugs. Bisphosphonates increase BMD in the hip and spine by up to 7% in one year [1457, 1459]. The optimal regimen for zoledronic acid for men on ADT with hormone-sensitive locally-advanced and metastatic PCa remains unclear: quarterly [1460] or yearly [1461] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1462]. A quarterly regimen should be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [1463, 1464]. Care should be taken when discontinuing treatment as rebound increased bone resorption can occur.

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after 2 years, using a 60 mg subcutaneous regimen every 6 months [1465]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, p = 0.006). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g., jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every 4 weeks), a delay in bone metastases of 4.2 months has been shown [1271] without any impact on OS, but with an increase in side effects. Therefore, this later regimen cannot be recommended.

8.3.2.3 Decision regret

Several treatments with curative intent for localised PCa are available all with comparable 10-year OS [485]. They vary in terms of the incidence of major side effects, including urinary symptoms, bowel symptoms and compromised sexual functioning [1357, 1358, 1466]. For this reason, patients' treatment preferences, in which they weigh expected benefits against likely side effects, are a central consideration in shared decision-making and in making informed treatment decisions [1467-1469].

It remains challenging, however, to evaluate whether the decision-making process can be viewed as successful; that is, whether the choice of treatment best reflects the patient's preferences and expectations [1470, 1471]. According to Decision Justification Theory (DJT), it is the more specific information on which treatment experiences lead to regret that decision regret needs to be better understood and to minimise it in future patients [1472]. About 25% of men with PCa undergoing either single or combined modality treatments report experiencing worse side effects than expected [1473]. Urinary incontinence most strongly correlates with regret after prostatectomy [1474].

Unmet expectations are comparable among the treatment groups, except for fatigue. Fatigue is less frequently reported as worse than expected by patients who received brachytherapy when compared to patients who received RP or EBRT. This could be explained by the less invasive treatment course of brachytherapy in comparison to EBRT with or without ADT and RP [1475]. Unmet expectations were more frequently reported by patients with positive surgical margins following surgery; having had a passive role in the decision-making process; and who had higher scores on the decisional conflict scale (i.e., more uncertainty about the treatment decision). Interestingly, positive surgical margins are not directly associated with an increased risk of PC-related mortality [1036]. Active participation and support in the process of forming a preference increases the chance of choosing a treatment that is in line with patients' expectations [1469, 1476-1478].

While it may seem desirable to tailor the patients' role in decision-making to their initial preference, and particularly to a preference for deferring to the advice of the clinician, this does not result in less decisional conflict or regret. Increasing patients' knowledge regardless of initial preference may actually be preferable [1474].

8.3.2.4 Decision aids in prostate cancer

Shared decision-making can increase patients' comfort when confronted with management decisions but has been shown to improve health outcome [1479] and more training seems needed for health care professionals

guiding patients [1480]. Patient education decreased PSA testing [1481] and increased adherence to AS protocols [1482, 1483]. Autonomous active decision-making by patients was associated with less regret after prostatectomy regardless of the method chosen and decision aids reduce decisional conflict [1484]. Still, guidance is needed to optimise patients' understanding of the options [1485]. Patients prioritised effectiveness and pain control over mode of administration and risk of fatigue when confronted with treatment choice in metastasised PCa [1486]. When implementing decision aids clinical validity and utility should be carefully evaluated and distinguished [1487]. A decision aid should educate as well as promote shared decision-making to optimise efficacy [1488] and pay attention to communicative aspects [1489].

8.3.2.5   Guidelines for quality of life in men undergoing systemic treatments

Recommendations	Strength rating
Offer men on androgen deprivation therapy (ADT), 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise men on ADT to maintain a healthy weight and diet, to stop smoking, reduce alcohol to ≤ 2 units daily and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men with T1-T3 disease specialist nurse-led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	Strong
Offer men starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Offer anti-resorptive therapy to men on long term ADT with either a BMD T-score of < -2.5 or with an additional clinical risk factor for fracture or annual bone loss on ADT is confirmed to exceed 5%.	Strong

9.   REFERENCES

1.   Mottet, N., *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.
https://pubmed.ncbi.nlm.nih.gov/33172724/

2.   Cornford, P., *et al*. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol, 2021. 79: 263.
https://pubmed.ncbi.nlm.nih.gov/33039206/

3.   Guyatt, G.H., *et al*. What is "quality of evidence" and why is it important to clinicians? BMJ, 2008. 336: 995.
https://pubmed.ncbi.nlm.nih.gov/18456631/

4.   Guyatt, G.H., *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008. 336: 924.
https://pubmed.ncbi.nlm.nih.gov/18436948/

5.   Phillips, B., *et al*. Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. Access date December 2022.
https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

6.   Guyatt, G.H., *et al*. Going from evidence to recommendations. BMJ, 2008. 336: 1049.
https://pubmed.ncbi.nlm.nih.gov/18467413/

7.   Culp, M.B., *et al*. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol, 2020. 77: 38.
https://pubmed.ncbi.nlm.nih.gov/31493960/

8.   IARC. WHO. Data visualization tools for exploring the global cancer burden in 2020. Access date December 2022.
https://gco.iarc.fr/today/home

9.   Bell, K.J., *et al*. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer, 2015. 137: 1749.
https://pubmed.ncbi.nlm.nih.gov/25821151/

10. Haas, G.P., *et al*. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. Can J Urol, 2008. 15: 3866.
https://pubmed.ncbi.nlm.nih.gov/18304396/

11. Fleshner, K., *et al*. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol, 2017. 14: 26.
https://pubmed.ncbi.nlm.nih.gov/27995937/

12. Kimura, T., *et al*. Global Trends of Latent Prostate Cancer in Autopsy Studies. Cancers (Basel), 2021. 13; 359.
https://pubmed.ncbi.nlm.nih.gov/33478075/

13. IARC France All Cancers (excluding non-melanoma skin cancer) Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Access date December 2022.
https://gco.iarc.fr/today/data/pdf/fact-sheets/cancers/cancer-fact-sheets-29.pdf

14. Hemminki, K. Familial risk and familial survival in prostate cancer. World J Urol, 2012. 30: 143.
https://pubmed.ncbi.nlm.nih.gov/22116601/

15. Jansson, K.F., *et al*. Concordance of tumor differentiation among brothers with prostate cancer. Eur Urol, 2012. 62: 656.
https://pubmed.ncbi.nlm.nih.gov/22386193/

16. Nyame, Y.A., *et al*. Deconstructing, Addressing, and Eliminating Racial and Ethnic Inequities in Prostate Cancer Care. Eur Urol, 2022. 82: 341.
https://pubmed.ncbi.nlm.nih.gov/35367082/

17. Karami, S., *et al*. Earlier age at diagnosis: another dimension in cancer disparity? Cancer Detect Prev, 2007. 31: 29.
https://pubmed.ncbi.nlm.nih.gov/17303347/

18. Sanchez-Ortiz, R.F., *et al*. African-American men with nonpalpable prostate cancer exhibit greater tumor volume than matched white men. Cancer, 2006. 107: 75.
https://pubmed.ncbi.nlm.nih.gov/16736511/

19. Mahal, B.A., *et al*. Prostate Cancer Racial Disparities: A Systematic Review by the Prostate Cancer Foundation Panel. Eur Urol Oncol, 2022. 5: 18.
https://pubmed.ncbi.nlm.nih.gov/34446369/

20. Randazzo, M., *et al*. A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). BJU Int, 2016. 117: 576.
https://pubmed.ncbi.nlm.nih.gov/26332304/

21. Beebe-Dimmer, J.L., *et al*. Risk of Prostate Cancer Associated With Familial and Hereditary Cancer Syndromes. J Clin Oncol, 2020. 38: 1807.
https://pubmed.ncbi.nlm.nih.gov/32208047/

22. Bratt, O., *et al*. Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study. J Natl Cancer Inst, 2016. 108.
https://pubmed.ncbi.nlm.nih.gov/27400876/

23. Amin Al Olama, A., *et al*. Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans. Hum Mol Genet, 2015. 24: 5589.
https://pubmed.ncbi.nlm.nih.gov/26025378/

24. Eeles, R.A., *et al*. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet, 2013. 45: 385.
https://pubmed.ncbi.nlm.nih.gov/23535732/

25. Schumacher, F.R., *et al*. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet, 2018. 50: 928.
https://pubmed.ncbi.nlm.nih.gov/29892016/

26. Bancroft, E.K., *et al*. Targeted Prostate Cancer Screening in BRCA1 and BRCA2 Mutation Carriers: Results from the Initial Screening Round of the IMPACT Study. Eur Urol, 2014. 66: 489.
https://pubmed.ncbi.nlm.nih.gov/24484606/

27. Gulati, R., *et al*. Screening Men at Increased Risk for Prostate Cancer Diagnosis: Model Estimates of Benefits and Harms. Cancer Epidemiol Biomarkers Prev, 2017. 26: 222.
https://pubmed.ncbi.nlm.nih.gov/27742670/

28. Giri, V.N., *et al*. Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. Prostate, 2019. 79: 333.
https://pubmed.ncbi.nlm.nih.gov/30450585/

29. Nicolosi, P., *et al*. Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines. JAMA Oncol, 2019. 5: 523.
https://pubmed.ncbi.nlm.nih.gov/30730552/

30.   Castro, E., *et al*. PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol, 2019. 37: 490.
        https://pubmed.ncbi.nlm.nih.gov/30625039/

31.   Pritchard, C.C., *et al*. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med, 2016. 375: 443.
        https://pubmed.ncbi.nlm.nih.gov/27433846/

32.   Ewing, C.M., *et al*. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med, 2012. 366: 141.
        https://pubmed.ncbi.nlm.nih.gov/22236224/

33.   Lynch, H.T., *et al*. Screening for familial and hereditary prostate cancer. Int J Cancer, 2016. 138: 2579.
        https://pubmed.ncbi.nlm.nih.gov/26638190/

34.   Nyberg, T., *et al*. Prostate Cancer Risks for Male BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. Eur Urol, 2020. 77: 24.
        https://pubmed.ncbi.nlm.nih.gov/31495749/

35.   Castro, E., *et al*. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol, 2013. 31: 1748.
        https://pubmed.ncbi.nlm.nih.gov/23569316/

36.   Castro, E., *et al*. Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer. Eur Urol, 2015. 68: 186.
        https://pubmed.ncbi.nlm.nih.gov/25454609/

37.   Na, R., *et al*. Germline Mutations in ATM and BRCA1/2 Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death. Eur Urol, 2017. 71: 740.
        https://pubmed.ncbi.nlm.nih.gov/27989354/

38.   Mano, R., *et al*. Malignant Abnormalities in Male BRCA Mutation Carriers: Results From a Prospectively Screened Cohort. JAMA Oncol, 2018. 4: 872.
        https://pubmed.ncbi.nlm.nih.gov/29710070/

39.   Edwards, S.M., *et al*. Two percent of men with early-onset prostate cancer harbor germline mutations in the BRCA2 gene. Am J Hum Genet, 2003. 72: 1.
        https://pubmed.ncbi.nlm.nih.gov/12474142/

40.   van Asperen, C.J., *et al*. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet, 2005. 42: 711.
        https://pubmed.ncbi.nlm.nih.gov/16141007/

41.   Agalliu, I., *et al*. Rare germline mutations in the BRCA2 gene are associated with early-onset prostate cancer. Br J Cancer, 2007. 97: 826.
        https://pubmed.ncbi.nlm.nih.gov/17700570/

42.   Leongamornlert, D., *et al*. Frequent germline deleterious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease. Br J Cancer, 2014. 110: 1663.
        https://pubmed.ncbi.nlm.nih.gov/24556621/

43.   Wang, Y., *et al*. CHEK2 mutation and risk of prostate cancer: a systematic review and meta-analysis. Int J Clin Exp Med, 2015. 8: 15708.
        https://pubmed.ncbi.nlm.nih.gov/26629066/

44.   Zhen, J.T., *et al*. Genetic testing for hereditary prostate cancer: Current status and limitations. Cancer, 2018. 124: 3105.
        https://pubmed.ncbi.nlm.nih.gov/29669169/

45.   Leongamornlert, D., *et al*. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer, 2012. 106: 1697.
        https://pubmed.ncbi.nlm.nih.gov/22516946/

46.   Thompson, D., *et al*. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst, 2002. 94: 1358.
        https://pubmed.ncbi.nlm.nih.gov/12237281/

47.   Karlsson, R., *et al*. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. Eur Urol, 2014. 65: 169.
        https://pubmed.ncbi.nlm.nih.gov/22841674/

48.   Storebjerg, T.M., *et al*. Prevalence of the HOXB13 G84E mutation in Danish men undergoing radical prostatectomy and its correlations with prostate cancer risk and aggressiveness. BJU Int, 2016. 118: 646.
        https://pubmed.ncbi.nlm.nih.gov/26779768/

49.   Ryan, S., *et al*. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev, 2014. 23: 437.
        https://pubmed.ncbi.nlm.nih.gov/24425144/

50. Carlsson, S., et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. Bmj, 2014. 348: g2296.
https://pubmed.ncbi.nlm.nih.gov/24682399/

51. Rosty, C., et al. High prevalence of mismatch repair deficiency in prostate cancers diagnosed in mismatch repair gene mutation carriers from the colon cancer family registry. Fam Cancer, 2014. 13: 573.
https://pubmed.ncbi.nlm.nih.gov/25117503/

52. Leitzmann, M.F., et al. Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. Clin Epidemiol, 2012. 4: 1.
https://pubmed.ncbi.nlm.nih.gov/22291478/

53. Cook, L.S., et al. Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. J Urol, 1999. 161: 152.
https://pubmed.ncbi.nlm.nih.gov/10037388/

54. Esposito, K., et al. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest, 2013. 36: 132.
https://pubmed.ncbi.nlm.nih.gov/23481613/

55. Blanc-Lapierre, A., et al. Metabolic syndrome and prostate cancer risk in a population-based case-control study in Montreal, Canada. BMC Public Health, 2015. 15: 913.
https://pubmed.ncbi.nlm.nih.gov/26385727/

56. Preston, M.A., et al. Metformin use and prostate cancer risk. Eur Urol, 2014. 66: 1012.
https://pubmed.ncbi.nlm.nih.gov/24857538/

57. Freedland, S.J., et al. Statin use and risk of prostate cancer and high-grade prostate cancer: results from the REDUCE study. Prostate Cancer Prostatic Dis, 2013. 16: 254.
https://pubmed.ncbi.nlm.nih.gov/23567655/

58. Li, Y., et al. Effect of Statins on the Risk of Different Stages of Prostate Cancer: A Meta-Analysis. Urol Int, 2022. 106: 869.
https://pubmed.ncbi.nlm.nih.gov/34518476/

59. Vidal, A.C., et al. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. Cancer Epidemiol Biomarkers Prev, 2014. 23: 2936.
https://pubmed.ncbi.nlm.nih.gov/25261967/

60. Davies, N.M., et al. The effects of height and BMI on prostate cancer incidence and mortality: a Mendelian randomization study in 20,848 cases and 20,214 controls from the PRACTICAL consortium. Cancer Causes Control, 2015. 26: 1603.
https://pubmed.ncbi.nlm.nih.gov/26387087/

61. Rivera-Izquierdo, M., et al. Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients. Cancers (Basel), 2021. 13; 4269.
https://pubmed.ncbi.nlm.nih.gov/34439328/

62. Dickerman, B.A., et al. Alcohol intake, drinking patterns, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. Cancer Causes Control, 2016. 27: 1049.
https://pubmed.ncbi.nlm.nih.gov/27351919/

63. Zhao, J., et al. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer, 2016. 16: 845.
https://pubmed.ncbi.nlm.nih.gov/27842506/

64. Chen, X., et al. Coffee consumption and risk of prostate cancer: a systematic review and meta-analysis. BMJ Open, 2021. 11: e038902.
https://pubmed.ncbi.nlm.nih.gov/33431520/

65. Key, T.J. Nutrition, hormones and prostate cancer risk: results from the European prospective investigation into cancer and nutrition. Recent Results Cancer Res, 2014. 202: 39.
https://pubmed.ncbi.nlm.nih.gov/24531775/

66. Alexander, D.D., et al. Meta-Analysis of Long-Chain Omega-3 Polyunsaturated Fatty Acids (LComega-3PUFA) and Prostate Cancer. Nutr Cancer, 2015. 67: 543.
https://pubmed.ncbi.nlm.nih.gov/25826711/

67. Lippi, G., et al. Fried food and prostate cancer risk: systematic review and meta-analysis. Int J Food Sci Nutr, 2015. 66: 587.
https://pubmed.ncbi.nlm.nih.gov/26114920/

68. Chen, P., et al. Lycopene and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis. Medicine (Baltimore), 2015. 94: e1260.
https://pubmed.ncbi.nlm.nih.gov/26287411/

69.   Rowles, J.L., 3rd, *et al*. Processed and raw tomato consumption and risk of prostate cancer: a systematic review and dose-response meta-analysis. Prostate Cancer Prostatic Dis, 2018. 21: 319.
        https://pubmed.ncbi.nlm.nih.gov/29317772/

70.   Ilic, D., *et al*. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. Maturitas, 2012. 72: 269.
        https://pubmed.ncbi.nlm.nih.gov/22633187/

71.   Bylsma, L.C., *et al*. A review and meta-analysis of prospective studies of red and processed meat, meat cooking methods, heme iron, heterocyclic amines and prostate cancer. Nutr J, 2015. 14: 125.
        https://pubmed.ncbi.nlm.nih.gov/26689289/

72.   Nouri-Majd, S., *et al*. Association Between Red and Processed Meat Consumption and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis. Front Nutr, 2022. 9: 801722.
        https://pubmed.ncbi.nlm.nih.gov/35198587/

73.   Zhang, M., *et al*. Is phytoestrogen intake associated with decreased risk of prostate cancer? A systematic review of epidemiological studies based on 17,546 cases. Andrology, 2016. 4: 745.
        https://pubmed.ncbi.nlm.nih.gov/27260185/

74.   Applegate, C.C., *et al*. Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. Nutrients, 2018. 10.
        https://pubmed.ncbi.nlm.nih.gov/29300347/

75.   Kristal, A.R., *et al*. Plasma vitamin D and prostate cancer risk: results from the Selenium and Vitamin E Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev, 2014. 23: 1494.
        https://pubmed.ncbi.nlm.nih.gov/24732629/

76.   Nyame, Y.A., *et al*. Associations Between Serum Vitamin D and Adverse Pathology in Men Undergoing Radical Prostatectomy. J Clin Oncol, 2016. 34: 1345.
        https://pubmed.ncbi.nlm.nih.gov/26903577/

77.   Cui, Z., *et al*. Serum selenium levels and prostate cancer risk: A MOOSE-compliant meta-analysis. Medicine (Baltimore), 2017. 96: e5944.
        https://pubmed.ncbi.nlm.nih.gov/28151881/

78.   Allen, N.E., *et al*. Selenium and Prostate Cancer: Analysis of Individual Participant Data From Fifteen Prospective Studies. J Natl Cancer Inst, 2016. 108: djw153.
        https://pubmed.ncbi.nlm.nih.gov/27385803/

79.   Lippman, S.M., *et al*. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA, 2009. 301: 39.
        https://pubmed.ncbi.nlm.nih.gov/19066370/

80.   Knijnik, P.G., *et al*. The impact of 5-alpha-reductase inhibitors on mortality in a prostate cancer chemoprevention setting: a meta-analysis. World J Urol, 2021. 39: 365.
        https://pubmed.ncbi.nlm.nih.gov/32314009/

81.   Hu, X., *et al*. Association of 5-alpha-reductase inhibitor and prostate cancer incidence and mortality: a meta-analysis. Transl Androl Urol, 2020. 9: 2519.
        https://pubmed.ncbi.nlm.nih.gov/33457226/

82.   Kramer, B.S., *et al*. Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Clin Oncol, 2009. 27: 1502.
        https://pubmed.ncbi.nlm.nih.gov/19252137/

83.   Andriole, G.L., *et al*. Effect of dutasteride on the risk of prostate cancer. N Engl J Med, 2010. 362: 1192.
        https://pubmed.ncbi.nlm.nih.gov/20357281/

84.   Thompson, I.M., *et al*. The influence of finasteride on the development of prostate cancer. N Engl J Med, 2003. 349: 215.
        https://pubmed.ncbi.nlm.nih.gov/12824459/

85.   Haider, A., *et al*. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. J Urol, 2015. 193: 80.
        https://pubmed.ncbi.nlm.nih.gov/24980615/

86.   Watts, E.L., *et al*. Low Free Testosterone and Prostate Cancer Risk: A Collaborative Analysis of 20 Prospective Studies. Eur Urol, 2018. 74: 585.
        https://pubmed.ncbi.nlm.nih.gov/30077399/

87.   Burns, J.A., *et al*. Inflammatory Bowel Disease and the Risk of Prostate Cancer. Eur Urol, 2019. 75: 846.
        https://pubmed.ncbi.nlm.nih.gov/30528221/

88.   Zhou, C.K., *et al*. Male Pattern Baldness in Relation to Prostate Cancer-Specific Mortality: A Prospective Analysis in the NHANES I Epidemiologic Follow-up Study. Am J Epidemiol, 2016. 183: 210.
        https://pubmed.ncbi.nlm.nih.gov/26764224/

89.   Lian, W.Q., *et al*. Gonorrhea and Prostate Cancer Incidence: An Updated Meta-Analysis of 21 Epidemiologic Studies. Med Sci Monit, 2015. 21: 1902.
        https://pubmed.ncbi.nlm.nih.gov/26126881/

90.   Rao, D., *et al*. Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. Onco Targets Ther, 2015. 8: 2817.
        https://pubmed.ncbi.nlm.nih.gov/26491356/

91.   Islami, F., *et al*. A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. Eur Urol, 2014. 66: 1054.
        https://pubmed.ncbi.nlm.nih.gov/25242554/

92.   Brookman-May, S.D., *et al*. Latest Evidence on the Impact of Smoking, Sports, and Sexual Activity as Modifiable Lifestyle Risk Factors for Prostate Cancer Incidence, Recurrence, and Progression: A Systematic Review of the Literature by the European Association of Urology Section of Oncological Urology (ESOU). Eur Urol Focus, 2019. 5: 756.
        https://pubmed.ncbi.nlm.nih.gov/29576530/

93.   Ju-Kun, S., *et al*. Association Between Cd Exposure and Risk of Prostate Cancer: A PRISMA-Compliant Systematic Review and Meta-Analysis. Medicine (Baltimore), 2016. 95: e2708.
        https://pubmed.ncbi.nlm.nih.gov/26871808/

94.   Russo, G.I., *et al*. Human papillomavirus and risk of prostate cancer: a systematic review and meta-analysis. Aging Male, 2020: 23: 132.
        https://pubmed.ncbi.nlm.nih.gov/29571270/

95.   Multigner, L., *et al*. Chlordecone exposure and risk of prostate cancer. J Clin Oncol, 2010. 28: 3457.
        https://pubmed.ncbi.nlm.nih.gov/20566993/

96.   Bhindi, B., *et al*. The Association Between Vasectomy and Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Intern Med, 2017. 177: 1273.
        https://pubmed.ncbi.nlm.nih.gov/28715534/

97.   Cremers, R.G., *et al*. Self-reported acne is not associated with prostate cancer. Urol Oncol, 2014. 32: 941.
        https://pubmed.ncbi.nlm.nih.gov/25011577/

98.   Huang, T.B., *et al*. Aspirin use and the risk of prostate cancer: a meta-analysis of 24 epidemiologic studies. Int Urol Nephrol, 2014. 46: 1715.
        https://pubmed.ncbi.nlm.nih.gov/24687637/

99.   Bhindi, B., *et al*. The impact of the use of aspirin and other nonsteroidal anti-inflammatory drugs on the risk of prostate cancer detection on biopsy. Urology, 2014. 84: 1073.
        https://pubmed.ncbi.nlm.nih.gov/25443907/

100.   Lin, S.W., *et al*. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. Int J Cancer, 2012. 131: E1015.
        https://pubmed.ncbi.nlm.nih.gov/22539073/

101.   Pabalan, N., *et al*. Association of male circumcision with risk of prostate cancer: a meta-analysis. Prostate Cancer Prostatic Dis, 2015. 18: 352.
        https://pubmed.ncbi.nlm.nih.gov/26215783/

102.   Rider, J.R., *et al*. Ejaculation Frequency and Risk of Prostate Cancer: Updated Results with an Additional Decade of Follow-up. Eur Urol, 2016. 70: 974.
        https://pubmed.ncbi.nlm.nih.gov/27033442/

103.   Brierley, J.D., *et al*., TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2017.
        https://www.uicc.org/resources/tnm-classification-malignant-tumours-8th-edition

104.   Cooperberg, M.R., *et al*. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol, 2005. 173: 1938.
        https://pubmed.ncbi.nlm.nih.gov/15879786/

105.   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.
        https://pubmed.ncbi.nlm.nih.gov/31838560/

106.   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.
        https://pubmed.ncbi.nlm.nih.gov/33604691/

107. van den Bergh, R.C.N., *et al*. Re: Andrew Vickers, Sigrid V. Carlsson, Matthew Cooperberg. Routine Use of Magnetic Resonance Imaging for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol 2020;78:304-6: Prebiopsy MRI: Through the Looking Glass. Eur Urol, 2020. 78: 310.
https://pubmed.ncbi.nlm.nih.gov/32660749/

108. Epstein, J.I., *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.
https://pubmed.ncbi.nlm.nih.gov/16096414/

109. Epstein, J.I., *et al*. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol, 2016. 40: 244.
https://pubmed.ncbi.nlm.nih.gov/26492179/

110. 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.
https://pubmed.ncbi.nlm.nih.gov/32459716/

111. Epstein, J.I., *et al*. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol, 2016. 69: 428.
https://pubmed.ncbi.nlm.nih.gov/26166626/

112. Moyer, V.A. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med, 2012. 157: 120.
https://pubmed.ncbi.nlm.nih.gov/22801674/

113. Sauter, G., *et al*. Integrating Tertiary Gleason 5 Patterns into Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens. Eur Urol, 2018. 73: 674.
https://pubmed.ncbi.nlm.nih.gov/28117112/

114. Anderson, B.B., *et al*. Extraprostatic Extension Is Extremely Rare for Contemporary Gleason Score 6 Prostate Cancer. Eur Urol, 2017. 72: 455.
https://pubmed.ncbi.nlm.nih.gov/27986368/

115. Ross, H.M., *et al*. Do adenocarcinomas of the prostate with Gleason score (GS) ≤ 6 have the potential to metastasize to lymph nodes? Am J Surg Pathol, 2012. 36: 1346.
https://pubmed.ncbi.nlm.nih.gov/22531173/

116. Alberts, A.R., *et al*. Biopsy undergrading in men with Gleason score 6 and fatal prostate cancer in the European Randomized study of Screening for Prostate Cancer Rotterdam. Int J Urol, 2017. 24: 281.
https://pubmed.ncbi.nlm.nih.gov/28173626/

117. Zareba, P., *et al*. The impact of the 2005 International Society of Urological Pathology (ISUP) consensus on Gleason grading in contemporary practice. Histopathology, 2009. 55: 384.
https://pubmed.ncbi.nlm.nih.gov/19817888/

118. Goel, S., *et al*. Concordance Between Biopsy and Radical Prostatectomy Pathology in the Era of Targeted Biopsy: A Systematic Review and Meta-analysis. Eur Urol Oncol, 2020. 3: 10.
https://pubmed.ncbi.nlm.nih.gov/31492650/

119. Inoue, L.Y., *et al*. Modeling grade progression in an active surveillance study. Stat Med, 2014. 33: 930.
https://pubmed.ncbi.nlm.nih.gov/24123208/

120. Van der Kwast, T.H., *et al*. Defining the threshold for significant versus insignificant prostate cancer. Nat Rev Urol, 2013. 10: 473.
https://pubmed.ncbi.nlm.nih.gov/23712205/

121. Preisser, F., *et al*. Intermediate-risk Prostate Cancer: Stratification and Management. Eur Urol Oncol, 2020. 3: 270.
https://pubmed.ncbi.nlm.nih.gov/32303478/

122. Overland, M.R., *et al*. Active surveillance for intermediate-risk prostate cancer: yes, but for whom? Curr Opin Urol, 2019. 29: 605.
https://pubmed.ncbi.nlm.nih.gov/31436567/

123. Kasivisvanathan, V., *et al*. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med, 2018. 378: 1767.
https://pubmed.ncbi.nlm.nih.gov/29552975/

124. 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.
https://pubmed.ncbi.nlm.nih.gov/30470502/

125. van der Leest, M., *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.
https://pubmed.ncbi.nlm.nih.gov/30477981/

126. 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.
https://pubmed.ncbi.nlm.nih.gov/34465492/

127. Ahmed, H.U., *et al*. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet, 2017. 389: 815.
https://pubmed.ncbi.nlm.nih.gov/28110982/

128. Thompson, J.E., *et al*. Multiparametric magnetic resonance imaging guided diagnostic biopsy detects significant prostate cancer and could reduce unnecessary biopsies and over detection: a prospective study. J Urol, 2014. 192: 67.
https://pubmed.ncbi.nlm.nih.gov/24518762/

129. Kane, C.J., *et al*. Variability in Outcomes for Patients with Intermediate-risk Prostate Cancer (Gleason Score 7, International Society of Urological Pathology Gleason Group 2-3) and Implications for Risk Stratification: A Systematic Review. Eur Urol Focus, 2017. 3: 487.
https://pubmed.ncbi.nlm.nih.gov/28753804/

130. Zumsteg, Z.S., *et al*. Unification of favourable intermediate-, unfavourable intermediate-, and very high-risk stratification criteria for prostate cancer. BJU Int, 2017. 120: E87.
https://pubmed.ncbi.nlm.nih.gov/28464446/

131. Etzioni, R., *et al*. Limitations of basing screening policies on screening trials: The US Preventive Services Task Force and Prostate Cancer Screening. Med Care, 2013. 51: 295.
https://pubmed.ncbi.nlm.nih.gov/23269114/

132. Ilic, D., *et al*. Screening for prostate cancer. Cochrane Database Syst Rev, 2013: CD004720.
https://pubmed.ncbi.nlm.nih.gov/23440794/

133. Hayes, J.H., *et al*. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA, 2014. 311: 1143.
https://pubmed.ncbi.nlm.nih.gov/24643604/

134. Ilic, D., *et al*. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. Bmj, 2018. 362: k3519.
https://pubmed.ncbi.nlm.nih.gov/30185521/

135. Hugosson, J., *et al*. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol, 2019. 76: 43.
https://pubmed.ncbi.nlm.nih.gov/30824296/

136. The benefits and harms of breast cancer screening: an independent review. Lancet, 2012. 380: 1778.
https://pubmed.ncbi.nlm.nih.gov/23117178/

137. Hugosson, J., *et al*. Eighteen-year follow-up of the Göteborg Randomized Population-based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. Scand J Urol, 2018. 52: 27.
https://pubmed.ncbi.nlm.nih.gov/29254399/

138. Arnsrud Godtman, R., *et al*. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. Eur Urol, 2015. 68: 354.
https://pubmed.ncbi.nlm.nih.gov/25556937/

139. Heijnsdijk, E.A., *et al*. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med, 2012. 367: 595.
https://pubmed.ncbi.nlm.nih.gov/22894572/

140. Booth, N., *et al*. Health-related quality of life in the Finnish trial of screening for prostate cancer. Eur Urol, 2014. 65: 39.
https://pubmed.ncbi.nlm.nih.gov/23265387/

141. Vasarainen, H., *et al*. Effects of prostate cancer screening on health-related quality of life: results of the Finnish arm of the European randomized screening trial (ERSPC). Acta Oncol, 2013. 52: 1615.
https://pubmed.ncbi.nlm.nih.gov/23786174/

142. Carter, H.B., *et al*. Early detection of prostate cancer: AUA Guideline. J Urol, 2013. 190: 419.
https://pubmed.ncbi.nlm.nih.gov/23659877/

143. Drazer, M.W., *et al*. National Prostate Cancer Screening Rates After the 2012 US Preventive Services Task Force Recommendation Discouraging Prostate-Specific Antigen-Based Screening. J Clin Oncol, 2015. 33: 2416.
https://pubmed.ncbi.nlm.nih.gov/26056181/

144. Hu, J.C., *et al*. Increase in Prostate Cancer Distant Metastases at Diagnosis in the United States. JAMA Oncol, 2017. 3: 705.
https://pubmed.ncbi.nlm.nih.gov/28033446/

145. Jemal, A., *et al*. Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations. JAMA, 2015. 314: 2054.
https://pubmed.ncbi.nlm.nih.gov/26575061/

146. Gaylis, F.D., *et al*. Change in prostate cancer presentation coinciding with USPSTF screening recommendations at a community-based Urology Practice. Urol Oncol, 2017. 35: 663.e1.
https://pubmed.ncbi.nlm.nih.gov/28736250/

147. Shah, N., *et al*. Prostate Biopsy Characteristics: A Comparison Between the Pre- and Post-2012 United States Preventive Services Task Force (USPSTF) Prostate Cancer Screening Guidelines. Rev Urol, 2018. 20: 77.
https://pubmed.ncbi.nlm.nih.gov/30288144/

148. Loeb, S. Guideline of guidelines: prostate cancer screening. BJU Int, 2014. 114: 323.
https://pubmed.ncbi.nlm.nih.gov/24981126/

149. Siegel, R.L., *et al*. Cancer statistics, 2019. CA Cancer J Clin, 2019. 69: 7.
https://pubmed.ncbi.nlm.nih.gov/30620402/

150. Fenton, J.J., *et al*. Prostate-Specific Antigen-Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA, 2018. 319: 1914.
https://pubmed.ncbi.nlm.nih.gov/29801018/

151. Grossman, D.C., *et al*. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA, 2018. 319: 1901.
https://pubmed.ncbi.nlm.nih.gov/29801017/

152. Bibbins-Domingo, K., *et al*. The US Preventive Services Task Force 2017 Draft Recommendation Statement on Screening for Prostate Cancer: An Invitation to Review and Comment. JAMA, 2017. 317: 1949.
https://pubmed.ncbi.nlm.nih.gov/28397958/

153. U.S. Preventive Services Task Force. Prostate Cancer Screening Draft Recommendations. 2018. Access date December 2022.
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening

154. Eklund, M., *et al*. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. N Engl J Med, 2021. 385: 908.
https://pubmed.ncbi.nlm.nih.gov/34237810/

155. Eldred-Evans, D., *et al*. Population-Based Prostate Cancer Screening With Magnetic Resonance Imaging or Ultrasonography: The IP1-PROSTAGRAM Study. JAMA Oncol, 2021. 7: 395.
https://pubmed.ncbi.nlm.nih.gov/33570542/

156. Van Poppel, H., *et al*. Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission. Eur Urol, 2021. 79: 327.
https://pubmed.ncbi.nlm.nih.gov/33384200/

157. Page, E.C., *et al*. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. Eur Urol, 2019. 76: 831.
https://pubmed.ncbi.nlm.nih.gov/31537406/

158. Bancroft, E.K., *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.
https://pubmed.ncbi.nlm.nih.gov/34678156/

159. Boyle, H.J., *et al*. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer, 2019. 116: 116.
https://pubmed.ncbi.nlm.nih.gov/31195356/

160. Loeb, S., *et al*. Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. J Urol, 2006. 175: 902.
https://pubmed.ncbi.nlm.nih.gov/16469576/

161. Naji, L., *et al*. Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A Systematic Review and Meta-Analysis. Ann Fam Med, 2018. 16: 149.
https://pubmed.ncbi.nlm.nih.gov/29531107/

162. Martin, R.M., *et al*. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA, 2018. 319: 883.
https://pubmed.ncbi.nlm.nih.gov/29509864/

163. Vickers, A.J., *et al*. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ, 2013. 346: f2023.
https://pubmed.ncbi.nlm.nih.gov/23596126/

164. Gelfond, J., *et al*. Intermediate-Term Risk of Prostate Cancer is Directly Related to Baseline Prostate Specific Antigen: Implications for Reducing the Burden of Prostate Specific Antigen Screening. J Urol, 2015. 194: 46.
https://pubmed.ncbi.nlm.nih.gov/25686543/

165. Roobol, M.J., *et al*. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology, 2005. 65: 343.
https://pubmed.ncbi.nlm.nih.gov/15708050/

166. Palsdottir, T. External Validation of the Rotterdam Prostate Cancer Risk Calculator and Comparison with Stockholm3 for Prostate Cancer Diagnosis in a Swedish Population-based Screening Cohort. Eur Urol Focus, 2022. 13: S2405.
https://pubmed.ncbi.nlm.nih.gov/36522257/

167. Roobol, M.J., *et al*. Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator for Initial Prostate Biopsy by Incorporating the 2014 International Society of Urological Pathology Gleason Grading and Cribriform growth. Eur Urol, 2017. 72: 45.
https://pubmed.ncbi.nlm.nih.gov/28162815/

168. Drost, F.H., *et al*. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev, 2019. 4: CD012663.
https://pubmed.ncbi.nlm.nih.gov/31022301/

169. Wagensveld, I.M., *et al*. A Prospective Multicenter Comparison Study of Risk-adapted Ultrasound-directed and Magnetic Resonance Imaging-directed Diagnostic Pathways for Suspected Prostate Cancer in Biopsy-naïve Men. Eur Urol, 2022. 82: 318.
https://pubmed.ncbi.nlm.nih.gov/35341658/

170. Schoots, I.G., *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.
https://pubmed.ncbi.nlm.nih.gov/33089586/

171. Deniffel, D., *et al*. Avoiding Unnecessary Biopsy: MRI-based Risk Models versus a PI-RADS and PSA Density Strategy for Clinically Significant Prostate Cancer. Radiology, 2021: 204112.
https://pubmed.ncbi.nlm.nih.gov/34032510/

172. Boesen, L., *et al*. Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7-10 Prostate Cancer in Biopsy-naive Men. Eur Urol Oncol, 2019. 2: 311.
https://pubmed.ncbi.nlm.nih.gov/31200846/

173. Falagario, U.G., *et al*. Avoiding Unnecessary Magnetic Resonance Imaging (MRI) and Biopsies: Negative and Positive Predictive Value of MRI According to Prostate-specific Antigen Density, 4Kscore and Risk Calculators. Eur Urol Oncol, 2020. 3: 700.
https://pubmed.ncbi.nlm.nih.gov/31548130/

174. Knaapila, J., *et al*. Prebiopsy IMPROD Biparametric Magnetic Resonance Imaging Combined with Prostate-Specific Antigen Density in the Diagnosis of Prostate Cancer: An External Validation Study. Eur Urol Oncol, 2019. 6: 30134.
https://euoncology.europeanurology.com/article/S2588-9311(19)30134-8/fulltext

175. Hansen, N.L., *et al*. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy. BJU Int, 2017. 120: 631.
https://pubmed.ncbi.nlm.nih.gov/27862869/

176. Kretschmer, A., *et al*. Biomarkers in prostate cancer - Current clinical utility and future perspectives. Crit Rev Oncol Hematol, 2017. 120: 180.
https://pubmed.ncbi.nlm.nih.gov/29198331/

177. Mark, J.R., *et al*. Genetic Testing Guidelines and Education of Health Care Providers Involved in Prostate Cancer Care. Urol Clin North Am, 2021. 48: 311.
https://pubmed.ncbi.nlm.nih.gov/34210487/

178. Giri, V.N., *et al*. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol, 2020. 38: 2798.
https://pubmed.ncbi.nlm.nih.gov/32516092/

179. John, E.M., *et al*. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA, 2007. 298: 2869.
https://pubmed.ncbi.nlm.nih.gov/18159056/

180. Carvalhal, G.F., *et al*. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. J Urol, 1999. 161: 835.
https://pubmed.ncbi.nlm.nih.gov/10022696/

181. Gosselaar, C., *et al*. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol, 2008. 54: 581.
https://pubmed.ncbi.nlm.nih.gov/18423977/

182. Herrera-Caceres, J.O., *et al*. Utility of digital rectal examination in a population with prostate cancer treated with active surveillance. Can Urol Assoc J, 2020. 14: E453.
https://pubmed.ncbi.nlm.nih.gov/32223879/

183. Okotie, O.T., *et al*. Characteristics of prostate cancer detected by digital rectal examination only. Urology, 2007. 70: 1117.
https://pubmed.ncbi.nlm.nih.gov/18158030/

184. Prebay, Z.J., *et al*. The prognostic value of digital rectal exam for the existence of advanced pathologic features after prostatectomy. Prostate, 2021. 81: 1064.
https://pubmed.ncbi.nlm.nih.gov/34297858/

185. Stamey, T.A., *et al*. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med, 1987. 317: 909.
https://pubmed.ncbi.nlm.nih.gov/2442609/

186. Merriel, S.W.D., *et al*. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. BMC Med, 2022. 20: 54.
https://pubmed.ncbi.nlm.nih.gov/35125113/

187. Habib, F.K., *et al*. Differential effect of finasteride on the tissue androgen concentrations in benign prostatic hyperplasia. Clin Endocrinol (Oxf), 1997. 46: 137.
https://pubmed.ncbi.nlm.nih.gov/9135694/

188. Semjonow, A., *et al*. Discordance of assay methods creates pitfalls for the interpretation of prostate-specific antigen values. Prostate Suppl, 1996. 7: 3.
https://pubmed.ncbi.nlm.nih.gov/8950358/

189. Thompson, I.M., *et al*. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med, 2004. 350: 2239.
https://pubmed.ncbi.nlm.nih.gov/15163773/

190. Wagaskar, V.G., *et al*. A 4K score/MRI-based nomogram for predicting prostate cancer, clinically significant prostate cancer, and unfavorable prostate cancer. Cancer Rep (Hoboken), 2021. 4: e1357.
https://pubmed.ncbi.nlm.nih.gov/33661541/

191. Hendriks, R.J., *et al*. Clinical use of the SelectMDx urinary-biomarker test with or without mpMRI in prostate cancer diagnosis: a prospective, multicenter study in biopsy-naïve men. Prostate Cancer Prostatic Dis, 2021. 24: 1110.
https://pubmed.ncbi.nlm.nih.gov/33941866/

192. Nordström, T., *et al*. Repeat Prostate-Specific Antigen Tests Before Prostate Biopsy Decisions. J Natl Cancer Inst, 2016. 108: djw165.
https://pubmed.ncbi.nlm.nih.gov/27418620/

193. Rosario, D.J., *et al*. Contribution of a single repeat PSA test to prostate cancer risk assessment: experience from the ProtecT study. Eur Urol, 2008. 53: 777.
https://pubmed.ncbi.nlm.nih.gov/18079051/

194. De Nunzio, C., *et al*. Repeat prostate-specific antigen (PSA) test before prostate biopsy: a 20% decrease in PSA values is associated with a reduced risk of cancer and particularly of high-grade cancer. BJU Int, 2018. 122: 83.
https://pubmed.ncbi.nlm.nih.gov/29533522/

195. Omri, N., *et al*. Association between PSA density and pathologically significant prostate cancer: The impact of prostate volume. Prostate, 2020. 80: 1444.
https://pubmed.ncbi.nlm.nih.gov/32970856/

196. Maggi, M., *et al*. Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus, 2020. 6: 463.
https://pubmed.ncbi.nlm.nih.gov/31279677/

197. Nordström, T., *et al*. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis, 2018. 21: 57.
https://pubmed.ncbi.nlm.nih.gov/29259293/

198. Yusim, I., *et al*. The use of prostate specific antigen density to predict clinically significant prostate cancer. Sci Rep, 2020. 10: 20015.
https://pubmed.ncbi.nlm.nih.gov/33203873/

199. Cuocolo, R., *et al*. PSA-density does not improve bi-parametric prostate MR detection of prostate cancer in a biopsy naïve patient population. Eur J Radiol, 2018. 104: 64.
https://pubmed.ncbi.nlm.nih.gov/29857868/

200. Stephan, C., *et al*. The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. Cancer, 1997. 79: 104.
https://pubmed.ncbi.nlm.nih.gov/8988733/

201. Huang, Y., *et al*. Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10 ng/mL: A meta-analysis. Medicine (Baltimore), 2018. 97: e0249.
https://pubmed.ncbi.nlm.nih.gov/29595681/

202. Bryant, R.J., *et al*. Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. J Natl Cancer Inst, 2015. 107: djv095.
https://pubmed.ncbi.nlm.nih.gov/25863334/

203. Loeb, S., *et al*. The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol, 2014. 6: 74.
https://pubmed.ncbi.nlm.nih.gov/24688603/

204. de la Calle, C., *et al*. Multicenter Evaluation of the Prostate Health Index to Detect Aggressive Prostate Cancer in Biopsy Naive Men. J Urol, 2015. 194: 65.
https://pubmed.ncbi.nlm.nih.gov/25636659/

205. Catalona, W.J., *et al*. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol, 2011. 185: 1650.
https://pubmed.ncbi.nlm.nih.gov/21419439/

206. Nordstrom, T., *et al*. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. Eur Urol, 2015. 68: 139.
https://pubmed.ncbi.nlm.nih.gov/25151013/

207. Klein, E.A., *et al*. The Single-parameter, Structure-based IsoPSA Assay Demonstrates Improved Diagnostic Accuracy for Detection of Any Prostate Cancer and High-grade Prostate Cancer Compared to a Concentration-based Assay of Total Prostate-specific Antigen: A Preliminary Report. Eur Urol, 2017. 72: 942.
https://pubmed.ncbi.nlm.nih.gov/28396176/

208. Stovsky, M., *et al*. Clinical Validation of IsoPSATM, a Single Parameter, Structure Based Assay for Improved Detection of High Grade Prostate Cancer. J Urol, 2019. 201: 1115.
https://pubmed.ncbi.nlm.nih.gov/30810464/

209. Wagaskar, V.G., *et al*. Clinical Utility of Negative Multiparametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer and Clinically Significant Prostate Cancer. Eur Urol Open Sci, 2021. 28: 9.
https://pubmed.ncbi.nlm.nih.gov/34337520/

210. Morote, J., *et al*. Improving the Early Detection of Clinically Significant Prostate Cancer in Men in the Challenging Prostate Imaging-Reporting and Data System 3 Category. Eur Urol Open Sci, 2022. 37: 38.
https://pubmed.ncbi.nlm.nih.gov/35243388/

211. Ploussard, G., *et al*. The role of prostate cancer antigen 3 (PCA3) in prostate cancer detection. Expert Rev Anticancer Ther, 2018. 18: 1013.
https://pubmed.ncbi.nlm.nih.gov/30016891/

212. Van Neste, L., *et al*. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. Eur Urol, 2016. 70: 740.
https://pubmed.ncbi.nlm.nih.gov/27108162/

213. Maggi, M., *et al*. SelectMDx and Multiparametric Magnetic Resonance Imaging of the Prostate for Men Undergoing Primary Prostate Biopsy: A Prospective Assessment in a Multi-Institutional Study. Cancers (Basel), 2021. 13: 2047.
https://pubmed.ncbi.nlm.nih.gov/33922626/

214. Lendínez-Cano, G., *et al*. Prospective study of diagnostic accuracy in the detection of high-grade prostate cancer in biopsy-naïve patients with clinical suspicion of prostate cancer who underwent the Select MDx test. Prostate, 2021. 81: 857.
https://pubmed.ncbi.nlm.nih.gov/34184761/

215. Roumiguié, M., *et al*. Independent Evaluation of the Respective Predictive Values for High-Grade Prostate Cancer of Clinical Information and RNA Biomarkers after Upfront MRI and Image-Guided Biopsies. Cancers (Basel), 2020. 12: 285.
https://pubmed.ncbi.nlm.nih.gov/31991591/

216. Tomlins, S.A., *et al*. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science, 2005. 310: 644.
https://pubmed.ncbi.nlm.nih.gov/16254181/

217. Tomlins, S.A., *et al*. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. Eur Urol, 2016. 70: 45.
https://pubmed.ncbi.nlm.nih.gov/25985884/

218. Donovan, M.J., *et al*. A molecular signature of PCA3 and ERG exosomal RNA from non-DRE urine is predictive of initial prostate biopsy result. Prostate Cancer Prostatic Dis, 2015. 18: 370.
https://pubmed.ncbi.nlm.nih.gov/26345389/

219. McKiernan, J., *et al*. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. JAMA Oncol, 2016. 2: 882.
https://pubmed.ncbi.nlm.nih.gov/27032035/

220. Vedder, M.M., *et al*. The added value of percentage of free to total prostate-specific antigen, PCA3, and a kallikrein panel to the ERSPC risk calculator for prostate cancer in prescreened men. Eur Urol, 2014. 66: 1109.
https://pubmed.ncbi.nlm.nih.gov/25168616/

221. Lamy, P.J., *et al*. Prognostic Biomarkers Used for Localised Prostate Cancer Management: A Systematic Review. Eur Urol Focus, 2018. 4: 790.
https://pubmed.ncbi.nlm.nih.gov/28753865/

222. Nicholson, A., *et al*. The clinical effectiveness and cost-effectiveness of the PROGENSA(R) prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. Health Technol Assess, 2015. 19: 1.
https://pubmed.ncbi.nlm.nih.gov/26507078/

223. Partin, A.W., *et al*. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. J Urol, 2014. 192: 1081.
https://pubmed.ncbi.nlm.nih.gov/24747657/

224. Smeenge, M., *et al*. Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel. BJU Int, 2012. 110: 942.
https://pubmed.ncbi.nlm.nih.gov/22462566/

225. Correas, J.M., *et al*. Advanced ultrasound in the diagnosis of prostate cancer. World J Urol, 2021. 39: 661.
https://pubmed.ncbi.nlm.nih.gov/32306060/

226. Mannaerts, C.K., *et al*. Detection of clinically significant prostate cancer in biopsy-naïve men: direct comparison of systematic biopsy, multiparametric MRI- and contrast-ultrasound-dispersion imaging-targeted biopsy. BJU Int, 2020. 126: 481.
https://pubmed.ncbi.nlm.nih.gov/32315112/

227. Grey, A.D.R., *et al*. Multiparametric ultrasound versus multiparametric MRI to diagnose prostate cancer (CADMUS): a prospective, multicentre, paired-cohort, confirmatory study. Lancet Oncol, 2022. 23: 428.
https://pubmed.ncbi.nlm.nih.gov/35240084/

228. Sountoulides, P., *et al*. Micro-Ultrasound-Guided vs Multiparametric Magnetic Resonance Imaging-Targeted Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-Analysis. J Urol, 2021. 205: 1254.
https://pubmed.ncbi.nlm.nih.gov/33577367/

229. Hofbauer, S.L., *et al*. A non-inferiority comparative analysis of micro-ultrasonography and MRI-targeted biopsy in men at risk of prostate cancer. BJU Int, 2022. 129: 648.
https://pubmed.ncbi.nlm.nih.gov/34773679/

230. Ghai, S., *et al*. Comparison of Micro-US and Multiparametric MRI for Prostate Cancer Detection in Biopsy-Naive Men. Radiology, 2022. 305: 390.
https://pubmed.ncbi.nlm.nih.gov/35852425/

231. Bratan, F., *et al*. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol, 2013. 23: 2019.
https://pubmed.ncbi.nlm.nih.gov/23494494/

232. Borofsky, S., *et al*. What Are We Missing? False-Negative Cancers at Multiparametric MR Imaging of the Prostate. Radiology, 2018. 286: 186.
https://pubmed.ncbi.nlm.nih.gov/29053402/

233. Johnson, D.C., *et al*. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. Eur Urol, 2019. 75: 712.
https://pubmed.ncbi.nlm.nih.gov/30509763/

234. Oerther, B., *et al*. Cancer detection rates of the PI-RADSv2.1 assessment categories: systematic review and meta-analysis on lesion level and patient level. Prostate Cancer Prostatic Dis, 2022. 25: 256.
https://pubmed.ncbi.nlm.nih.gov/34230616/

235. Goldberg, H., *et al*. Comparison of Magnetic Resonance Imaging and Transrectal Ultrasound Informed Prostate Biopsy for Prostate Cancer Diagnosis in Biopsy Naïve Men: A Systematic Review and Meta-Analysis. J Urol, 2020. 203: 1085.
https://pubmed.ncbi.nlm.nih.gov/31609177/

236. 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.
https://pubmed.ncbi.nlm.nih.gov/30522912/

237. 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.
https://pubmed.ncbi.nlm.nih.gov/31239236/

238. Hugosson, J., *et al*. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. N Engl J Med, 2022. 387: 2126.
https://pubmed.ncbi.nlm.nih.gov/36477032/

239. Weinreb, J.C., *et al*. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol, 2016. 69: 16.
https://pubmed.ncbi.nlm.nih.gov/26427566/

240. Stabile, A., *et al*. Factors Influencing Variability in the Performance of Multiparametric Magnetic Resonance Imaging in Detecting Clinically Significant Prostate Cancer: A Systematic Literature Review. Eur Urol Oncol, 2020. 3: 145.
https://pubmed.ncbi.nlm.nih.gov/32192942/

241. Farrell, C., *et al*. Prostate Multiparametric Magnetic Resonance Imaging Program Implementation and Impact: Initial Clinical Experience in a Community Based Health System. Urol Pract, 2018. 5: 165.
https://www.auajournals.org/doi/abs/10.1016/j.urpr.2017.03.009

242. Meng, X., *et al*. The Institutional Learning Curve of Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy: Temporal Improvements in Cancer Detection in 4 Years. J Urol, 2018. 200: 1022.
https://pubmed.ncbi.nlm.nih.gov/29886090/

243. Raeside, M., *et al*. Prostate MRI evolution in clinical practice: Audit of tumour detection and staging versus prostatectomy with staged introduction of multiparametric MRI and Prostate Imaging Reporting and Data System v2 reporting. J Med Imaging Radiat Oncol, 2019. 63: 487.
https://pubmed.ncbi.nlm.nih.gov/30951248/

244. Shaish, H., *et al*. Impact of a Structured Reporting Template on Adherence to Prostate Imaging Reporting and Data System Version 2 and on the Diagnostic Performance of Prostate MRI for Clinically Significant Prostate Cancer. J Am Coll Radiol, 2018. 15: 749.
https://pubmed.ncbi.nlm.nih.gov/29506919/

245. Turkbey, B., *et al*. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol, 2019. 76: 340.
https://pubmed.ncbi.nlm.nih.gov/30898406/

246. Penzkofer, T., *et al*. ESUR/ESUI position paper: developing artificial intelligence for precision diagnosis of prostate cancer using magnetic resonance imaging. Eur Radiol, 2021. 31: 9567.
https://pubmed.ncbi.nlm.nih.gov/33991226/

247. de Rooij, M., *et al*. ESUR/ESUI consensus statements on multi-parametric MRI for the detection of clinically significant prostate cancer: quality requirements for image acquisition, interpretation and radiologists' training. Eur Radiol, 2020. 30: 5404.
https://pubmed.ncbi.nlm.nih.gov/32424596/

248. Barrett, T., *et al*. Certification in reporting multiparametric magnetic resonance imaging of the prostate: recommendations of a UK consensus meeting. BJU Int, 2021. 127: 304.
https://pubmed.ncbi.nlm.nih.gov/33113258/

249. Giganti, F., *et al*. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. Eur Urol Oncol, 2020. 3: 615.
https://pubmed.ncbi.nlm.nih.gov/32646850/

250. Bryk, D.J., *et al*. The Role of Ipsilateral and Contralateral Transrectal Ultrasound-guided Systematic Prostate Biopsy in Men With Unilateral Magnetic Resonance Imaging Lesion Undergoing Magnetic Resonance Imaging-ultrasound Fusion-targeted Prostate Biopsy. Urology, 2017. 102: 178.
https://pubmed.ncbi.nlm.nih.gov/27871829/

251. Freifeld, Y., *et al*. Optimal sampling scheme in men with abnormal multiparametric MRI undergoing MRI-TRUS fusion prostate biopsy. Urol Oncol, 2019. 37: 57.
https://pubmed.ncbi.nlm.nih.gov/30446460/

252. Kenigsberg, A.P., *et al*. Optimizing the Number of Cores Targeted During Prostate Magnetic Resonance Imaging Fusion Target Biopsy. Eur Urol Oncol, 2018. 1: 418.
https://pubmed.ncbi.nlm.nih.gov/31158081/

253. Zhang, M., *et al*. Value of Increasing Biopsy Cores per Target with Cognitive MRI-targeted Transrectal US Prostate Biopsy. Radiology, 2019. 291: 83.
https://pubmed.ncbi.nlm.nih.gov/30694165/

254. Lu, A.J., *et al*. Role of Core Number and Location in Targeted Magnetic Resonance Imaging-Ultrasound Fusion Prostate Biopsy. Eur Urol, 2019. 76: 14.
https://pubmed.ncbi.nlm.nih.gov/31047733/

255. Hagens, M.J., *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.
https://pubmed.ncbi.nlm.nih.gov/35540708/

256. Distler, F.A., *et al*. The Value of PSA Density in Combination with PI-RADS for the Accuracy of Prostate Cancer Prediction. J Urol, 2017. 198: 575.
https://pubmed.ncbi.nlm.nih.gov/28373135/

257. Washino, S., *et al*. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naive patients. BJU Int, 2017. 119: 225.
https://pubmed.ncbi.nlm.nih.gov/26935594/

258. Pagniez, M.A., *et al*. Predictive Factors of Missed Clinically Significant Prostate Cancers in Men with Negative Magnetic Resonance Imaging: A Systematic Review and Meta-Analysis. J Urol, 2020. 204: 24.
https://pubmed.ncbi.nlm.nih.gov/31967522/

259. Hansen, N.L., *et al*. The influence of prostate-specific antigen density on positive and negative predictive values of multiparametric magnetic resonance imaging to detect Gleason score 7-10 prostate cancer in a repeat biopsy setting. BJU Int, 2017. 119: 724.
https://pubmed.ncbi.nlm.nih.gov/27488931/

260. Hansen, N.L., *et al*. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naive men with suspicion of prostate cancer. BJU Int, 2018. 122: 40.
https://pubmed.ncbi.nlm.nih.gov/29024425/

261. Oishi, M., *et al*. Which Patients with Negative Magnetic Resonance Imaging Can Safely Avoid Biopsy for Prostate Cancer? J Urol, 2019. 201: 268.
https://pubmed.ncbi.nlm.nih.gov/30189186/

262. Stevens, E., *et al*. Clinical utility of PSAD combined with PI-RADS category for the detection of clinically significant prostate cancer. Urol Oncol, 2020. 38: 846.e9.
https://pubmed.ncbi.nlm.nih.gov/32576527/

263. Schoots, I.G., *et al*. Multivariate risk prediction tools including MRI for individualized biopsy decision in prostate cancer diagnosis: current status and future directions. World J Urol, 2020. 38: 517.
https://pubmed.ncbi.nlm.nih.gov/30868240/

264. Saba, K., *et al*. External Validation and Comparison of Prostate Cancer Risk Calculators Incorporating Multiparametric Magnetic Resonance Imaging for Prediction of Clinically Significant Prostate Cancer. J Urol, 2020. 203: 719.
https://pubmed.ncbi.nlm.nih.gov/31651228/

265. Radtke, J.P., *et al*. Prediction of significant prostate cancer in biopsy-naïve men: Validation of a novel risk model combining MRI and clinical parameters and comparison to an ERSPC risk calculator and PI-RADS. PLoS One, 2019. 14: e0221350.
https://pubmed.ncbi.nlm.nih.gov/31450235/

266. Mannaerts, C.K., *et al*. Prostate Cancer Risk Assessment in Biopsy-naïve Patients: The Rotterdam Prostate Cancer Risk Calculator in Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound (TRUS) Fusion Biopsy and Systematic TRUS Biopsy. Eur Urol Oncol, 2018. 1: 109.
https://pubmed.ncbi.nlm.nih.gov/31100233/

267. Kim, L., *et al*. Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to Reflne Mri) study. BMC Med, 2020. 18: 95.
https://pubmed.ncbi.nlm.nih.gov/32299423/

268. 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.
https://pubmed.ncbi.nlm.nih.gov/30001824/

269. Dell'Oglio, P., *et al*. Impact of multiparametric MRI and MRI-targeted biopsy on pre-therapeutic risk assessment in prostate cancer patients candidate for radical prostatectomy. World J Urol, 2019. 37: 221.
https://pubmed.ncbi.nlm.nih.gov/29948044/

270. Woo, S., *et al*. Prognostic Value of Pretreatment MRI in Patients With Prostate Cancer Treated With Radiation Therapy: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol, 2020. 214: 597.
https://pubmed.ncbi.nlm.nih.gov/31799874/

271. Faiena, I., *et al*. PI-RADS Version 2 Category on 3 Tesla Multiparametric Prostate Magnetic Resonance Imaging Predicts Oncologic Outcomes in Gleason 3 + 4 Prostate Cancer on Biopsy. J Urol, 2019. 201: 91.
https://pubmed.ncbi.nlm.nih.gov/30142318/

272. Houlahan, K.E., *et al*. Molecular Hallmarks of Multiparametric Magnetic Resonance Imaging Visibility in Prostate Cancer. Eur Urol, 2019. 76: 18.
https://pubmed.ncbi.nlm.nih.gov/30685078/

273. Lam, T.B.L., *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.
https://pubmed.ncbi.nlm.nih.gov/31587989/

274. Roobol, M.J., *et al*. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol, 2010. 57: 79.
https://pubmed.ncbi.nlm.nih.gov/19733959/

275. Eastham, J.A., *et al*. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA, 2003. 289: 2695.
https://pubmed.ncbi.nlm.nih.gov/12771116/

276. Stephan, C., *et al*. Interchangeability of measurements of total and free prostate-specific antigen in serum with 5 frequently used assay combinations: an update. Clin Chem, 2006. 52: 59.
https://pubmed.ncbi.nlm.nih.gov/16391327/

277. Eggener, S.E., *et al*. Empiric antibiotics for an elevated prostate-specific antigen (PSA) level: a randomised, prospective, controlled multi-institutional trial. BJU Int, 2013. 112: 925.
https://pubmed.ncbi.nlm.nih.gov/23890317/

278. Roberts, M.J., *et al*. Prostate Biopsy-related Infection: A Systematic Review of Risk Factors, Prevention Strategies, and Management Approaches. Urology, 2017. 104: 11.
https://pubmed.ncbi.nlm.nih.gov/28007492/

279. Pilatz, A., *et al*. Update on Strategies to Reduce Infectious Complications After Prostate Biopsy. Eur Urol Focus, 2019. 5: 20.
https://pubmed.ncbi.nlm.nih.gov/30503175/

280. Zigeuner, R., *et al*. Detection of prostate cancer by TURP or open surgery in patients with previously negative transrectal prostate biopsies. Urology, 2003. 62: 883.
https://pubmed.ncbi.nlm.nih.gov/14624913/

281.   Ericson, K.J., *et al*. Prostate cancer detection following diagnosis of atypical small acinar proliferation. Can J Urol, 2017. 24: 8714.
        https://pubmed.ncbi.nlm.nih.gov/28436357/

282.   Wiener, S., *et al*. Incidence of Clinically Significant Prostate Cancer After a Diagnosis of Atypical Small Acinar Proliferation, High-grade Prostatic Intraepithelial Neoplasia, or Benign Tissue. Urology, 2017. 110: 161.
        https://pubmed.ncbi.nlm.nih.gov/28888752/

283.   Walz, J., *et al*. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. Eur Urol, 2006. 50: 498.
        https://pubmed.ncbi.nlm.nih.gov/16631303/

284.   Moran, B.J., *et al*. Re-biopsy of the prostate using a stereotactic transperineal technique. J Urol, 2006. 176: 1376.
        https://pubmed.ncbi.nlm.nih.gov/16952636/

285.   Nakai, Y., *et al*. Transperineal template-guided saturation biopsy aimed at sampling one core for each milliliter of prostate volume: 103 cases requiring repeat prostate biopsy. BMC Urol, 2017. 17: 28.
        https://pubmed.ncbi.nlm.nih.gov/28381267/

286.   Ekwueme, K., *et al*. Transperineal template-guided saturation biopsy using a modified technique: outcome of 270 cases requiring repeat prostate biopsy. BJU Int, 2013. 111: E365.
        https://pubmed.ncbi.nlm.nih.gov/23714648/

287.   Pepdjonovic, L., *et al*. Zero hospital admissions for infection after 577 transperineal prostate biopsies using single-dose cephazolin prophylaxis. World J Urol, 2017. 35: 1199.
        https://pubmed.ncbi.nlm.nih.gov/27987032/

288.   Panebianco, V., *et al*. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? Eur Urol, 2018. 74: 48.
        https://pubmed.ncbi.nlm.nih.gov/29566957/

289.   Eichler, K., *et al*. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol, 2006. 175: 1605.
        https://pubmed.ncbi.nlm.nih.gov/16600713/

290.   Wegelin, O., *et al*. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? Eur Urol, 2017. 71: 517.
        https://pubmed.ncbi.nlm.nih.gov/27568655/

291.   Hamid, S., *et al*. The SmartTarget Biopsy Trial: A Prospective, Within-person Randomised, Blinded Trial Comparing the Accuracy of Visual-registration and Magnetic Resonance Imaging/Ultrasound Image-fusion Targeted Biopsies for Prostate Cancer Risk Stratification. Eur Urol, 2019. 75: 733.
        https://pubmed.ncbi.nlm.nih.gov/30527787/

292.   Simmons, L.A.M., *et al*. Accuracy of Transperineal Targeted Prostate Biopsies, Visual Estimation and Image Fusion in Men Needing Repeat Biopsy in the PICTURE Trial. J Urol, 2018. 200: 1227.
        https://pubmed.ncbi.nlm.nih.gov/30017964/

293.   Watts, K.L., *et al*. Systematic review and meta-analysis comparing cognitive vs. image-guided fusion prostate biopsy for the detection of prostate cancer. Urol Oncol, 2020. 38: 734.e19.
        https://pubmed.ncbi.nlm.nih.gov/32321689/

294.   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.
        https://pubmed.ncbi.nlm.nih.gov/31281065/

295.   Tschirdewahn, S., *et al*. Detection of Significant Prostate Cancer Using Target Saturation in Transperineal Magnetic Resonance Imaging/Transrectal Ultrasonography-fusion Biopsy. Eur Urol Focus, 2021. 7: 1300.
        https://pubmed.ncbi.nlm.nih.gov/32660838/

296.   Raman, A.G., *et al*. Optimizing Spatial Biopsy Sampling for the Detection of Prostate Cancer. J Urol, 2021. 206: 595.
        https://pubmed.ncbi.nlm.nih.gov/33908801/

297.   Park, M.Y., *et al*. Comparison of biopsy strategies for prostate biopsy according to lesion size and PSA density in MRI-directed biopsy pathway. Abdom Radiol (NY), 2020. 45: 4166.
        https://pubmed.ncbi.nlm.nih.gov/32737545/

298.   Hansen, N.L., *et al*. Optimising the number of cores for magnetic resonance imaging-guided targeted and systematic transperineal prostate biopsy. BJU Int, 2020. 125: 260.
        https://pubmed.ncbi.nlm.nih.gov/31306539/

299. Presti, J.C., Jr. Prostate biopsy: how many cores are enough? Urol Oncol, 2003. 21: 135.
https://pubmed.ncbi.nlm.nih.gov/12856642/

300. Lam, W., et al. Prostate cancer detection, tolerability and safety of transperineal prostate biopsy under local-anaesthesia vs standard transrectal biopsy in biopsy-naive men: a pragmatic, parallel group, randomized controlled study. BJU Int, 2022. 129: 9.
https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15675?af=R

301. Pradere, B., et al. Nonantibiotic Strategies for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta-Analysis. J Urol, 2021. 205: 653.
https://pubmed.ncbi.nlm.nih.gov/33026903/

302. Bennett, H.Y., et al. The global burden of major infectious complications following prostate biopsy. Epidemiol Infect, 2016. 144: 1784.
https://pubmed.ncbi.nlm.nih.gov/26645476/

303. Berry, B., et al. Comparison of complications after transrectal and transperineal prostate biopsy: a national population-based study. BJU Int, 2020. 126: 97.
https://pubmed.ncbi.nlm.nih.gov/32124525/

304. Castellani, D., et al. Infection Rate after Transperineal Prostate Biopsy with and without Prophylactic Antibiotics: Results from a Systematic Review and Meta-Analysis of Comparative Studies. J Urol, 2022. 207: 25.
https://pubmed.ncbi.nlm.nih.gov/34555932/

305. Basourakos, S.P., et al. Role of Prophylactic Antibiotics in Transperineal Prostate Biopsy: A Systematic Review and Meta-analysis. Eur Urol Open Sci, 2022. 37: 53.
https://pubmed.ncbi.nlm.nih.gov/35243391/

306. Chernysheva, D.Y., et al. The first experience of transperineal prostate biopsy without antibiotic prophylaxis. Cancer Urol, 2021. 17: 46.
https://oncourology.abvpress.ru/oncur/article/view/1392?locale=en_US

307. Jacewicz, M., et al. Antibiotic prophylaxis versus no antibiotic prophylaxis in transperineal prostate biopsies (NORAPP): a randomised, open-label, non-inferiority trial. Lancet Infect Dis, 2022. 22: 1465.
https://pubmed.ncbi.nlm.nih.gov/35839791/

308. Abdulbaki, M.S., et al. Does The Use Of Povidone Iodine Suppository Decrease The Infective Complications Of TRUS Guided Prostate Biopsies? A Randomized Prospective Study. QJM: An In J Med, 2020. 113: Suppl. 1.
https://academic.oup.com/qjmed/article/113/Supplement_1/hcaa070.024/5829649308

309. Ergani, B., et al. Effect of rectal mucosa cleansing on acute prostatitis during prostate biopsy: A randomized prospective study. Turk J Urol, 2020. 46: 159.
https://pubmed.ncbi.nlm.nih.gov/31922485/

310. Farooq, K., et al. Role of povidone-iodine-soaked gauze in preventing infectious complications following trans rectal digital guided prostate biopsy. J Postgrad Med Inst, 2021. 35: 225.
https://jpmi.org.pk/index.php/jpmi/article/view/2849

311. Taher, Y., et al. MP48-11 Prospective randomized controlled study to assess the effect of perineal region cleansing with povidone iodine before transrectal needle biopsy of the prostate on infectious complications. J Urol, 2015. 193: e598.
https://www.auajournals.org/doi/10.1016/j.juro.2015.02.1685

312. Yu, L., et al. [Impact of insertion timing of iodophor cotton ball on the control of infection complications after transrectal ultrasound guided prostate biopsy]. Zhonghua Yi Xue Za Zhi, 2014. 94: 609.
https://pubmed.ncbi.nlm.nih.gov/24762693/

313. Ezenwa, E., et al. Apical peri-prostatic nerve block versus intra-rectal xylocaine gel for trans- rectal ultrasound guided prostate biopsy among Nigerian patients: A prospective randomized study. Nigerian J Clin Pract, 2020. 23: 1183.
https://pubmed.ncbi.nlm.nih.gov/32913154/

314. Pilatz, A., et al. Antibiotic Prophylaxis for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta-Analysis. J Urol, 2020. 204: 224.
https://pubmed.ncbi.nlm.nih.gov/32105195/

315. European Medicine Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. 2019. Access date December 2022.
https://www.ema.europa.eu/en/news/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone

316. Carignan, A., *et al*. Effectiveness of fosfomycin tromethamine prophylaxis in preventing infection following transrectal ultrasound-guided prostate needle biopsy: Results from a large Canadian cohort. J Glob Antimicrob Resist, 2019. 17: 112.
https://pubmed.ncbi.nlm.nih.gov/30553114/

317. von Knobloch, R., *et al*. Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. Eur Urol, 2002. 41: 508.
https://pubmed.ncbi.nlm.nih.gov/12074792/

318. Adamakis, I., *et al*. Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocain cream. World J Urol, 2004. 22: 281.
https://pubmed.ncbi.nlm.nih.gov/14689224/

319. Bass, E.J., *et al*. Magnetic resonance imaging targeted transperineal prostate biopsy: a local anaesthetic approach. Prostate Cancer Prostatic Dis, 2017. 20: 311.
https://pubmed.ncbi.nlm.nih.gov/28485391/

320. Xiang, J., *et al*. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol, 2019. 17: 31.
https://pubmed.ncbi.nlm.nih.gov/30760274/

321. Iremashvili, V.V., *et al*. Periprostatic local anesthesia with pudendal block for transperineal ultrasound-guided prostate biopsy: a randomized trial. Urology, 2010. 75: 1023.
https://pubmed.ncbi.nlm.nih.gov/20080288/

322. Meyer, A.R., *et al*. Initial Experience Performing In-office Ultrasound-guided Transperineal Prostate Biopsy Under Local Anesthesia Using the PrecisionPoint Transperineal Access System. Urology, 2018. 115: 8.
https://pubmed.ncbi.nlm.nih.gov/29409845/

323. Kum, F., *et al*. Initial outcomes of local anaesthetic freehand transperineal prostate biopsies in the outpatient setting. BJU Int, 2020. 125: 244.
https://pubmed.ncbi.nlm.nih.gov/30431694/

324. Wegelin, O., *et al*. Complications and Adverse Events of Three Magnetic Resonance Imaging-based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. Eur Urol Oncol, 2019. 2: 617.
https://pubmed.ncbi.nlm.nih.gov/31519516/

325. Borghesi, M., *et al*. Complications After Systematic, Random, and Image-guided Prostate Biopsy. Eur Urol, 2017. 71: 353.
https://pubmed.ncbi.nlm.nih.gov/27543165/

326. Giannarini, G., *et al*. Continuing or discontinuing low-dose aspirin before transrectal prostate biopsy: results of a prospective randomized trial. Urology, 2007. 70: 501.
https://pubmed.ncbi.nlm.nih.gov/17688919/

327. Garcia, C., *et al*. Does transperineal prostate biopsy reduce complications compared with transrectal biopsy? a systematic review and meta-analysis of randomised controlled trials. J Urol, 2016. 195: e328.
https://www.researchgate.net/publication/299479974

328. Xue, J., *et al*. Comparison between transrectal and transperineal prostate biopsy for detection of prostate cancer: a meta-analysis and trial sequential analysis. Oncotarget, 2017. 8: 23322.
https://pubmed.ncbi.nlm.nih.gov/28177897/

329. Linzer, D.G., *et al*. Seminal vesicle biopsy: accuracy and implications for staging of prostate cancer. Urology, 1996. 48: 757.
https://pubmed.ncbi.nlm.nih.gov/8911521/

330. Pelzer, A.E., *et al*. Are transition zone biopsies still necessary to improve prostate cancer detection? Results from the tyrol screening project. Eur Urol, 2005. 48: 916.
https://pubmed.ncbi.nlm.nih.gov/16126324/

331. Iczkowski, K.A., *et al*. Needle core length in sextant biopsy influences prostate cancer detection rate. Urology, 2002. 59: 698.
https://pubmed.ncbi.nlm.nih.gov/11992843/

332. Van der Kwast, T., *et al*. Guidelines on processing and reporting of prostate biopsies: the 2013 update of the pathology committee of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Virchows Arch, 2013. 463: 367.
https://pubmed.ncbi.nlm.nih.gov/23918245/

333. Bostwick, D.G., *et al*. Adequate histologic sectioning of prostate needle biopsies. Ann Diagn Pathol, 2013. 17: 357.
https://pubmed.ncbi.nlm.nih.gov/23764163/

334. Egevad, L., *et al*. Dataset for the reporting of prostate carcinoma in core needle biopsy and transurethral resection and enucleation specimens: recommendations from the International Collaboration on Cancer Reporting (ICCR). Pathology, 2019. 51: 11.
https://pubmed.ncbi.nlm.nih.gov/30477882/

335. Epstein, J.I., *et al*. Best practices recommendations in the application of immunohistochemistry in the prostate: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol, 2014. 38: e6.
https://pubmed.ncbi.nlm.nih.gov/25029122/

336. Deng, F.M., *et al*. Size-adjusted Quantitative Gleason Score as a Predictor of Biochemical Recurrence after Radical Prostatectomy. Eur Urol, 2016. 70: 248.
https://pubmed.ncbi.nlm.nih.gov/26525839/

337. Sauter, G., *et al*. Clinical Utility of Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens. Eur Urol, 2016. 69: 592.
https://pubmed.ncbi.nlm.nih.gov/26542947/

338. Chen, R.C., *et al*. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol, 2016. 34: 2182.
https://pubmed.ncbi.nlm.nih.gov/26884580/

339. Kweldam, C.F., *et al*. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. Mod Pathol, 2016. 29: 630.
https://pubmed.ncbi.nlm.nih.gov/26939875/

340. Kweldam, C.F., *et al*. On cribriform prostate cancer. Transl Androl Urol, 2018. 7: 145.
https://pubmed.ncbi.nlm.nih.gov/29594028/

341. van der Kwast, T.H., *et al*. ISUP Consensus Definition of Cribriform Pattern Prostate Cancer. Am J Surg Pathol, 2021. 45: 1118.
https://pubmed.ncbi.nlm.nih.gov/33999555/

342. Zhou, M. High-grade prostatic intraepithelial neoplasia, PIN-like carcinoma, ductal carcinoma, and intraductal carcinoma of the prostate. Mod Pathol, 2018. 31: S71.
https://pubmed.ncbi.nlm.nih.gov/29297491/

343. Saeter, T., *et al*. Intraductal Carcinoma of the Prostate on Diagnostic Needle Biopsy Predicts Prostate Cancer Mortality: A Population-Based Study. Prostate, 2017. 77: 859.
https://pubmed.ncbi.nlm.nih.gov/28240424/

344. Miura, N., *et al*. The Prognostic Impact of Intraductal Carcinoma of the Prostate: A Systematic Review and Meta-Analysis. J Urol, 2020. 204: 909.
https://pubmed.ncbi.nlm.nih.gov/32698712/

345. Epstein, J.I., *et al*. The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer. Arch Pathol Lab Med, 2021. 145: 461.
https://pubmed.ncbi.nlm.nih.gov/32589068/

346. WHO Classification of Tumours. Urinary and male genital tumours. 2022, 8th edn, IARC. Lyon (France).
https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Urinary-And-Male-Genital-Tumours-2022

347. Gordetsky, J.B., *et al*. Histologic findings associated with false-positive multiparametric magnetic resonance imaging performed for prostate cancer detection. Hum Pathol, 2019. 83: 159.
https://pubmed.ncbi.nlm.nih.gov/30179687/

348. Srigley, J.R., *et al*. Controversial issues in Gleason and International Society of Urological Pathology (ISUP) prostate cancer grading: proposed recommendations for international implementation. Pathology, 2019. 51: 463.
https://pubmed.ncbi.nlm.nih.gov/31279442/

349. Ström, P., *et al*. Prognostic value of perineural invasion in prostate needle biopsies: a population-based study of patients treated by radical prostatectomy. J Clin Pathol, 2020. 73: 630.
https://pubmed.ncbi.nlm.nih.gov/32034057/

350. Delahunt, B., *et al*. Perineural invasion by prostate adenocarcinoma in needle biopsies predicts bone metastasis: Ten year data from the TROG 03.04 RADAR Trial. Histopathology, 2020. 77: 284.
https://pubmed.ncbi.nlm.nih.gov/32285460/

351.   Fleshner, K., *et al*. Clinical Findings and Treatment Outcomes in Patients with Extraprostatic Extension Identified on Prostate Biopsy. J Urol, 2016. 196: 703.
https://pubmed.ncbi.nlm.nih.gov/27049874/

352.   Grossklaus, D.J., *et al*. Percent of cancer in the biopsy set predicts pathological findings after prostatectomy. J Urol, 2002. 167: 2032.
https://pubmed.ncbi.nlm.nih.gov/11956432/

353.   Freedland, S.J., *et al*. Preoperative model for predicting prostate specific antigen recurrence after radical prostatectomy using percent of biopsy tissue with cancer, biopsy Gleason grade and serum prostate specific antigen. J Urol, 2004. 171: 2215.
https://pubmed.ncbi.nlm.nih.gov/15126788/

354.   Brimo, F., *et al*. Prognostic value of various morphometric measurements of tumour extent in prostate needle core tissue. Histopathology, 2008. 53: 177.
https://pubmed.ncbi.nlm.nih.gov/18752501/

355.   Bangma, C.H., *et al*. Active surveillance for low-risk prostate cancer. Crit Rev Oncol Hematol, 2013. 85: 295.
https://pubmed.ncbi.nlm.nih.gov/22878262/

356.   Eggener, S.E., *et al*. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol, 2019: JCO1902768.
https://pubmed.ncbi.nlm.nih.gov/31829902/

357.   Taylor, A.S., *et al*. Correlation between cribriform/intraductal prostatic adenocarcinoma and percent Gleason pattern 4 to a 22-gene genomic classifier. Prostate, 2020. 80: 146.
https://pubmed.ncbi.nlm.nih.gov/31737920/

358.   Ramotar, M., *et al*. Subpathologies and genomic classifier for treatment individualization of post-prostatectomy radiotherapy. Urol Oncol, 2022. 40: 5.e1.
https://pubmed.ncbi.nlm.nih.gov/34538726/

359.   Lone, Z., *et al*. Transcriptomic Features of Cribriform and Intraductal Carcinoma of the Prostate. Eur Urol Focus, 2022. 8: 1575.
https://pubmed.ncbi.nlm.nih.gov/35662504/

360.   Iremashvili, V., *et al*. Partial sampling of radical prostatectomy specimens: detection of positive margins and extraprostatic extension. Am J Surg Pathol, 2013. 37: 219.
https://pubmed.ncbi.nlm.nih.gov/23095506/

361.   Kench, J.G., *et al*. Dataset for the reporting of prostate carcinoma in radical prostatectomy specimens: updated recommendations from the International Collaboration on Cancer Reporting. Virchows Arch, 2019. 475: 263.
https://pubmed.ncbi.nlm.nih.gov/31098802/

362.   Partin, A.W., *et al*. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology, 2001. 58: 843.
https://pubmed.ncbi.nlm.nih.gov/11744442/

363.   Mazzone, E., *et al*. Risk Stratification of Patients Candidate to Radical Prostatectomy Based on Clinical and Multiparametric Magnetic Resonance Imaging Parameters: Development and External Validation of Novel Risk Groups. Eur Urol, 2022. 81: 193.
https://pubmed.ncbi.nlm.nih.gov/34399996/

364.   Gandaglia, G., *et al*. A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. Eur Urol, 2019. 75: 506.
https://pubmed.ncbi.nlm.nih.gov/30342844/

365.   Magi-Galluzzi, C., *et al*. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. Mod Pathol, 2011. 24: 26.
https://pubmed.ncbi.nlm.nih.gov/20802467/

366.   van Veggel, B.A., *et al*. Quantification of extraprostatic extension in prostate cancer: different parameters correlated to biochemical recurrence after radical prostatectomy. Histopathology, 2011. 59: 692.
https://pubmed.ncbi.nlm.nih.gov/22014050/

367.   Aydin, H., *et al*. Positive proximal (bladder neck) margin at radical prostatectomy confers greater risk of biochemical progression. Urology, 2004. 64: 551.
https://pubmed.ncbi.nlm.nih.gov/15351591/

368.   Ploussard, G., *et al*. The prognostic significance of bladder neck invasion in prostate cancer: is microscopic involvement truly a T4 disease? BJU Int, 2010. 105: 776.
https://pubmed.ncbi.nlm.nih.gov/19863529/

369. Stamey, T.A., et al. Prostate cancer is highly predictable: a prognostic equation based on all morphological variables in radical prostatectomy specimens. J Urol, 2000. 163: 1155.
https://pubmed.ncbi.nlm.nih.gov/10737486/

370. Epstein, J.I., et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. Scand J Urol Nephrol Suppl, 2005: 34.
https://pubmed.ncbi.nlm.nih.gov/16019758/

371. Kikuchi, E., et al. Is tumor volume an independent prognostic factor in clinically localized prostate cancer? J Urol, 2004. 172: 508.
https://pubmed.ncbi.nlm.nih.gov/15247716/

372. van Oort, I.M., et al. Maximum tumor diameter is not an independent prognostic factor in high-risk localized prostate cancer. World J Urol, 2008. 26: 237.
https://pubmed.ncbi.nlm.nih.gov/18265988/

373. van der Kwast, T.H., et al. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 2: T2 substaging and prostate cancer volume. Mod Pathol, 2011. 24: 16.
https://pubmed.ncbi.nlm.nih.gov/20818340/

374. Evans, A.J., et al. Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. Am J Surg Pathol, 2008. 32: 1503.
https://pubmed.ncbi.nlm.nih.gov/18708939/

375. Chuang, A.Y., et al. Positive surgical margins in areas of capsular incision in otherwise organ-confined disease at radical prostatectomy: histologic features and pitfalls. Am J Surg Pathol, 2008. 32: 1201.
https://pubmed.ncbi.nlm.nih.gov/18580493/

376. Hollemans, E., et al. Prostate Carcinoma Grade and Length But Not Cribriform Architecture at Positive Surgical Margins Are Predictive for Biochemical Recurrence After Radical Prostatectomy. Am J Surg Pathol, 2020. 44: 191.
https://pubmed.ncbi.nlm.nih.gov/31592799/

377. Cao, D., et al. Ability of linear length of positive margin in radical prostatectomy specimens to predict biochemical recurrence. Urology, 2011. 77: 1409.
https://pubmed.ncbi.nlm.nih.gov/21256540/

378. Sammon, J.D., et al. Risk factors for biochemical recurrence following radical perineal prostatectomy in a large contemporary series: a detailed assessment of margin extent and location. Urol Oncol, 2013. 31: 1470.
https://pubmed.ncbi.nlm.nih.gov/22534086/

379. Chapin, B.F., et al. Positive margin length and highest Gleason grade of tumor at the margin predict for biochemical recurrence after radical prostatectomy in patients with organ-confined prostate cancer. Prostate Cancer Prostatic Dis, 2018. 21: 221.
https://pubmed.ncbi.nlm.nih.gov/29230008/

380. Paner, G.P., et al. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. Eur Urol, 2018. 73: 560.
https://pubmed.ncbi.nlm.nih.gov/29325693/

381. Coakley, F.V., et al. ACR Appropriateness Criteria(®) Prostate Cancer-Pretreatment Detection, Surveillance, and Staging. J Am Coll Radiol, 2017. 14: S245.
https://pubmed.ncbi.nlm.nih.gov/28473080/

382. de Rooij, M., et al. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol, 2016. 70: 233.
https://pubmed.ncbi.nlm.nih.gov/26215604/

383. Christophe, C., et al. Prostate cancer local staging using biparametric MRI: assessment and comparison with multiparametric MRI. Eur J Radiol, 2020. 132: 109350.
https://pubmed.ncbi.nlm.nih.gov/33080549/

384. Soeterik, T.F.W., 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.
https://pubmed.ncbi.nlm.nih.gov/33129868/

385. Futterer, J.J., et al. Staging prostate cancer with dynamic contrast-enhanced endorectal MR imaging prior to radical prostatectomy: experienced versus less experienced readers. Radiology, 2005. 237: 541.
https://pubmed.ncbi.nlm.nih.gov/16244263/

386.   Kim, T.H., *et al*. The Diagnostic Performance of the Length of Tumor Capsular Contact on MRI for Detecting Prostate Cancer Extraprostatic Extension: A Systematic Review and Meta-Analysis. Korean J Radiol, 2020. 21: 684.
https://pubmed.ncbi.nlm.nih.gov/32410407/

387.   Valentin, B., *et al*. Magnetic resonance imaging improves the prediction of tumor staging in localized prostate cancer. Abdom Radiol (NY), 2021. 46: 2751.
https://pubmed.ncbi.nlm.nih.gov/33452898/

388.   Park, K.J., *et al*. Extraprostatic Tumor Extension: Comparison of Preoperative Multiparametric MRI Criteria and Histopathologic Correlation after Radical Prostatectomy. Radiology, 2020. 296: 87.
https://pubmed.ncbi.nlm.nih.gov/32368959/

389.   Morlacco, A., *et al*. Nomograms in Urologic Oncology: Lights and Shadows. J Clin Med, 2021. 10: 980.
https://pubmed.ncbi.nlm.nih.gov/33801184/

390.   Leyh-Bannurah, S.R., *et al*. Combined systematic versus stand-alone multiparametric MRI-guided targeted fusion biopsy: nomogram prediction of non-organ-confined prostate cancer. World J Urol, 2021. 39: 81.
https://pubmed.ncbi.nlm.nih.gov/32248363/

391.   Diamand, R., *et al*. External Validation of a Multiparametric Magnetic Resonance Imaging-based Nomogram for the Prediction of Extracapsular Extension and Seminal Vesicle Invasion in Prostate Cancer Patients Undergoing Radical Prostatectomy. Eur Urol, 2021. 79: 180.
https://pubmed.ncbi.nlm.nih.gov/33023770/

392.   Alves, J.R., *et al*. Independent external validation of nomogram to predict extracapsular extension in patients with prostate cancer. Eur Radiol, 2020. 30: 5004.
https://pubmed.ncbi.nlm.nih.gov/32307562/

393.   Abuzallouf, S., *et al*. Baseline staging of newly diagnosed prostate cancer: a summary of the literature. J Urol, 2004. 171: 2122.
https://pubmed.ncbi.nlm.nih.gov/15126770/

394.   Kiss, B., *et al*. Current Status of Lymph Node Imaging in Bladder and Prostate Cancer. Urology, 2016. 96: 1.
https://pubmed.ncbi.nlm.nih.gov/26966038/

395.   Harisinghani, M.G., *et al*. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med, 2003. 348: 2491.
https://pubmed.ncbi.nlm.nih.gov/12815134/

396.   Hovels, A.M., *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.
https://pubmed.ncbi.nlm.nih.gov/18325358/

397.   Valentin, B., *et al*. Comparison of 3 T mpMRI and pelvic CT examinations for detection of lymph node metastases in patients with prostate cancer. Eur J Radiol, 2022. 147: 110110.
https://pubmed.ncbi.nlm.nih.gov/34952329/

398.   Lebastchi, A.H., *et al*. Comparison of cross-sectional imaging techniques for the detection of prostate cancer lymph node metastasis: a critical review. Transl Androl Urol, 2020. 9: 1415.
https://pubmed.ncbi.nlm.nih.gov/32676426/

399.   M.S.K.C.C. Dynamic Prostate Cancer Nomogram: Coefficients. Access date December 2022.
https://www.mskcc.org/nomograms/prostate/post_op/coefficients

400.   Briganti, A., *et al*. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol, 2012. 61: 480.
https://pubmed.ncbi.nlm.nih.gov/22078338/

401.   Gandaglia, G., *et al*. Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer. Eur Urol, 2017. 72: 632.
https://pubmed.ncbi.nlm.nih.gov/28412062/

402.   Draulans, C., *et al*. Development and External Validation of a Multiparametric Magnetic Resonance Imaging and International Society of Urological Pathology Based Add-On Prediction Tool to Identify Prostate Cancer Candidates for Pelvic Lymph Node Dissection. J Urol, 2020. 203: 713.
https://pubmed.ncbi.nlm.nih.gov/31718396/

403.   Gandaglia, G., *et al*. External Validation of the 2019 Briganti Nomogram for the Identification of Prostate Cancer Patients Who Should Be Considered for an Extended Pelvic Lymph Node Dissection. Eur Urol, 2020. 78: 138.
https://pubmed.ncbi.nlm.nih.gov/32268944/

404. von Eyben, F.E., *et al*. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. Nucl Med Commun, 2014. 35: 221.
https://pubmed.ncbi.nlm.nih.gov/24240194/

405. Van den Bergh, L., *et al*. Final analysis of a prospective trial on functional imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. Urol Oncol, 2015. 33: 109 e23.
https://pubmed.ncbi.nlm.nih.gov/25655681/

406. Schiavina, R., *et al*. Preoperative Staging With (11)C-Choline PET/CT Is Adequately Accurate in Patients With Very High-Risk Prostate Cancer. Clin Genitourin Cancer, 2018. 16: 305.
https://pubmed.ncbi.nlm.nih.gov/29859737/

407. Maurer, T., *et al*. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol, 2016. 13: 226.
https://pubmed.ncbi.nlm.nih.gov/26902337/

408. Dias, A.H., *et al*. Prostate-Specific Membrane Antigen PET/CT: Uptake in Lymph Nodes With Active Sarcoidosis. Clin Nucl Med, 2017. 42: e175.
https://pubmed.ncbi.nlm.nih.gov/28045734/

409. Froehner, M., *et al*. PSMA-PET/CT-Positive Paget Disease in a Patient with Newly Diagnosed Prostate Cancer: Imaging and Bone Biopsy Findings. Case Rep Urol, 2017. 2017: 1654231.
https://pubmed.ncbi.nlm.nih.gov/28396816/

410. Jochumsen, M.R., *et al*. Benign Traumatic Rib Fracture: A Potential Pitfall on 68Ga-Prostate-Specific Membrane Antigen PET/CT for Prostate Cancer. Clin Nucl Med, 2018. 43: 38.
https://pubmed.ncbi.nlm.nih.gov/29076907/

411. Werner, R.A., *et al*. (18)F-Labeled, PSMA-Targeted Radiotracers: Leveraging the Advantages of Radiofluorination for Prostate Cancer Molecular Imaging. Theranostics, 2020. 10: 1.
https://pubmed.ncbi.nlm.nih.gov/31903102/

412. Hope, T.A., *et al*. Diagnostic Accuracy of 68Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection: A Multicenter Prospective Phase 3 Imaging Trial. JAMA Oncol, 2021. 7: 1635.
https://pubmed.ncbi.nlm.nih.gov/34529005/

413. van Kalmthout, L.W.M., *et al*. Prospective Validation of Gallium-68 Prostate Specific Membrane Antigen-Positron Emission Tomography/Computerized Tomography in Primary Staging of Patients with Prostate Cancer. J Urol, 2020. 203: 537.
https://pubmed.ncbi.nlm.nih.gov/31487220/

414. Jansen, B.H.E., *et al*. Pelvic lymph-node staging with (18)F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer - the SALT trial. Eur J Nucl Med Mol Imaging, 2021. 48: 509.
https://pubmed.ncbi.nlm.nih.gov/32789599/

415. Pienta, K.J., *et al*. A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with (18)F-DCFPyL in Prostate Cancer Patients (OSPREY). J Urol, 2021. 206: 52.
https://pubmed.ncbi.nlm.nih.gov/33634707/

416. 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.
https://pubmed.ncbi.nlm.nih.gov/30773328/

417. Wu, H., *et al*. Diagnostic Performance of (6)(8)Gallium Labelled Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography and Magnetic Resonance Imaging for Staging the Prostate Cancer with Intermediate or High Risk Prior to Radical Prostatectomy: A Systematic Review and Meta-analysis. World J Mens Health, 2020. 38: 208.
https://pubmed.ncbi.nlm.nih.gov/31081294/

418. Van Damme, J., *et al*. Comparison of (68)Ga-Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography Computed Tomography (PET-CT) and Whole-Body Magnetic Resonance Imaging (WB-MRI) with Diffusion Sequences (DWI) in the Staging of Advanced Prostate Cancer. Cancers (Basel), 2021. 13: 5286.
https://pubmed.ncbi.nlm.nih.gov/34771449/

419. Meijer, D., *et al*. External Validation and Addition of Prostate-specific Membrane Antigen Positron Emission Tomography to the Most Frequently Used Nomograms for the Prediction of Pelvic Lymph-node Metastases: an International Multicenter Study. Eur Urol, 2021. 80: 234.
https://pubmed.ncbi.nlm.nih.gov/34024652/

420. Shen, G., *et al*. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. Skeletal Radiol, 2014. 43: 1503.
https://pubmed.ncbi.nlm.nih.gov/24841276/

421. Briganti, A., *et al*. When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines and proposal of a novel risk stratification tool. Eur Urol, 2010. 57: 551.
https://pubmed.ncbi.nlm.nih.gov/20034730/

422. Lin, Y., *et al*. When to perform bone scintigraphy in patients with newly diagnosed prostate cancer? a retrospective study. BMC Urol, 2017. 17: 41.
https://pubmed.ncbi.nlm.nih.gov/28606069/

423. O'Sullivan, J.M., *et al*. Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. BJU Int, 2003. 92: 685.
https://pubmed.ncbi.nlm.nih.gov/14616446/

424. Ayyathurai, R., *et al*. A study on staging bone scans in newly diagnosed prostate cancer. Urol Int, 2006. 76: 209.
https://pubmed.ncbi.nlm.nih.gov/16601380/

425. Tateishi, U., *et al*. A meta-analysis of (18)F-Fluoride positron emission tomography for assessment of metastatic bone tumor. Ann Nucl Med, 2010. 24: 523.
https://pubmed.ncbi.nlm.nih.gov/20559896/

426. Evangelista, L., *et al*. Diagnostic imaging to detect and evaluate response to therapy in bone metastases from prostate cancer: current modalities and new horizons. Eur J Nucl Med Mol Imaging, 2016. 43: 1546.
https://pubmed.ncbi.nlm.nih.gov/26956538/

427. Zacho, H.D., *et al*. Observer Agreement and Accuracy of (18)F-Sodium Fluoride PET/CT in the Diagnosis of Bone Metastases in Prostate Cancer. J Nucl Med, 2020. 61: 344.
https://pubmed.ncbi.nlm.nih.gov/31481577/

428. Uprimny, C., *et al*. 68Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. Eur J Nucl Med Mol Imaging, 2017. 44: 941.
https://pubmed.ncbi.nlm.nih.gov/28138747/

429. Brogsitter, C., *et al*. 18F-Choline, 11C-choline and 11C-acetate PET/CT: comparative analysis for imaging prostate cancer patients. Eur J Nucl Med Mol Imaging, 2013. 40 Suppl 1: S18.
https://pubmed.ncbi.nlm.nih.gov/23579863/

430. Picchio, M., *et al*. [11C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging, 2012. 39: 13.
https://pubmed.ncbi.nlm.nih.gov/21932120/

431. Van Nieuwenhove, S., *et al*. Whole-body magnetic resonance imaging for prostate cancer assessment: Current status and future directions. J Magn Reson Imaging, 2022. 55: 653.
https://pubmed.ncbi.nlm.nih.gov/33382151/

432. Corfield, J., *et al*. (68)Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. World J Urol, 2018. 36: 519.
https://pubmed.ncbi.nlm.nih.gov/29344682/

433. Hofman, M.S., *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.
https://pubmed.ncbi.nlm.nih.gov/32209449/

434. Anttinen, M., *et al*. A Prospective Comparison of (18)F-prostate-specific Membrane Antigen-1007 Positron Emission Tomography Computed Tomography, Whole-body 1.5 T Magnetic Resonance Imaging with Diffusion-weighted Imaging, and Single-photon Emission Computed Tomography/ Computed Tomography with Traditional Imaging in Primary Distant Metastasis Staging of Prostate Cancer (PROSTAGE). Eur Urol Oncol, 2021. 4: 635.
https://pubmed.ncbi.nlm.nih.gov/32675047/

435. Cornford, P., *et al*. Prostate-specific Membrane Antigen Positron Emission Tomography Scans Before Curative Treatment: Ready for Prime Time? Eur Urol, 2020. 78: e125.
https://pubmed.ncbi.nlm.nih.gov/32624287/

436. Hicks, R.J., *et al*. Seduction by Sensitivity: Reality, Illusion, or Delusion? The Challenge of Assessing Outcomes after PSMA Imaging Selection of Patients for Treatment. J Nucl Med, 2017. 58: 1969.
https://pubmed.ncbi.nlm.nih.gov/28935839/

437. Hofman, M.S., *et al*. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol. BJU Int, 2018. 122: 783.
https://pubmed.ncbi.nlm.nih.gov/29726071/

438. Smith, B.D., *et al*. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol, 2009. 27: 2758.
https://pubmed.ncbi.nlm.nih.gov/19403886/

439. Arnold, M., *et al*. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer, 2015. 51: 1164.
https://pubmed.ncbi.nlm.nih.gov/24120180/

440. Liu, D., *et al*. Active surveillance versus surgery for low risk prostate cancer: a clinical decision analysis. J Urol, 2012. 187: 1241.
https://pubmed.ncbi.nlm.nih.gov/22335873/

441. Bill-Axelson, A., *et al*. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med, 2014. 370: 932.
https://pubmed.ncbi.nlm.nih.gov/24597866/

442. Kupelian, P.A., *et al*. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. J Clin Oncol, 2002. 20: 3376.
https://pubmed.ncbi.nlm.nih.gov/12177097/

443. Bubolz, T., *et al*. Treatments for prostate cancer in older men: 1984-1997. Urology, 2001. 58: 977.
https://pubmed.ncbi.nlm.nih.gov/11744472/

444. Houterman, S., *et al*. Impact of comorbidity on treatment and prognosis of prostate cancer patients: a population-based study. Crit Rev Oncol Hematol, 2006. 58: 60.
https://pubmed.ncbi.nlm.nih.gov/16213153/

445. Ries, L.A.G., *et al*. eds. SEER cancer Statistics Review, 1975-2011. 2022.
https://seer.cancer.gov/archive/csr/1975_2011/

446. Scosyrev, E., *et al*. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer, 2012. 118: 3062.
https://pubmed.ncbi.nlm.nih.gov/22006014/

447. Richstone, L., *et al*. Radical prostatectomy in men aged >or=70 years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. BJU Int, 2008. 101: 541.
https://pubmed.ncbi.nlm.nih.gov/18257855/

448. Sun, L., *et al*. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. J Urol, 2009. 182: 2242.
https://pubmed.ncbi.nlm.nih.gov/19758616/

449. Hamilton, A.S., *et al*. Trends in the treatment of localized prostate cancer using supplemented cancer registry data. BJU Int, 2011. 107: 576.
https://pubmed.ncbi.nlm.nih.gov/20735387/

450. Studenski, S., *et al*. Gait speed and survival in older adults. JAMA, 2011. 305: 50.
https://pubmed.ncbi.nlm.nih.gov/21205966/

451. Ethun, C.G., *et al*. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin, 2017. 67: 362.
https://pubmed.ncbi.nlm.nih.gov/28731537/

452. Bellera, C.A., *et al*. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol, 2012. 23: 2166.
https://pubmed.ncbi.nlm.nih.gov/22250183/

453. Hamaker, M.E., *et al*. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - A systematic review. J Geriatr Oncol, 2018. 9: 430.
https://pubmed.ncbi.nlm.nih.gov/29631898/

454. Rockwood, K., *et al*. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J, 2020. 23: 210.
https://pubmed.ncbi.nlm.nih.gov/32904824/

455. McIsaac, D.I., *et al*. Frailty as a Predictor of Death or New Disability After Surgery: A Prospective Cohort Study. Ann Surg, 2020. 271: 283.
https://pubmed.ncbi.nlm.nih.gov/30048320/

456. van Walree, I.C., *et al*. Clinical judgment versus geriatric assessment for frailty in older patients with cancer. J Geriatr Oncol, 2020. 11: 1138.
https://pubmed.ncbi.nlm.nih.gov/32576520/

457.   Albertsen, P.C., *et al*. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol, 2011. 29: 1335.
https://pubmed.ncbi.nlm.nih.gov/21357791/

458.   Tewari, A., *et al*. Long-term survival probability in men with clinically localized prostate cancer: a case-control, propensity modeling study stratified by race, age, treatment and comorbidities. J Urol, 2004. 171: 1513.
https://pubmed.ncbi.nlm.nih.gov/15017210/

459.   Parmelee, P.A., *et al*. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc, 1995. 43: 130.
https://pubmed.ncbi.nlm.nih.gov/7836636/

460.   Groome, P.A., *et al*. Assessing the impact of comorbid illnesses on death within 10 years in prostate cancer treatment candidates. Cancer, 2011. 117: 3943.
https://pubmed.ncbi.nlm.nih.gov/21858801/

461.   Charlson, M.E., *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis, 1987. 40: 373.
https://pubmed.ncbi.nlm.nih.gov/3558716/

462.   Blanc-Bisson, C., *et al*. Undernutrition in elderly patients with cancer: target for diagnosis and intervention. Crit Rev Oncol Hematol, 2008. 67: 243.
https://pubmed.ncbi.nlm.nih.gov/18554922/

463.   Sachs, G.A., *et al*. Cognitive impairment: an independent predictor of excess mortality: a cohort study. Ann Intern Med, 2011. 155: 300.
https://pubmed.ncbi.nlm.nih.gov/21893623/

464.   Robinson, T.N., *et al*. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg, 2012. 215: 12.
https://pubmed.ncbi.nlm.nih.gov/22626912/

465.   Borson, S., *et al*. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc, 2003. 51: 1451.
https://pubmed.ncbi.nlm.nih.gov/14511167/

466.   Korc-Grodzicki, B., *et al*. Prevention of post-operative delirium in older patients with cancer undergoing surgery. J Geriatr Oncol, 2015. 6: 60.
https://pubmed.ncbi.nlm.nih.gov/25454768/

467.   Oken, M.M., *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol, 1982. 5: 649.
https://pubmed.ncbi.nlm.nih.gov/7165009/

468.   Katz, S., *et al*. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. JAMA, 1963. 185: 914.
https://pubmed.ncbi.nlm.nih.gov/14044222/

469.   Lawton, M.P., *et al*. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist, 1969. 9: 179.
https://pubmed.ncbi.nlm.nih.gov/5349366/

470.   Stineman, M.G., *et al*. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. J Am Geriatr Soc, 2012. 60: 485.
https://pubmed.ncbi.nlm.nih.gov/22352414/

471.   Paladino, J., *et al*. Communication Strategies for Sharing Prognostic Information With Patients: Beyond Survival Statistics. JAMA, 2019. 322: 1345.
https://pubmed.ncbi.nlm.nih.gov/31415085/

472.   Rostoft, S., *et al*. Shared decision-making in older patients with cancer - What does the patient want? J Geriatr Oncol, 2021. 12: 339.
https://pubmed.ncbi.nlm.nih.gov/32839118/

473.   Soubeyran, P., *et al*. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. PLoS One, 2014. 9: e115060.
https://pubmed.ncbi.nlm.nih.gov/25503576/

474.   Klotz, L. Overdiagnosis in urologic cancer : For World Journal of Urology Symposium on active surveillance in prostate and renal cancer. World J Urol, 2022. 40: 1.
https://pubmed.ncbi.nlm.nih.gov/33492425/

475.   Johansson, J.E., *et al*. Natural history of localised prostatic cancer. A population-based study in 223 untreated patients. Lancet, 1989. 1: 799.
https://pubmed.ncbi.nlm.nih.gov/2564901/

476. Bill-Axelson, A., *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med, 2005. 352: 1977.
https://pubmed.ncbi.nlm.nih.gov/15888698/

477. Adolfsson, J., *et al*. The 20-Yr outcome in patients with well- or moderately differentiated clinically localized prostate cancer diagnosed in the pre-PSA era: the prognostic value of tumour ploidy and comorbidity. Eur Urol, 2007. 52: 1028.
https://pubmed.ncbi.nlm.nih.gov/17467883/

478. Jonsson, E., *et al*. Adenocarcinoma of the prostate in Iceland: a population-based study of stage, Gleason grade, treatment and long-term survival in males diagnosed between 1983 and 1987. Scand J Urol Nephrol, 2006. 40: 265.
https://pubmed.ncbi.nlm.nih.gov/16916765/

479. Lu-Yao, G.L., *et al*. Outcomes of localized prostate cancer following conservative management. JAMA, 2009. 302: 1202.
https://pubmed.ncbi.nlm.nih.gov/19755699/

480. Hayes, J.H., *et al*. Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis. Ann Intern Med, 2013. 158: 853.
https://pubmed.ncbi.nlm.nih.gov/23778902/

481. Albertsen, P.C. Observational studies and the natural history of screen-detected prostate cancer. Curr Opin Urol, 2015. 25: 232.
https://pubmed.ncbi.nlm.nih.gov/25692723/

482. Bruinsma, S.M., *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.
https://pubmed.ncbi.nlm.nih.gov/28290462/

483. Thomsen, F.B., *et al*. Active surveillance for clinically localized prostate cancer--a systematic review. J Surg Oncol, 2014. 109: 830.
https://pubmed.ncbi.nlm.nih.gov/24610744/

484. Tosoian, J.J., *et al*. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. J Clin Oncol, 2015. 33: 3379.
https://pubmed.ncbi.nlm.nih.gov/26324359/

485. Hamdy, F.C., *et al*. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med, 2016. 375: 1415.
https://pubmed.ncbi.nlm.nih.gov/27626136/

486. Bryant, R.J., *et al*. The ProtecT trial: analysis of the patient cohort, baseline risk stratification and disease progression. BJU Int, 2020. 125: 506.
https://pubmed.ncbi.nlm.nih.gov/31900963/

487. van As, N.J., *et al*. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol, 2008. 54: 1297.
https://pubmed.ncbi.nlm.nih.gov/18342430/

488. Carter, H.B., *et al*. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol, 2007. 178: 2359.
https://pubmed.ncbi.nlm.nih.gov/17936806/

489. Adamy, A., *et al*. Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. J Urol, 2011. 185: 477.
https://pubmed.ncbi.nlm.nih.gov/21167529/

490. Soloway, M.S., *et al*. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. Eur Urol, 2010. 58: 831.
https://pubmed.ncbi.nlm.nih.gov/20800964/

491. Roemeling, S., *et al*. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. Eur Urol, 2007. 51: 1244.
https://pubmed.ncbi.nlm.nih.gov/17161520/

492. Godtman, R.A., *et al*. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Göteborg randomised population-based prostate cancer screening trial. Eur Urol, 2013. 63: 101.
https://pubmed.ncbi.nlm.nih.gov/22980443/

493. Klotz, L., *et al*. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol, 2015. 33: 272.
https://pubmed.ncbi.nlm.nih.gov/25512465/

494.   Tosoian, J.J., *et al*. Active Surveillance of Grade Group 1 Prostate Cancer: Long-term Outcomes from a Large Prospective Cohort. Eur Urol, 2020. 77: 675.
https://pubmed.ncbi.nlm.nih.gov/31918957/

495.   Carlsson, S., *et al*. Long-Term Outcomes of Active Surveillance for Prostate Cancer: The Memorial Sloan Kettering Cancer Center Experience. J Urol, 2020. 203: 1122.
https://pubmed.ncbi.nlm.nih.gov/31868556/

496.   Bill-Axelson, A., *et al*. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med, 2018. 379: 2319.
https://pubmed.ncbi.nlm.nih.gov/30575473/

497.   Wilt, T.J., *et al*. Radical Prostatectomy or Observation for Clinically Localized Prostate Cancer: Extended Follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT). Eur Urol, 2020. 77: 713.
https://pubmed.ncbi.nlm.nih.gov/32089359/

498.   Steineck, G., *et al*. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med, 2002. 347: 790.
https://pubmed.ncbi.nlm.nih.gov/12226149/

499.   Vernooij, R.W., *et al*. Radical prostatectomy versus deferred treatment for localised prostate cancer. Cochrane Database Syst Rev, 2020. 6: CD006590.
https://pubmed.ncbi.nlm.nih.gov/32495338/

500.   Graversen, P.H., *et al*. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up. Urology, 1990. 36: 493.
https://pubmed.ncbi.nlm.nih.gov/2247914/

501.   Adolfsson, J. Watchful waiting and active surveillance: the current position. BJU Int, 2008. 102: 10.
https://pubmed.ncbi.nlm.nih.gov/18422774/

502.   Hatzinger, M., *et al*. [The history of prostate cancer from the beginning to DaVinci]. Aktuelle Urol, 2012. 43: 228.
https://pubmed.ncbi.nlm.nih.gov/23035261/

503.   Wilt, T.J., *et al*. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med, 2017. 377: 132.
https://pubmed.ncbi.nlm.nih.gov/28700844/

504.   Kretschmer, A., *et al*. Perioperative patient education improves long-term satisfaction rates of low-risk prostate cancer patients after radical prostatectomy. World J Urol, 2017. 35: 1205.
https://pubmed.ncbi.nlm.nih.gov/28093628/

505.   Gyomber, D., *et al*. Improving informed consent for patients undergoing radical prostatectomy using multimedia techniques: a prospective randomized crossover study. BJU Int, 2010. 106: 1152.
https://pubmed.ncbi.nlm.nih.gov/20346048/

506.   Huber, J., *et al*. Multimedia support for improving preoperative patient education: a randomized controlled trial using the example of radical prostatectomy. Ann Surg Oncol, 2013. 20: 15.
https://pubmed.ncbi.nlm.nih.gov/22851045/

507.   Wake, N., *et al*. Patient-specific 3D printed and augmented reality kidney and prostate cancer models: impact on patient education. 3D Print Med, 2019. 5: 4.
https://pubmed.ncbi.nlm.nih.gov/30783869/

508.   De Nunzio, C., *et al*. The EORTC quality of life questionnaire predicts early and long-term incontinence in patients treated with robotic assisted radical prostatectomy: Analysis of a large single center cohort. Urol Oncol, 2019. 37: 1006.
https://pubmed.ncbi.nlm.nih.gov/31326315/

509.   Chang, J.I., *et al*. Preoperative Pelvic Floor Muscle Exercise and Postprostatectomy Incontinence: A Systematic Review and Meta-analysis. Eur Urol, 2016. 69: 460.
https://pubmed.ncbi.nlm.nih.gov/26610857/

510.   Bonkat, G., *et al*. EAU Guidelines on Urological Infections. In: EAU Guidelines published at the 38th EAU Annual Congress, Milan. EAU Guidelines Office, Arnhem, The Netherlands.
https://uroweb.org/guidelines/urological-infections

511.   Kumar, S., *et al*. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Cochrane Database Syst Rev, 2006: CD006019.
https://pubmed.ncbi.nlm.nih.gov/17054269/

512.   Liu, W., *et al*. Neoadjuvant hormone therapy for patients with high-risk prostate cancer: a systematic review and meta-analysis. Asian J Androl, 2021. 23: 429.
https://pubmed.ncbi.nlm.nih.gov/33586699/

513. Efstathiou, E., *et al*. Clinical and Biological Characterisation of Localised High-risk Prostate Cancer: Results of a Randomised Preoperative Study of a Luteinising Hormone-releasing Hormone Agonist with or Without Abiraterone Acetate plus Prednisone. Eur Urol, 2019. 76: 418.
https://pubmed.ncbi.nlm.nih.gov/31176622/

514. McKay, R.R., *et al*. Outcomes of Post-Neoadjuvant Intense Hormone Therapy and Surgery for High Risk Localized Prostate Cancer: Results of a Pooled Analysis of Contemporary Clinical Trials. J Urol, 2021. 205: 1689.
https://pubmed.ncbi.nlm.nih.gov/33502237/

515. Eastham, J.A., *et al*. Cancer and Leukemia Group B 90203 (Alliance): Radical Prostatectomy With or Without Neoadjuvant Chemohormonal Therapy in Localized, High-Risk Prostate Cancer. J Clin Oncol, 2020. 38: 3042.
https://pubmed.ncbi.nlm.nih.gov/32706639/

516. Laukhtina, E., *et al*. Oncologic impact of delaying radical prostatectomy in men with intermediate- and high-risk prostate cancer: a systematic review. World J Urol, 2021. 39: 4085.
https://pubmed.ncbi.nlm.nih.gov/34047825/

517. Walsh, P.C., *et al*. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol, 1982. 128: 492.
https://pubmed.ncbi.nlm.nih.gov/7120554/

518. Binder, J., *et al*. [Robot-assisted laparoscopy in urology. Radical prostatectomy and reconstructive retroperitoneal interventions]. Urologe A, 2002. 41: 144.
https://pubmed.ncbi.nlm.nih.gov/11993092/

519. Yaxley, J.W., *et al*. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet, 2016. 388: 1057.
https://pubmed.ncbi.nlm.nih.gov/27474375/

520. Coughlin, G.D., *et al*. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol, 2018. 19: 1051.
https://pubmed.ncbi.nlm.nih.gov/30017351/

521. Albertsen, P.C., *et al*. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. Jama, 1998. 280: 975.
https://pubmed.ncbi.nlm.nih.gov/9749479/

522. Albertsen, P.C., *et al*. Statistical considerations when assessing outcomes following treatment for prostate cancer. J Urol, 1999. 162: 439.
https://pubmed.ncbi.nlm.nih.gov/10411053/

523. Iversen, P., *et al*. Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. J Urol, 2004. 172: 1871.
https://pubmed.ncbi.nlm.nih.gov/15540741/

524. Jacobs, B.L., *et al*. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. JAMA, 2013. 309: 2587.
https://pubmed.ncbi.nlm.nih.gov/23800935/

525. Allan, C., *et al*. Laparoscopic versus Robotic-Assisted Radical Prostatectomy for the Treatment of Localised Prostate Cancer: A Systematic Review. Urol Int, 2016. 96: 373.
https://pubmed.ncbi.nlm.nih.gov/26201500/

526. Ilic, D., *et al*. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Syst Rev, 2017. 9: CD009625.
https://pubmed.ncbi.nlm.nih.gov/28895658/

527. Begg, C.B., *et al*. Variations in morbidity after radical prostatectomy. N Engl J Med, 2002. 346: 1138.
https://pubmed.ncbi.nlm.nih.gov/11948274/

528. Gershman, B., *et al*. Redefining and Contextualizing the Hospital Volume-Outcome Relationship for Robot-Assisted Radical Prostatectomy: Implications for Centralization of Care. J Urol, 2017. 198: 92.
https://pubmed.ncbi.nlm.nih.gov/28153509/

529. Galfano, A., *et al*. A new anatomic approach for robot-assisted laparoscopic prostatectomy: a feasibility study for completely intrafascial surgery. Eur Urol, 2010. 58: 457.
https://pubmed.ncbi.nlm.nih.gov/20566236/

530. Checcucci, E., *et al*. Retzius-sparing robot-assisted radical prostatectomy vs the standard approach: a systematic review and analysis of comparative outcomes. BJU Int, 2020. 125: 8.
https://pubmed.ncbi.nlm.nih.gov/31373142/

531. Phukan, C., *et al*. Retzius sparing robotic assisted radical prostatectomy vs. conventional robotic assisted radical prostatectomy: a systematic review and meta-analysis. World J Urol, 2020. 38: 1123.
https://pubmed.ncbi.nlm.nih.gov/31089802/

532.	Tai, T.E., *et al*. Effects of Retzius sparing on robot-assisted laparoscopic prostatectomy: a systematic review with meta-analysis. Surg Endosc, 2020. 34: 4020.
https://pubmed.ncbi.nlm.nih.gov/31617093/

533.	Rosenberg, J.E., *et al*. Retzius-sparing versus standard robotic-assisted laparoscopic prostatectomy for the treatment of clinically localized prostate cancer. Cochrane Database Syst Rev, 2020. 8: CD013641.
https://pubmed.ncbi.nlm.nih.gov/32813279/

534.	Lee, J., *et al*. Retzius Sparing Robot-Assisted Radical Prostatectomy Conveys Early Regain of Continence over Conventional Robot-Assisted Radical Prostatectomy: A Propensity Score Matched Analysis of 1,863 Patients. J Urol, 2020. 203: 137.
https://pubmed.ncbi.nlm.nih.gov/31347951/

535.	Stonier, T., *et al*. Retzius-sparing robot-assisted radical prostatectomy (RS-RARP) vs standard RARP: it's time for critical appraisal. BJU Int, 2019. 123: 5.
https://pubmed.ncbi.nlm.nih.gov/29959814/

536.	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.
https://pubmed.ncbi.nlm.nih.gov/28126351/

537.	Lestingi, J.F.P., *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.
https://pubmed.ncbi.nlm.nih.gov/33293077/

538.	Touijer, K.A., *et al*. Limited versus Extended Pelvic Lymph Node Dissection for Prostate Cancer: A Randomized Clinical Trial. Eur Urol Oncol, 2021. 4: 532.
https://pubmed.ncbi.nlm.nih.gov/33865797/

539.	Mattei, A., *et al*. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. Eur Urol, 2008. 53: 118.
https://pubmed.ncbi.nlm.nih.gov/17709171/

540.	Cimino, S., *et al*. Comparison between Briganti, Partin and MSKCC tools in predicting positive lymph nodes in prostate cancer: a systematic review and meta-analysis. Scand J Urol, 2017. 51: 345.
https://pubmed.ncbi.nlm.nih.gov/28644701/

541.	Abdollah, F., *et al*. Indications for pelvic nodal treatment in prostate cancer should change. Validation of the Roach formula in a large extended nodal dissection series. Int J Radiat Oncol Biol Phys, 2012. 83: 624.
https://pubmed.ncbi.nlm.nih.gov/22099031/

542.	Dell'Oglio, P., *et al*. External validation of the European association of urology recommendations for pelvic lymph node dissection in patients treated with robot-assisted radical prostatectomy. J Endourol, 2014. 28: 416.
https://pubmed.ncbi.nlm.nih.gov/24188052/

543.	Hinev, A.I., *et al*. Validation of nomograms predicting lymph node involvement in patients with prostate cancer undergoing extended pelvic lymph node dissection. Urol Int, 2014. 92: 300.
https://pubmed.ncbi.nlm.nih.gov/24480972/

544.	Stabile, A., *et al*. Can Negative Prostate-specific Membrane Antigen Positron Emission Tomography/ Computed Tomography Avoid the Need for Pelvic Lymph Node Dissection in Newly Diagnosed Prostate Cancer Patients? A Systematic Review and Meta-analysis with Backup Histology as Reference Standard. Eur Urol Oncol, 2022. 5: 1.
https://pubmed.ncbi.nlm.nih.gov/34538770/

545.	Burkhard, F.C., *et al*. The role of lymphadenectomy in prostate cancer. Nat Clin Pract Urol, 2005. 2: 336.
https://pubmed.ncbi.nlm.nih.gov/16474786/

546.	Ploussard, G., *et al*. Pelvic lymph node dissection during robot-assisted radical prostatectomy: efficacy, limitations, and complications-a systematic review of the literature. Eur Urol, 2014. 65: 7.
https://pubmed.ncbi.nlm.nih.gov/23582879/

547.	Davis, J.W., *et al*. Robot-assisted extended pelvic lymph node dissection (PLND) at the time of radical prostatectomy (RP): a video-based illustration of technique, results, and unmet patient selection needs. BJU Int, 2011. 108: 993.
https://pubmed.ncbi.nlm.nih.gov/21917102/

548.	Briganti, A., *et al*. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol, 2006. 50: 1006.
https://pubmed.ncbi.nlm.nih.gov/16959399/

549. Tyritzis, S.I., *et al.* Thromboembolic complications in 3,544 patients undergoing radical prostatectomy with or without lymph node dissection. J Urol, 2015. 193: 117.
https://pubmed.ncbi.nlm.nih.gov/25158271/

550. van der Poel, H.G., *et al.* Sentinel node biopsy for prostate cancer: report from a consensus panel meeting. BJU Int, 2017. 120: 204.
https://pubmed.ncbi.nlm.nih.gov/28188689/

551. Harke, N.N., *et al.* Fluorescence-supported lymphography and extended pelvic lymph node dissection in robot-assisted radical prostatectomy: a prospective, randomized trial. World J Urol, 2018. 36: 1817.
https://pubmed.ncbi.nlm.nih.gov/29767326/

552. Wit, E.M.K., *et al.* Sentinel Node Procedure in Prostate Cancer: A Systematic Review to Assess Diagnostic Accuracy. Eur Urol, 2017. 71: 596.
https://pubmed.ncbi.nlm.nih.gov/27639533/

553. Weng, W.C., *et al.* Impact of prostatic anterior fat pads with lymph node staging in prostate cancer. J Cancer, 2018. 9: 3361.
https://pubmed.ncbi.nlm.nih.gov/30271497/

554. Hosny, M., *et al.* Can Anterior Prostatic Fat Harbor Prostate Cancer Metastasis? A Prospective Cohort Study. Curr Urol, 2017. 10: 182.
https://pubmed.ncbi.nlm.nih.gov/29234260/

555. Ball, M.W., *et al.* Pathological analysis of the prostatic anterior fat pad at radical prostatectomy: insights from a prospective series. BJU Int, 2017. 119: 444.
https://pubmed.ncbi.nlm.nih.gov/27611825/

556. Kwon, Y.S., *et al.* Oncologic outcomes in men with metastasis to the prostatic anterior fat pad lymph nodes: a multi-institution international study. BMC Urol, 2015. 15: 79.
https://pubmed.ncbi.nlm.nih.gov/26231860/

557. Ozkan, B., *et al.* Role of anterior prostatic fat pad dissection for extended lymphadenectomy in prostate cancer: a non-randomized study of 100 patients. Int Urol Nephrol, 2015. 47: 959.
https://pubmed.ncbi.nlm.nih.gov/25899767/

558. Kim, I.Y., *et al.* Detailed analysis of patients with metastasis to the prostatic anterior fat pad lymph nodes: a multi-institutional study. J Urol, 2013. 190: 527.
https://pubmed.ncbi.nlm.nih.gov/23485503/

559. Hansen, J., *et al.* Assessment of rates of lymph nodes and lymph node metastases in periprostatic fat pads in a consecutive cohort treated with retropubic radical prostatectomy. Urology, 2012. 80: 877.
https://pubmed.ncbi.nlm.nih.gov/22950996/

560. Rainwater, L.M., *et al.* Technical consideration in radical retropubic prostatectomy: blood loss after ligation of dorsal venous complex. J Urol, 1990. 143: 1163.
https://pubmed.ncbi.nlm.nih.gov/2342176/

561. Woldu, S.L., *et al.* Outcomes with delayed dorsal vein complex ligation during robotic assisted laparoscopic prostatectomy. Can J Urol, 2013. 20: 7079.
https://pubmed.ncbi.nlm.nih.gov/24331354/

562. Lei, Y., *et al.* Athermal division and selective suture ligation of the dorsal vein complex during robot-assisted laparoscopic radical prostatectomy: description of technique and outcomes. Eur Urol, 2011. 59: 235.
https://pubmed.ncbi.nlm.nih.gov/20863611/

563. Wu, S.D., *et al.* Suture versus staple ligation of the dorsal venous complex during robot-assisted laparoscopic radical prostatectomy. BJU Int, 2010. 106: 385.
https://pubmed.ncbi.nlm.nih.gov/20067457/

564. Walsh, P.C., *et al.* Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. Br J Urol, 1984. 56: 694.
https://pubmed.ncbi.nlm.nih.gov/6534493/

565. Walz, J., *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.
https://pubmed.ncbi.nlm.nih.gov/26850969/

566. Stolzenburg, J.U., *et al.* A comparison of outcomes for interfascial and intrafascial nerve-sparing radical prostatectomy. Urology, 2010. 76: 743.
https://pubmed.ncbi.nlm.nih.gov/20573384/

567. Steineck, G., *et al*. Degree of preservation of the neurovascular bundles during radical prostatectomy and urinary continence 1 year after surgery. Eur Urol, 2015. 67: 559.
https://pubmed.ncbi.nlm.nih.gov/25457018/

568. Shikanov, S., *et al*. Extrafascial versus interfascial nerve-sparing technique for robotic-assisted laparoscopic prostatectomy: comparison of functional outcomes and positive surgical margins characteristics. Urology, 2009. 74: 611.
https://pubmed.ncbi.nlm.nih.gov/19616830/

569. Tewari, A.K., *et al*. Anatomical grades of nerve sparing: a risk-stratified approach to neural-hammock sparing during robot-assisted radical prostatectomy (RARP). BJU Int, 2011. 108: 984.
https://pubmed.ncbi.nlm.nih.gov/21917101/

570. Nielsen, M.E., *et al*. High anterior release of the levator fascia improves sexual function following open radical retropubic prostatectomy. J Urol, 2008. 180: 2557.
https://pubmed.ncbi.nlm.nih.gov/18930504/

571. Ko, Y.H., *et al*. Retrograde versus antegrade nerve sparing during robot-assisted radical prostatectomy: which is better for achieving early functional recovery? Eur Urol, 2013. 63: 169.
https://pubmed.ncbi.nlm.nih.gov/23092543/

572. Tewari, A.K., *et al*. Functional outcomes following robotic prostatectomy using athermal, traction free risk-stratified grades of nerve sparing. World J Urol, 2013. 31: 471.
https://pubmed.ncbi.nlm.nih.gov/23354288/

573. Basourakos, S.P., *et al*. Clipless Robotic-assisted Radical Prostatectomy and Impact on Outcomes. Eur Urol Focus, 2022. 8: 1176.
https://pubmed.ncbi.nlm.nih.gov/34246618/

574. Preisser, F., *et al*. Association of neurovascular bundle preservation with oncological outcomes in patients with high-risk prostate cancer. Prostate Cancer Prostatic Dis, 2021. 24: 193.
https://pubmed.ncbi.nlm.nih.gov/32814844/

575. Vis, A.N., *et al*. Selection of patients for nerve sparing surgery in robot-assisted radical prostatectomy. BJUI Compass, 2022. 3: 6.
https://pubmed.ncbi.nlm.nih.gov/35475150/

576. Moris, L., *et al*. Evaluation of Oncological Outcomes and Data Quality in Studies Assessing Nerve-sparing Versus Non-Nerve-sparing Radical Prostatectomy in Nonmetastatic Prostate Cancer: A Systematic Review. Eur Urol Focus, 2022. 8: 690.
https://pubmed.ncbi.nlm.nih.gov/34147405/

577. Kozikowski, M., *et al*. Clinical utility of MRI in the decision-making process before radical prostatectomy: Systematic review and meta-analysis. PLoS One, 2019. 14: e0210194.
https://pubmed.ncbi.nlm.nih.gov/30615661/

578. Michl, U., *et al*. Nerve-sparing Surgery Technique, Not the Preservation of the Neurovascular Bundles, Leads to Improved Long-term Continence Rates After Radical Prostatectomy. Eur Urol, 2016. 69: 584.
https://pubmed.ncbi.nlm.nih.gov/26277303/

579. Avulova, S., *et al*. The Effect of Nerve Sparing Status on Sexual and Urinary Function: 3-Year Results from the CEASAR Study. J Urol, 2018. 199: 1202.
https://pubmed.ncbi.nlm.nih.gov/29253578/

580. Engel, J., *et al*. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. Eur Urol, 2010. 57: 754.
https://pubmed.ncbi.nlm.nih.gov/20106588/

581. Beulens, A.J.W., *et al*. Linking surgical skills to postoperative outcomes: a Delphi study on the robot-assisted radical prostatectomy. J Robot Surg, 2019. 13: 675.
https://pubmed.ncbi.nlm.nih.gov/30610535/

582. Gilbert, S.M., *et al*. Functional Outcomes Following Nerve Sparing Prostatectomy Augmented with Seminal Vesicle Sparing Compared to Standard Nerve Sparing Prostatectomy: Results from a Randomized Controlled Trial. J Urol, 2017. 198: 600.
https://pubmed.ncbi.nlm.nih.gov/28392393/

583. Steiner, M.S., *et al*. Impact of anatomical radical prostatectomy on urinary continence. J Urol, 1991. 145: 512.
https://pubmed.ncbi.nlm.nih.gov/1997701/

584. Li, H., *et al*. The Use of Unidirectional Barbed Suture for Urethrovesical Anastomosis during Robot-Assisted Radical Prostatectomy: A Systematic Review and Meta-Analysis of Efficacy and Safety. PLoS One, 2015. 10: e0131167.
https://pubmed.ncbi.nlm.nih.gov/26135310/

585. Kowalewski, K.F., *et al*. Interrupted versus Continuous Suturing for Vesicourethral Anastomosis During Radical Prostatectomy: A Systematic Review and Meta-analysis. Eur Urol Focus, 2019. 5: 980.
https://pubmed.ncbi.nlm.nih.gov/29907547/

586. Matsuyama, H., *et al*. Running suture versus interrupted suture for vesicourethral anastomosis in retropubic radical prostatectomy: a randomized study. Int J Urol, 2015. 22: 271.
https://pubmed.ncbi.nlm.nih.gov/25400263/

587. Wiatr, T., *et al*. Single Running Suture versus Single-Knot Running Suture for Vesicourethral Anastomosis in Laparoscopic Radical Prostatectomy: A Prospective Randomised Comparative Study. Urol Int, 2015. 95: 445.
https://pubmed.ncbi.nlm.nih.gov/26655169/

588. Van Velthoven, R.F., *et al*. Technique for laparoscopic running urethrovesical anastomosis:the single knot method. Urology, 2003. 61: 699.
https://pubmed.ncbi.nlm.nih.gov/12670546/

589. Schoeppler, G.M., *et al*. The impact of bladder neck mucosal eversion during open radical prostatectomy on bladder neck stricture and urinary extravasation. Int Urol Nephrol, 2012. 44: 1403.
https://pubmed.ncbi.nlm.nih.gov/22585294/

590. Borboroglu, P.G., *et al*. Risk factors for vesicourethral anastomotic stricture after radical prostatectomy. Urology, 2000. 56: 96.
https://pubmed.ncbi.nlm.nih.gov/10869633/

591. Modig, K.K., *et al*. Vesicourethral Anastomotic Stenosis After Open or Robot-assisted Laparoscopic Retropubic Prostatectomy-Results from the Laparoscopic Prostatectomy Robot Open Trial. Eur Urol Focus, 2021. 7: 317.
https://pubmed.ncbi.nlm.nih.gov/31711932/

592. Bellangino, M., *et al*. Systematic Review of Studies Reporting Positive Surgical Margins After Bladder Neck Sparing Radical Prostatectomy. Curr Urol Rep, 2017. 18: 99.
https://pubmed.ncbi.nlm.nih.gov/29116405/

593. Nyarangi-Dix, J.N., *et al*. Complete bladder neck preservation promotes long-term post-prostatectomy continence without compromising midterm oncological outcome: analysis of a randomised controlled cohort. World J Urol, 2018. 36: 349.
https://pubmed.ncbi.nlm.nih.gov/29214353/

594. Ma, X., *et al*. Bladder neck preservation improves time to continence after radical prostatectomy: a systematic review and meta-analysis. Oncotarget, 2016. 7: 67463.
https://pubmed.ncbi.nlm.nih.gov/27634899/

595. Mungovan, S.F., *et al*. Preoperative Membranous Urethral Length Measurement and Continence Recovery Following Radical Prostatectomy: A Systematic Review and Meta-analysis. Eur Urol, 2017. 71: 368.
https://pubmed.ncbi.nlm.nih.gov/27394644/

596. Lardas, M., *et al*. Patient- and Tumour-related Prognostic Factors for Urinary Incontinence After Radical Prostatectomy for Nonmetastatic Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus, 2022. 8: 674.
https://pubmed.ncbi.nlm.nih.gov/33967010/

597. Guru, K.A., *et al*. Is a cystogram necessary after robot-assisted radical prostatectomy? Urol Oncol, 2007. 25: 465.
https://pubmed.ncbi.nlm.nih.gov/18047953/

598. Tillier, C., *et al*. Vesico-urethral anastomosis (VUA) evaluation of short- and long-term outcome after robot-assisted laparoscopic radical prostatectomy (RARP): selective cystogram to improve outcome. J Robot Surg, 2017. 11: 441.
https://pubmed.ncbi.nlm.nih.gov/28078524/

599. Yadav, R., *et al*. Selective indication for check cystogram before catheter removal following robot assisted radical prostatectomy. Indian J Urol, 2016. 32: 120.
https://pubmed.ncbi.nlm.nih.gov/27127354/

600. Schoeppler, G.M., *et al*. Detection of urinary leakage after radical retropubic prostatectomy by contrast enhanced ultrasound - do we still need conventional retrograde cystography? BJU Int, 2010. 106: 1632.
https://pubmed.ncbi.nlm.nih.gov/20590540/

601. Gratzke, C., *et al*. Early Catheter Removal after Robot-assisted Radical Prostatectomy: Surgical Technique and Outcomes for the Aalst Technique (ECaRemA Study). Eur Urol, 2016. 69: 917.
https://pubmed.ncbi.nlm.nih.gov/26578444/

602.   James, P., *et al*. Safe removal of the urethral catheter 2 days following laparoscopic radical prostatectomy. ISRN Oncol, 2012. 2012: 912642.
https://pubmed.ncbi.nlm.nih.gov/22957273/

603.   Lista, G., *et al*. Early Catheter Removal After Robot-assisted Radical Prostatectomy: Results from a Prospective Single-institutional Randomized Trial (Ripreca Study). Eur Urol Focus, 2020. 6: 259.
https://pubmed.ncbi.nlm.nih.gov/30413390/

604.   Brassetti, A., *et al*. Removing the urinary catheter on post-operative day 2 after robot-assisted laparoscopic radical prostatectomy: a feasibility study from a single high-volume referral centre. J Robot Surg, 2018. 12: 467.
https://pubmed.ncbi.nlm.nih.gov/29177945/

605.   Tilki, D., *et al*. The impact of time to catheter removal on short-, intermediate- and long-term urinary continence after radical prostatectomy. World J Urol, 2018. 36: 1247.
https://pubmed.ncbi.nlm.nih.gov/29582100/

606.   Berrondo, C., *et al*. Antibiotic prophylaxis at the time of catheter removal after radical prostatectomy: A prospective randomized clinical trial. Urol Oncol, 2019. 37: 181 e7.
https://pubmed.ncbi.nlm.nih.gov/30558984/

607.   Martinschek, A., *et al*. Transurethral versus suprapubic catheter at robot-assisted radical prostatectomy: a prospective randomized trial with 1-year follow-up. World J Urol, 2016. 34: 407.
https://pubmed.ncbi.nlm.nih.gov/26337521/

608.   Harke, N., *et al*. Postoperative patient comfort in suprapubic drainage versus transurethral catheterization following robot-assisted radical prostatectomy: a prospective randomized clinical trial. World J Urol, 2017. 35: 389.
https://pubmed.ncbi.nlm.nih.gov/27334135/

609.   Krane, L.S., *et al*. Impact of percutaneous suprapubic tube drainage on patient discomfort after radical prostatectomy. Eur Urol, 2009. 56: 325.
https://pubmed.ncbi.nlm.nih.gov/19394131/

610.   Morgan, M.S., *et al*. An Assessment of Patient Comfort and Morbidity After Robot-Assisted Radical Prostatectomy with Suprapubic Tube Versus Urethral Catheter Drainage. J Endourol, 2016. 30: 300.
https://pubmed.ncbi.nlm.nih.gov/26472083/

611.   Galfano, A., *et al*. Pain and discomfort after Retzius-sparing robot-assisted radical prostatectomy: a comparative study between suprapubic cystostomy and urethral catheter as urinary drainage. Minerva Urol Nefrol, 2019. 71: 381.
https://pubmed.ncbi.nlm.nih.gov/31144484/

612.   Prasad, S.M., *et al*. Early removal of urethral catheter with suprapubic tube drainage versus urethral catheter drainage alone after robot-assisted laparoscopic radical prostatectomy. J Urol, 2014. 192: 89.
https://pubmed.ncbi.nlm.nih.gov/24440236/

613.   Afzal, M.Z., *et al*. Modification of Technique for Suprapubic Catheter Placement After Robot-assisted Radical Prostatectomy Reduces Catheter-associated Complications. Urology, 2015. 86: 401.
https://pubmed.ncbi.nlm.nih.gov/26189333/

614.   Porcaro, A.B., *et al*. Is a Drain Needed After Robotic Radical Prostatectomy With or Without Pelvic Lymph Node Dissection? Results of a Single-Center Randomized Clinical Trial. J Endourol, 2021. 35: 922.
https://pubmed.ncbi.nlm.nih.gov/30398382/

615.   Chenam, A., *et al*. Prospective randomised non-inferiority trial of pelvic drain placement vs no pelvic drain placement after robot-assisted radical prostatectomy. BJU Int, 2018. 121: 357.
https://pubmed.ncbi.nlm.nih.gov/28872774/

616.   Ramsay, 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.
https://pubmed.ncbi.nlm.nih.gov/23127367/

617.   Novara, G., *et al*. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur Urol, 2012. 62: 382.
https://pubmed.ncbi.nlm.nih.gov/22749851/

618.   Novara, G., *et al*. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol, 2012. 62: 431.
https://pubmed.ncbi.nlm.nih.gov/22749853/

619.   Ficarra, V., *et al*. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol, 2012. 62: 418.
https://pubmed.ncbi.nlm.nih.gov/22749850/

620. Ficarra, V., *et al*. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol, 2012. 62: 405.
https://pubmed.ncbi.nlm.nih.gov/22749852/

621. Maffezzini, M., *et al*. Evaluation of complications and results in a contemporary series of 300 consecutive radical retropubic prostatectomies with the anatomic approach at a single institution. Urology, 2003. 61: 982.
https://pubmed.ncbi.nlm.nih.gov/12736020/

622. Haglind, E., *et al*. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol, 2015. 68: 216.
https://pubmed.ncbi.nlm.nih.gov/25770484/

623. Mukkala, A.N., *et al*. A systematic review and meta-analysis of unplanned hospital visits and re-admissions following radical prostatectomy for prostate cancer. Can Urol Assoc J, 2021. 15: E531.
https://pubmed.ncbi.nlm.nih.gov/33750517/

624. Dindo, D., *et al*. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg, 2004. 240: 205.
https://pubmed.ncbi.nlm.nih.gov/15273542/

625. Joshi, N., *et al*. Impact of posterior musculofascial reconstruction on early continence after robot-assisted laparoscopic radical prostatectomy: results of a prospective parallel group trial. Eur Urol, 2010. 58: 84.
https://pubmed.ncbi.nlm.nih.gov/20362386/

626. Sutherland, D.E., *et al*. Posterior rhabdosphincter reconstruction during robotic assisted radical prostatectomy: results from a phase II randomized clinical trial. J Urol, 2011. 185: 1262.
https://pubmed.ncbi.nlm.nih.gov/21334025/

627. Jeong, C.W., *et al*. Effects of new 1-step posterior reconstruction method on recovery of continence after robot-assisted laparoscopic prostatectomy: results of a prospective, single-blind, parallel group, randomized, controlled trial. J Urol, 2015. 193: 935.
https://pubmed.ncbi.nlm.nih.gov/25315960/

628. Menon, M., *et al*. Assessment of early continence after reconstruction of the periprostatic tissues in patients undergoing computer assisted (robotic) prostatectomy: results of a 2 group parallel randomized controlled trial. J Urol, 2008. 180: 1018.
https://pubmed.ncbi.nlm.nih.gov/18639300/

629. Stolzenburg, J.U., *et al*. Influence of bladder neck suspension stitches on early continence after radical prostatectomy: a prospective randomized study of 180 patients. Asian J Androl, 2011. 13: 806.
https://pubmed.ncbi.nlm.nih.gov/21909121/

630. Hurtes, X., *et al*. Anterior suspension combined with posterior reconstruction during robot-assisted laparoscopic prostatectomy improves early return of urinary continence: a prospective randomized multicentre trial. BJU Int, 2012. 110: 875.
https://pubmed.ncbi.nlm.nih.gov/22260307/

631. Student, V., Jr., *et al*. Advanced Reconstruction of Vesicourethral Support (ARVUS) during Robot-assisted Radical Prostatectomy: One-year Functional Outcomes in a Two-group Randomised Controlled Trial. Eur Urol, 2017. 71: 822.
https://pubmed.ncbi.nlm.nih.gov/27283216/

632. Noguchi, M., *et al*. A randomized clinical trial of suspension technique for improving early recovery of urinary continence after radical retropubic prostatectomy. BJU Int, 2008. 102: 958.
https://pubmed.ncbi.nlm.nih.gov/18485031/

633. Tikkinen, K.A.O., *et al*. EAU Guidelines on Thromboprophylaxis in Urological Surgery. In: EAU Guidelines presented at the 32rd EAU Annual Congress London 2017. EAU Guidelines Office, Arnhem, the Netherlands.
https://uroweb.org/guidelines/archive/thromboprophylaxis

634. Viani, G.A., *et al*. Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: A randomized clinical trial. Cancer, 2016. 122: 2004.
https://pubmed.ncbi.nlm.nih.gov/27028170/

635. Yu, T., *et al*. The Effectiveness of Intensity Modulated Radiation Therapy versus Three-Dimensional Radiation Therapy in Prostate Cancer: A Meta-Analysis of the Literatures. PLoS One, 2016. 11: e0154499.
https://pubmed.ncbi.nlm.nih.gov/27171271/

636. 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.
https://pubmed.ncbi.nlm.nih.gov/28374321/

637. de Crevoisier, R., *et al*. Daily Versus Weekly Prostate Cancer Image Guided Radiation Therapy: Phase 3 Multicenter Randomized Trial. Int J Radiat Oncol Biol Phys, 2018. 102: 1420.
https://pubmed.ncbi.nlm.nih.gov/30071296/

638. Murray, J., *et al*. A randomised assessment of image guided radiotherapy within a phase 3 trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer. Radiother Oncol, 2020. 142: 62.
https://pubmed.ncbi.nlm.nih.gov/31767473/

639. Tocco, B.R., *et al*. MR-Guided Radiotherapy for Prostate Cancer. Front Oncol, 2020. 10: 616291.
https://pubmed.ncbi.nlm.nih.gov/33363041/

640. Christiansen, R.L., *et al*. Online adaptive radiotherapy potentially reduces toxicity for high-risk prostate cancer treatment. Radiother Oncol, 2022. 167: 165.
https://pubmed.ncbi.nlm.nih.gov/34923034/

641. Tetar, S.U., *et al*. Magnetic Resonance-guided Stereotactic Radiotherapy for Localized Prostate Cancer: Final Results on Patient-reported Outcomes of a Prospective Phase 2 Study. Eur Urol Oncol, 2021. 4: 628.
https://pubmed.ncbi.nlm.nih.gov/32536573/

642. Ugurluer, G., *et al*. Magnetic resonance image-guided adaptive stereotactic body radiotherapy for prostate cancer: preliminary results of outcome and toxicity. Br J Radiol, 2021. 94: 20200696.
https://pubmed.ncbi.nlm.nih.gov/33095670/

643. Ma, T.M., *et al*. Magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer (mirage): a phase iii randomized trial. BMC Cancer, 2021. 21: 538.
https://pubmed.ncbi.nlm.nih.gov/33975579/

644. Kishan, A.U., *et al*. Local Failure and Survival After Definitive Radiotherapy for Aggressive Prostate Cancer: An Individual Patient-level Meta-analysis of Six Randomized Trials. Eur Urol, 2020. 77: 201.
https://pubmed.ncbi.nlm.nih.gov/31718822/

645. Michalski, J.M., *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.
https://pubmed.ncbi.nlm.nih.gov/29543933/

646. Zietman, A.L., *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol, 2010. 28: 1106.
https://pubmed.ncbi.nlm.nih.gov/20124169/

647. Viani, G.A., *et al*. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys, 2009. 74: 1405.
https://pubmed.ncbi.nlm.nih.gov/19616743/

648. Peeters, S.T., *et al*. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol, 2006. 24: 1990.
https://pubmed.ncbi.nlm.nih.gov/16648499/

649. Beckendorf, V., *et al*. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys, 2011. 80: 1056.
https://pubmed.ncbi.nlm.nih.gov/21147514/

650. Heemsbergen, W.D., *et al*. 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.
https://pubmed.ncbi.nlm.nih.gov/24246414/

651. Dearnaley, D.P., *et al*. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol, 2014. 15: 464.
https://pubmed.ncbi.nlm.nih.gov/24581940/

652. Pasalic, D., *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.
https://pubmed.ncbi.nlm.nih.gov/30836166/

653. Kalbasi, A., *et al*. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. JAMA Oncol, 2015. 1: 897.
https://pubmed.ncbi.nlm.nih.gov/26181727/

654. Kerkmeijer, L.G.W., *et al*. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. J Clin Oncol, 2021. 39: 787.
https://pubmed.ncbi.nlm.nih.gov/33471548/

655. Groen, V.H., *et al*. Patterns of Failure Following External Beam Radiotherapy With or Without an Additional Focal Boost in the Randomized Controlled FLAME Trial for Localized Prostate Cancer. Eur Urol, 2022. 82: 252.
https://pubmed.ncbi.nlm.nih.gov/34953603/

656. Fowler, J.F. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncol, 2005. 44: 265.
https://pubmed.ncbi.nlm.nih.gov/16076699/

657. Dasu, A., *et al*. Prostate alpha/beta revisited -- an analysis of clinical results from 14 168 patients. Acta Oncol, 2012. 51: 963.
https://pubmed.ncbi.nlm.nih.gov/22966812/

658. Kuban, D.A., *et al*. Preliminary Report of a Randomized Dose Escalation Trial for Prostate Cancer using Hypofractionation. Int J Radiat Oncol Biol Phys, 2010. 78: S58.
https://www.redjournal.org/article/S0360-3016(10)01144-2/fulltext

659. Pollack, A., *et al*. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol, 2013. 31: 3860.
https://pubmed.ncbi.nlm.nih.gov/24101042/

660. Lee, W.R., *et al*. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. J Clin Oncol, 2016. 34: 2325.
https://pubmed.ncbi.nlm.nih.gov/27044935/

661. Dearnaley, D., *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.
https://pubmed.ncbi.nlm.nih.gov/27339115/

662. Incrocci, L., *et al*. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol, 2016. 17: 1061.
https://pubmed.ncbi.nlm.nih.gov/27339116/

663. Catton, C.N., *et al*. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. J Clin Oncol, 2017. 35: 1884.
https://pubmed.ncbi.nlm.nih.gov/28296582/

664. Koontz, B.F., *et al*. A systematic review of hypofractionation for primary management of prostate cancer. Eur Urol, 2015. 68: 683.
https://pubmed.ncbi.nlm.nih.gov/25171903/

665. Hocht, S., *et al*. Hypofractionated radiotherapy for localized prostate cancer. Strahlenther Onkol, 2017. 193: 1.
https://pubmed.ncbi.nlm.nih.gov/27628966/

666. Hickey, B.E., *et al*. Hypofractionation for clinically localized prostate cancer. Cochrane Database Syst Rev, 2019. 9: CD011462.
https://pubmed.ncbi.nlm.nih.gov/31476800/

667. de Vries, K.C., *et al*. Hyprofractionated Versus Conventionally Fractionated Radiation Therapy for Patients with Intermediate- or High-Risk, Localized, Prostate Cancer: 7-Year Outcomes From the Randomized, Multicenter, Open-Label, Phase 3 HYPRO Trial. Int J Radiat Oncol Biol Phys, 2020. 106: 108.
https://pubmed.ncbi.nlm.nih.gov/31593756/

668. Widmark, A., *et al*. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet, 2019. 394: 385.
https://pubmed.ncbi.nlm.nih.gov/31227373/

669. Jackson, W.C., *et al*. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. Int J Radiat Oncol Biol Phys, 2019. 104: 778.
https://pubmed.ncbi.nlm.nih.gov/30959121/

670. Cushman, T.R., *et al*. Stereotactic body radiation therapy for prostate cancer: systematic review and meta-analysis of prospective trials. Oncotarget, 2019. 10: 5660.
https://pubmed.ncbi.nlm.nih.gov/31608141/

671. Brand, D.H., *et al*. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol, 2019. 20: 1531.
https://pubmed.ncbi.nlm.nih.gov/31540791/

672. Rasmusson, E., *et al*. Erectile Dysfunction and Absorbed Dose to Penile Base Structures in a Randomized Trial Comparing Ultrahypofractionated and Conventionally Fractionated Radiation Therapy for Prostate Cancer. Int J Radiat Oncol Biol Phys, 2020. 107: 143.
https://pubmed.ncbi.nlm.nih.gov/32004582/

673. Greco, C., *et al*. Safety and Efficacy of Virtual Prostatectomy With Single-Dose Radiotherapy in Patients With Intermediate-Risk Prostate Cancer: Results From the PROSINT Phase 2 Randomized Clinical Trial. JAMA Oncol, 2021. 7: 700.
https://pubmed.ncbi.nlm.nih.gov/33704378/

674. Bolla, M., *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.
https://pubmed.ncbi.nlm.nih.gov/20933466/

675. Pilepich, M.V., *et al*. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys, 2005. 61: 1285.
https://pubmed.ncbi.nlm.nih.gov/15817329/

676. Roach, M., 3rd, *et al*. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol, 2008. 26: 585.
https://pubmed.ncbi.nlm.nih.gov/18172188/

677. D'Amico, A.V., *et al*. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA, 2008. 299: 289.
https://pubmed.ncbi.nlm.nih.gov/18212313/

678. Denham, J.W., *et al*. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol, 2011. 12: 451.
https://pubmed.ncbi.nlm.nih.gov/21440505/

679. Lawton, C.A., *et al*. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys, 2007. 69: 646.
https://pubmed.ncbi.nlm.nih.gov/17531401/

680. Horwitz, E.M., *et al*. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol, 2008. 26: 2497.
https://pubmed.ncbi.nlm.nih.gov/18413638/

681. Bolla, M., *et al*. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med, 2009. 360: 2516.
https://pubmed.ncbi.nlm.nih.gov/19516032/

682. Pisansky, T.M., *et al*. Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. J Clin Oncol, 2015. 33: 332.
https://pubmed.ncbi.nlm.nih.gov/25534388/

683. Nabid, A., *et al*. Androgen deprivation therapy and radiotherapy in intermediate-risk prostate cancer: A randomised phase III trial. Eur J Cancer, 2021. 143: 64.
https://pubmed.ncbi.nlm.nih.gov/33279855/

684. Fossa, S.D., *et al*. Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7. Eur Urol, 2016. 70: 684.
https://pubmed.ncbi.nlm.nih.gov/27025586/

685. Mason, M.D., *et al*. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. J Clin Oncol, 2015. 33: 2143.
https://pubmed.ncbi.nlm.nih.gov/25691677/

686. Sargos, P., *et al*. Long-term androgen deprivation, with or without radiotherapy, in locally advanced prostate cancer: updated results from a phase III randomised trial. BJU Int, 2020. 125: 810.
https://pubmed.ncbi.nlm.nih.gov/30946523/

687. Kishan, A.U., *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.
https://pubmed.ncbi.nlm.nih.gov/35051385/

688. Zapatero, A., *et al*. Risk-Adapted Androgen Deprivation and Escalated Three-Dimensional Conformal Radiotherapy for Prostate Cancer: Does Radiation Dose Influence Outcome of Patients Treated With Adjuvant Androgen Deprivation? A GICOR Study. J Clin Oncol, 2005. 23: 6561.
https://pubmed.ncbi.nlm.nih.gov/16170164/

689. Zapatero, A., *et al*. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet Oncol, 2015. 16: 320.
https://pubmed.ncbi.nlm.nih.gov/25702876/

690. Bolla, M., *et al*. Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. J Clin Oncol, 2016. 34: 1748.
https://pubmed.ncbi.nlm.nih.gov/26976418/

691. Spratt, D.E., *et al*. Prostate Radiotherapy With Adjuvant Androgen Deprivation Therapy (ADT) Improves Metastasis-Free Survival Compared to Neoadjuvant ADT: An Individual Patient Meta-Analysis. J Clin Oncol, 2021. 39: 136.
https://pubmed.ncbi.nlm.nih.gov/33275486/

692. Malone, S., *et al*. Sequencing of Androgen-Deprivation Therapy With External-Beam Radiotherapy in Localized Prostate Cancer: A Phase III Randomized Controlled Trial. J Clin Oncol, 2020. 38: 593.
https://pubmed.ncbi.nlm.nih.gov/31829912/

693. Gray, P.J., *et al*. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. Cancer, 2013. 119: 1729.
https://pubmed.ncbi.nlm.nih.gov/23436283/

694. Sheets, N.C., *et al*. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012. 307: 1611.
https://pubmed.ncbi.nlm.nih.gov/22511689/

695. NICE. Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. Interventional procedures guidance [IPG590]. 2017. Access date December 2022.
https://www.nice.org.uk/guidance/ipg590

696. Miller, L.E., *et al*. Association of the Placement of a Perirectal Hydrogel Spacer With the Clinical Outcomes of Men Receiving Radiotherapy for Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open, 2020. 3: e208221.
https://pubmed.ncbi.nlm.nih.gov/32585020/

697. Hamstra, D.A., *et al*. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Int J Radiat Oncol Biol Phys, 2017. 97: 976.
https://pubmed.ncbi.nlm.nih.gov/28209443/

698. Aminsharifi, A., *et al*. Major Complications and Adverse Events Related to the Injection of the SpaceOAR Hydrogel System Before Radiotherapy for Prostate Cancer: Review of the Manufacturer and User Facility Device Experience Database. J Endourol, 2019. 33: 868.
https://pubmed.ncbi.nlm.nih.gov/31452385/

699. Pinkawa, M., *et al*. Learning curve in the application of a hydrogel spacer to protect the rectal wall during radiotherapy of localized prostate cancer. Urology, 2013. 82: 963.
https://pubmed.ncbi.nlm.nih.gov/24074991/

700. Henry, A., *et al*. GEC-ESTRO ACROP prostate brachytherapy guidelines. Radiother Oncol, 2022. 167: 244.
https://pubmed.ncbi.nlm.nih.gov/34999134/

701. 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.
https://pubmed.ncbi.nlm.nih.gov/16563992/

702. Le, H., *et al*. The influence of prostate volume on outcome after high-dose-rate brachytherapy alone for localized prostate cancer. Int J Radiat Oncol Biol Phys, 2013. 87: 270.
https://pubmed.ncbi.nlm.nih.gov/23849693/

703. 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 Brachyther, 2020. 12: 1.
https://pubmed.ncbi.nlm.nih.gov/32190063/

704. Salembier, C., *et al*. Prospective multi-center dosimetry study of low-dose Iodine-125 prostate brachytherapy performed after transurethral resection. J Contemp Brachyther, 2013. 5: 63.
https://pubmed.ncbi.nlm.nih.gov/23878549/

705. Stone, N.N., *et al*. Prostate brachytherapy in men with gland volume of 100cc or greater: Technique, cancer control, and morbidity. Brachytherapy, 2013. 12: 217.
https://pubmed.ncbi.nlm.nih.gov/23384439/

706. Crook, J.M., *et al*. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. J Clin Oncol, 2011. 29: 362.
https://pubmed.ncbi.nlm.nih.gov/21149658/

707. Sylvester, J.E., *et al*. Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: Seattle experience. Int J Radiat Oncol Biol Phys, 2011. 81: 376.
https://pubmed.ncbi.nlm.nih.gov/20864269/

708. Potters, L., *et al*. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol, 2005. 173: 1562.
https://pubmed.ncbi.nlm.nih.gov/15821486/

709. Stone, N.N., *et al*. Intermediate term biochemical-free progression and local control following 125iodine brachytherapy for prostate cancer. J Urol, 2005. 173: 803.
https://pubmed.ncbi.nlm.nih.gov/15711273/

710. Zelefsky, M.J., *et al*. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys, 2007. 67: 327.
https://pubmed.ncbi.nlm.nih.gov/17084558/

711. Lawton, C.A., *et al*. Results of a phase II trial of transrectal ultrasound-guided permanent radioactive implantation of the prostate for definitive management of localized adenocarcinoma of the prostate (radiation therapy oncology group 98-05). Int J Radiat Oncol Biol Phys, 2007. 67: 39.
https://pubmed.ncbi.nlm.nih.gov/17084551/

712. Stock, R.G., *et al*. Importance of post-implant dosimetry in permanent prostate brachytherapy. Eur Urol, 2002. 41: 434.
https://pubmed.ncbi.nlm.nih.gov/12074816/

713. Keyes, M., *et al*. American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy-A systematic literature review. Brachytherapy, 2017. 16: 245.
https://pubmed.ncbi.nlm.nih.gov/28110898/

714. Morris, W.J., *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.
https://pubmed.ncbi.nlm.nih.gov/28262473/

715. 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.
https://pubmed.ncbi.nlm.nih.gov/28433432/

716. Hoskin, P.J., *et al*. GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol, 2013. 107: 325.
https://pubmed.ncbi.nlm.nih.gov/23773409/

717. Galalae, R.M., *et al*. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys, 2002. 52: 81.
https://pubmed.ncbi.nlm.nih.gov/11777625/

718. Pieters, B.R., *et al*. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. Radiother Oncol, 2009. 93: 168.
https://pubmed.ncbi.nlm.nih.gov/19748692/

719. Parry, M.G., *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.
https://pubmed.ncbi.nlm.nih.gov/33279595/

720. Hoskin, P.J., *et al*. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results. Radiother Oncol, 2021. 154: 214.
https://pubmed.ncbi.nlm.nih.gov/33011207/

721. Joseph, D., *et al*. Radiation Dose Escalation or Longer Androgen Suppression to Prevent Distant Progression in Men With Locally Advanced Prostate Cancer: 10-Year Data From the TROG 03.04 RADAR Trial. Int J Radiat Oncol Biol Phys, 2020. 106: 693.
https://pubmed.ncbi.nlm.nih.gov/32092343/

722. Jackson, W.C., *et al*. Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials. J Clin Oncol, 2020. 38: 3024.
https://pubmed.ncbi.nlm.nih.gov/32396488/

723. Viani, G.A., *et al*. HDR brachytherapy as monotherapy for prostate cancer: A systematic review with meta-analysis. Brachytherapy, 2021. 20: 307.
https://pubmed.ncbi.nlm.nih.gov/33461894/

724. Morton, G., *et al*. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19Gy or two fractions of 13.5Gy. Radiother Oncol, 2017. 122: 87.
https://pubmed.ncbi.nlm.nih.gov/27823821/

725. Matzinger, O., *et al*. Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991. Eur J Cancer, 2009. 45: 2825.
https://pubmed.ncbi.nlm.nih.gov/19682889/

726. Hoskin, P., *et al*. High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: acute toxicity. Radiother Oncol, 2014. 110: 268.
https://pubmed.ncbi.nlm.nih.gov/24231242/

727. King, C.R., *et al*. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys, 2013. 87: 939.
https://pubmed.ncbi.nlm.nih.gov/24119836/

728. Pagliarulo, V., *et al*. Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol, 2012. 61: 11.
https://pubmed.ncbi.nlm.nih.gov/21871711/

729. Oefelein, M.G., *et al*. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. Urology, 2000. 56: 1021.
https://pubmed.ncbi.nlm.nih.gov/11113751/

730. Morote, J., *et al*. Individual variations of serum testosterone in patients with prostate cancer receiving androgen deprivation therapy. BJU Int, 2009. 103: 332.
https://pubmed.ncbi.nlm.nih.gov/19007366/

731. Pickles, T., *et al*. Incomplete testosterone suppression with luteinizing hormone-releasing hormone agonists: does it happen and does it matter? BJU Int, 2012. 110: E500.
https://pubmed.ncbi.nlm.nih.gov/22564197/

732. Klotz, L., *et al*. MP74-01 Nadir testosterone on ADT predicts for time to castrate resistant progression: A secondary analysis of the PR-7 intermittent vs continuous ADT trial. J Urol. 191: e855.
https://www.auajournals.org/doi/10.1016/j.juro.2014.02.2334

733. Desmond, A.D., *et al*. Subcapsular orchiectomy under local anaesthesia. Technique, results and implications. Br J Urol, 1988. 61: 143.
https://pubmed.ncbi.nlm.nih.gov/3349279/

734. Scherr, D.S., *et al*. The nonsteroidal effects of diethylstilbestrol: the rationale for androgen deprivation therapy without estrogen deprivation in the treatment of prostate cancer. J Urol, 2003. 170: 1703.
https://pubmed.ncbi.nlm.nih.gov/14532759/

735. Farrugia, D., *et al*. Stilboestrol plus adrenal suppression as salvage treatment for patients failing treatment with luteinizing hormone-releasing hormone analogues and orchidectomy. BJU Int, 2000. 85: 1069.
https://pubmed.ncbi.nlm.nih.gov/10848697/

736. Hedlund, P.O., *et al*. Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. Scand J Urol Nephrol, 2008. 42: 220.
https://pubmed.ncbi.nlm.nih.gov/18432528/

737. Gilbert, D.C., *et al*. Transdermal oestradiol as a method of androgen suppression for prostate cancer within the STAMPEDE trial platform. BJU Int, 2018. 121: 680.
https://pubmed.ncbi.nlm.nih.gov/29388336/

738. Bubley, G.J. Is the flare phenomenon clinically significant? Urology, 2001. 58: 5.
https://pubmed.ncbi.nlm.nih.gov/11502435/

739. Krakowsky, Y., *et al*. Risk of Testosterone Flare in the Era of the Saturation Model: One More Historical Myth. Eur Urol Focus, 2019. 5: 81.
https://pubmed.ncbi.nlm.nih.gov/28753828/

740. Klotz, L., *et al*. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int, 2008. 102: 1531.
https://pubmed.ncbi.nlm.nih.gov/19035858/

741. Seidenfeld, J., *et al*. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med, 2000. 132: 566.
https://pubmed.ncbi.nlm.nih.gov/10744594/

742. Ostergren, P.B., *et al*. Luteinizing Hormone-Releasing Hormone Agonists are Superior to Subcapsular Orchiectomy in Lowering Testosterone Levels of Men with Prostate Cancer: Results from a Randomized Clinical Trial. J Urol, 2017. 197: 1441.
https://pubmed.ncbi.nlm.nih.gov/27939836/

743. Shore, N.D. Experience with degarelix in the treatment of prostate cancer. Ther Adv Urol, 2013. 5: 11.
https://pubmed.ncbi.nlm.nih.gov/23372607/

744. Sciarra, A., *et al*. A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer. Medicine (Baltimore), 2016. 95: e3845.
https://pubmed.ncbi.nlm.nih.gov/27399062/

745. Cirne, F., *et al*. The cardiovascular effects of gonadotropin-releasing hormone antagonists in men with prostate cancer. Eur Heart J Cardiovasc Pharmacother, 2022. 8: 253.
https://pubmed.ncbi.nlm.nih.gov/33470403/

746. Abufaraj, M., *et al*. Differential Impact of Gonadotropin-releasing Hormone Antagonist Versus Agonist on Clinical Safety and Oncologic Outcomes on Patients with Metastatic Prostate Cancer: A Meta-analysis of Randomized Controlled Trials. Eur Urol, 2021. 79: 44.
https://pubmed.ncbi.nlm.nih.gov/32605859/

747. Shore, N.D., *et al*. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med, 2020. 382: 2187.
https://pubmed.ncbi.nlm.nih.gov/32469183/

748. U.S. Food & Drug Adminstration. FDA approves relugolix for advanced prostate cancer. 2020. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-relugolix-advanced-prostate-cancer

749. European Medicines Agency. Orgovyx approved for advanced prostate cancer. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/orgovyx

750. Moffat, L.E. Comparison of Zoladex, diethylstilbestrol and cyproterone acetate treatment in advanced prostate cancer. Eur Urol, 1990. 18 Suppl 3: 26.
https://pubmed.ncbi.nlm.nih.gov/2151272/

751. Schroder, F.H., *et al*. Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the "European Organization for Research and Treatment of Cancer" (EORTC) Protocol 30892. Eur Urol, 2004. 45: 457.
https://pubmed.ncbi.nlm.nih.gov/15041109/

752. Smith, M.R., *et al*. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol, 2004. 22: 2546.
https://pubmed.ncbi.nlm.nih.gov/15226323/

753. Iversen, P. Antiandrogen monotherapy: indications and results. Urology, 2002. 60: 64.
https://pubmed.ncbi.nlm.nih.gov/12231053/

754. Wadhwa, V.K., *et al*. Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for prostate cancer, with stratification of treatment based on presenting values. BJU Int, 2009. 104: 800.
https://pubmed.ncbi.nlm.nih.gov/19338564/

755. Montgomery, R.B., *et al*. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res, 2008. 68: 4447.
https://pubmed.ncbi.nlm.nih.gov/18519708/

756. U.S. Food & Drug Adminstration. FDA approves abiraterone acetate in combination with prednisone for high-risk metastatic castration-sensitive prostate cancer. 2018. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abiraterone-acetate-combination-prednisone-high-risk-metastatic-castration-sensitive

757. U.S. Food & Drug Adminstration. FDA approves enzalutamide for metastatic castration-sensitive prostate cancer. 2019. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enzalutamide-metastatic-castration-sensitive-prostate-cancer

758. U.S. Food & Drug Adminstration. FDA approves apalutamide for metastatic castration-sensitive prostate cancer. 2019. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-metastatic-castration-sensitive-prostate-cancer

759. European Medicines Agency. Zytiga. 2011. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/zytiga

760. European Medicines Agency. Erleada (apalutamide). 2019. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/erleada

761. European Medicines Agency. Nubeqa (darolutamide). 2020. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/nubeqa

762. European Medicines Agency. Xtandi (enzalutamide). 2013. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/xtandi

763. Chi, K.N., et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med, 2019. 381: 13.
https://pubmed.ncbi.nlm.nih.gov/31150574/

764. Armstrong, A.J., et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol, 2019. 37: 2974.
https://pubmed.ncbi.nlm.nih.gov/31329516/

765. Fizazi, K., et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med, 2017. 377: 352.
https://pubmed.ncbi.nlm.nih.gov/28578607/

766. Moilanen, A.M., et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. Sci Rep, 2015. 5: 12007.
https://pubmed.ncbi.nlm.nih.gov/26137992/

767. Zurth, C., et al. Blood-brain barrier penetration of [14C]darolutamide compared with [14C] enzalutamide in rats using whole body autoradiography. J Clin Oncol, 2018. 36: 345.
https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.6_suppl.345

768. Lord, C.J., et al. PARP inhibitors: Synthetic lethality in the clinic. Science, 2017. 355: 1152.
https://pubmed.ncbi.nlm.nih.gov/28302823/

769. Hargadon, K.M., et al. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol, 2018. 62: 29.
https://pubmed.ncbi.nlm.nih.gov/29990692/

770. Le, D.T., et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med, 2015. 372: 2509.
https://pubmed.ncbi.nlm.nih.gov/26028255/

771. de Bono, J.S., et al. Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss. Clin Cancer Res, 2019. 25: 928.
https://pubmed.ncbi.nlm.nih.gov/30037818/

772. Sarker, D., et al. Targeting the PI3K/AKT pathway for the treatment of prostate cancer. Clin Cancer Res, 2009. 15: 4799.
https://pubmed.ncbi.nlm.nih.gov/19638457/

773. Sgouros, G., et al. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov, 2020. 19: 589.
https://pubmed.ncbi.nlm.nih.gov/32728208/

774. U.S. Food & Drug Administration. FDA approval of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) for the treatment of adult patients with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-pluvicto-lutetium-lu-177-vipivotide-tetraxetan-treatment-adult

775. Fahmy, W.E., et al. Cryosurgery for prostate cancer. Arch Androl, 2003. 49: 397.
https://pubmed.ncbi.nlm.nih.gov/12893518/

776. Rees, J., et al. Cryosurgery for prostate cancer. BJU Int, 2004. 93: 710.
https://pubmed.ncbi.nlm.nih.gov/15049977/

777. Han, K.R., et al. Third-generation cryosurgery for primary and recurrent prostate cancer. BJU Int, 2004. 93: 14.
https://pubmed.ncbi.nlm.nih.gov/14678360/

778.   van der Poel, H.G., *et al*. Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position in 2018. Eur Urol, 2018. 74: 84.
        https://pubmed.ncbi.nlm.nih.gov/29373215/

779.   Valerio, M., *et al*. New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. Eur Urol, 2017. 71: 17.
        https://pubmed.ncbi.nlm.nih.gov/27595377/

780.   Ramsay, C.R., *et al*. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess, 2015. 19: 1.
        https://pubmed.ncbi.nlm.nih.gov/26140518/

781.   Madersbacher, S., *et al*. High-energy shockwaves and extracorporeal high-intensity focused ultrasound. J Endourol, 2003. 17: 667.
        https://pubmed.ncbi.nlm.nih.gov/14622487/

782.   Mouraviev, V., *et al*. Pathologic basis of focal therapy for early-stage prostate cancer. Nat Rev Urol, 2009. 6: 205.
        https://pubmed.ncbi.nlm.nih.gov/19352395/

783.   Cooperberg, M.R., *et al*. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J Urol, 2007. 178: S14.
        https://pubmed.ncbi.nlm.nih.gov/17644125/

784.   Polascik, T.J., *et al*. Pathologic stage T2a and T2b prostate cancer in the recent prostate-specific antigen era: implications for unilateral ablative therapy. Prostate, 2008. 68: 1380.
        https://pubmed.ncbi.nlm.nih.gov/18543281/

785.   Ahmed, H.U., *et al*. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol, 2007. 4: 632.
        https://pubmed.ncbi.nlm.nih.gov/17965641/

786.   Eggener, S.E., *et al*. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol, 2007. 178: 2260.
        https://pubmed.ncbi.nlm.nih.gov/17936815/

787.   Crawford, E.D., *et al*. Targeted focal therapy: a minimally invasive ablation technique for early prostate cancer. Oncology (Williston Park), 2007. 21: 27.
        https://pubmed.ncbi.nlm.nih.gov/17313155/

788.   Hopstaken, J.S., *et al*. An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years? Eur Urol, 2022. 81: 5.
        https://pubmed.ncbi.nlm.nih.gov/34489140/

789.   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.
        https://pubmed.ncbi.nlm.nih.gov/29960750/

790.   Hamdy, F.C., *et al*. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess, 2018. 22: 1.
        https://pubmed.ncbi.nlm.nih.gov/30264692/

791.   Baco, E., *et al*. MP21-7901 Focal ablation versus radical prostatectomy for intermediate-risk prostate cancer: interim analysis of a randomized controlled Trial. J Urol, 2021. 206: e815.
        https://www.auajournals.org/doi/abs/10.1097/JU.0000000000002067.06

792.   Reddy, D., *et al*. Comparative healthcare research outcomes of novel Surgery in prostate cancer (IP4-CHRONOS): Pilot RCT assessing feasibility of randomization for focal therapy in localized prostate cancer. J Clin Oncol, 2022. 40: 5086.
        https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.5086

793.   Shah, T.T., *et al*. Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score-matched study. Prostate Cancer Prostatic Dis, 2021. 24: 567.
        https://pubmed.ncbi.nlm.nih.gov/33504940/

794.   van Son, M.J., *et al*. Conventional radical versus focal treatment for localised prostate cancer: a propensity score weighted comparison of 6-year tumour control. Prostate Cancer Prostatic Dis, 2021. 24: 1120.
        https://pubmed.ncbi.nlm.nih.gov/33934114/

795.   Lovegrove, C.E., *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.
        https://pubmed.ncbi.nlm.nih.gov/31971335/

796.   Gill, I.S., *et al*. Randomized Trial of Partial Gland Ablation with Vascular Targeted Phototherapy versus Active Surveillance for Low Risk Prostate Cancer: Extended Followup and Analyses of Effectiveness. J Urol, 2018. 200: 786.
https://pubmed.ncbi.nlm.nih.gov/29864437/

797.   Bates, A.S., *et al*. A Systematic Review of Focal Ablative Therapy for Clinically Localised Prostate Cancer in Comparison with Standard Management Options: Limitations of the Available Evidence and Recommendations for Clinical Practice and Further Research. Eur Urol Oncol, 2021. 4: 405.
https://pubmed.ncbi.nlm.nih.gov/33423943/

798.   Azzouzi, A.R., *et al*. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol, 2017. 18: 181.
https://pubmed.ncbi.nlm.nih.gov/28007457/

799.   Albisinni, S., *et al*. Comparing High-Intensity Focal Ultrasound Hemiablation to Robotic Radical Prostatectomy in the Management of Unilateral Prostate Cancer: A Matched-Pair Analysis. J Endourol, 2017. 31: 14.
https://pubmed.ncbi.nlm.nih.gov/27799004/

800.   Zheng, X., *et al*. Focal Laser Ablation Versus Radical Prostatectomy for Localized Prostate Cancer: Survival Outcomes From a Matched Cohort. Clin Genitourin Cancer, 2019. 17: 464.
https://pubmed.ncbi.nlm.nih.gov/31594734/

801.   Zhou, X., *et al*. Comparative Effectiveness of Radiotherapy versus Focal Laser Ablation in Patients with Low and Intermediate Risk Localized Prostate Cancer. Sci Rep, 2020. 10: 9112.
https://pubmed.ncbi.nlm.nih.gov/32499484/

802.   Marconi, L., *et al*. Robot-assisted Radical Prostatectomy After Focal Therapy: Oncological, Functional Outcomes and Predictors of Recurrence. Eur Urol, 2019. 76: 27.
https://pubmed.ncbi.nlm.nih.gov/30904357/

803.   Spitznagel, T., *et al*. Salvage Robotic-assisted Laparoscopic Radical Prostatectomy Following Focal High-Intensity Focused Ultrasound for ISUP 2/3 Cancer. Urology, 2021. 156: 147.
https://pubmed.ncbi.nlm.nih.gov/34186136/

804.   MacLennan, S., *et al*. A core outcome set for localised prostate cancer effectiveness trials. BJU Int, 2017. 120: E64.
https://pubmed.ncbi.nlm.nih.gov/28346770/

805.   Willemse, P.M., *et al*. Systematic Review of Active Surveillance for Clinically Localised Prostate Cancer to Develop Recommendations Regarding Inclusion of Intermediate-risk Disease, Biopsy Characteristics at Inclusion and Monitoring, and Surveillance Repeat Biopsy Strategy. Eur Urol, 2022. 81: 337.
https://pubmed.ncbi.nlm.nih.gov/34980492/

806.   Loeb, S., *et al*. Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. Eur Urol, 2015. 67: 619.
https://pubmed.ncbi.nlm.nih.gov/25457014/

807.   Ha, Y.S., *et al*. Prostate-specific antigen density toward a better cutoff to identify better candidates for active surveillance. Urology, 2014. 84: 365.
https://pubmed.ncbi.nlm.nih.gov/24925834/

808.   Petrelli, F., *et al*. Predictive Factors for Reclassification and Relapse in Prostate Cancer Eligible for Active Surveillance: A Systematic Review and Meta-analysis. Urology, 2016. 91: 136.
https://pubmed.ncbi.nlm.nih.gov/26896733/

809.   Marks, R.A., *et al*. The relationship between the extent of surgical margin positivity and prostate specific antigen recurrence in radical prostatectomy specimens. Hum Pathol, 2007. 38: 1207.
https://pubmed.ncbi.nlm.nih.gov/17490720/

810.   Moreira, D.M., *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.
https://pubmed.ncbi.nlm.nih.gov/25988518/

811.   Schoots, I.G., *et al*. Is magnetic resonance imaging-targeted biopsy a useful addition to systematic confirmatory biopsy in men on active surveillance for low-risk prostate cancer? A systematic review and meta-analysis. BJU Int, 2018. 122: 946.
https://pubmed.ncbi.nlm.nih.gov/29679430/

812.   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 Postbiopsy Follow-up. Eur Urol, 2019.
https://pubmed.ncbi.nlm.nih.gov/31708295/

813. Chiam, K., *et al*. Use of multiparametric magnetic resonance imaging (mpMRI) in active surveillance for low-risk prostate cancer: a scoping review on the benefits and harm of mpMRI in different biopsy scenarios. Prostate Cancer Prostatic Dis, 2021. 24: 662.
https://pubmed.ncbi.nlm.nih.gov/33654249/

814. Dieffenbacher, S., *et al*. Standardized Magnetic Resonance Imaging Reporting Using the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation Criteria and Magnetic Resonance Imaging/Transrectal Ultrasound Fusion with Transperineal Saturation Biopsy to Select Men on Active Surveillance. Eur Urol Focus, 2021. 7: 102.
https://pubmed.ncbi.nlm.nih.gov/30878348/

815. Schiavina, R., *et al*. The role of multiparametric MRI in active surveillance for low-risk prostate cancer: The ROMAS randomized controlled trial. Urol Oncol, 2021. 39: 433.e1.
https://pubmed.ncbi.nlm.nih.gov/33191117/

816. Bratt, O., *et al*. The Swedish national guidelines on prostate cancer, part 1: early detection, diagnostics, staging, patient support and primary management of non-metastatic disease. Scand J Urol, 2022. 56: 265.
https://pubmed.ncbi.nlm.nih.gov/35811480/

817. Yerram, N.K., *et al*. Magnetic Resonance Imaging-Targeted and Systematic Biopsy for Detection of Grade Progression in Patients on Active Surveillance for Prostate Cancer. J Urol, 2021. 205: 1352.
https://pubmed.ncbi.nlm.nih.gov/33356479/

818. Moore, C.M., *et al*. Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations-A Report of a European School of Oncology Task Force. Eur Urol, 2017. 71: 648.
https://pubmed.ncbi.nlm.nih.gov/27349615/

819. Schoots, I.G., *et al*. Role of MRI in low-risk prostate cancer: finding the wolf in sheep's clothing or the sheep in wolf's clothing? Curr Opin Urol, 2017. 27: 238.
https://pubmed.ncbi.nlm.nih.gov/28306604/

820. Chu, C.E., *et al*. Diagnostic Accuracy and Prognostic Value of Serial Prostate Multiparametric Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer. Eur Urol Oncol, 2022. 5: 537.
https://pubmed.ncbi.nlm.nih.gov/33483265/

821. Hettiarachchi, D., *et al*. Can the Use of Serial Multiparametric Magnetic Resonance Imaging During Active Surveillance of Prostate Cancer Avoid the Need for Prostate Biopsies?-A Systematic Diagnostic Test Accuracy Review. Eur Urol Oncol, 2021. 4: 426.
https://pubmed.ncbi.nlm.nih.gov/32972894/

822. Rajwa, P., *et al*. Reliability of Serial Prostate Magnetic Resonance Imaging to Detect Prostate Cancer Progression During Active Surveillance: A Systematic Review and Meta-analysis. Eur Urol, 2021. 80: 549.
https://pubmed.ncbi.nlm.nih.gov/34020828/

823. Caglic, I., *et al*. MRI-derived PRECISE scores for predicting pathologically-confirmed radiological progression in prostate cancer patients on active surveillance. Eur Radiol, 2021. 31: 2696.
https://pubmed.ncbi.nlm.nih.gov/33196886/

824. Olivier, J., *et al*. Prostate Cancer Patients Under Active Surveillance with a Suspicious Magnetic Resonance Imaging Finding Are at Increased Risk of Needing Treatment: Results of the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium. Eur Urol Open Sci, 2022. 35: 59.
https://pubmed.ncbi.nlm.nih.gov/35024633/

825. 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.
https://pubmed.ncbi.nlm.nih.gov/33958731/

826. Chu, C.E., *et al*. Multiparametric Magnetic Resonance Imaging Alone is Insufficient to Detect Grade Reclassification in Active Surveillance for Prostate Cancer. Eur Urol, 2020. 78: 515.
https://pubmed.ncbi.nlm.nih.gov/32631744/

827. Deniffel, D., *et al*. Does the Visibility of Grade Group 1 Prostate Cancer on Baseline Multiparametric Magnetic Resonance Imaging Impact Clinical Outcomes? J Urol, 2020. 204: 1187.
https://pubmed.ncbi.nlm.nih.gov/32496160/

828. Fujihara, A., *et al*. Multiparametric magnetic resonance imaging facilitates reclassification during active surveillance for prostate cancer. BJU Int, 2021. 127: 712.
https://pubmed.ncbi.nlm.nih.gov/33043575/

829. 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.
https://pubmed.ncbi.nlm.nih.gov/31825297/

830. Mamawala, M.K., *et al*. Utility of multiparametric magnetic resonance imaging in the risk stratification of men with Grade Group 1 prostate cancer on active surveillance. BJU Int, 2020. 125: 861.
https://pubmed.ncbi.nlm.nih.gov/32039537/

831. Gallagher, K.M., *et al*. Four-year outcomes from a multiparametric magnetic resonance imaging (MRI)-based active surveillance programme: PSA dynamics and serial MRI scans allow omission of protocol biopsies. BJU Int, 2019. 123: 429.
https://pubmed.ncbi.nlm.nih.gov/30113755/

832. 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.
https://pubmed.ncbi.nlm.nih.gov/30039385/

833. Chu, C.E., *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.
https://pubmed.ncbi.nlm.nih.gov/33198555/

834. O'Connor, L.P., *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.
https://pubmed.ncbi.nlm.nih.gov/33867045/

835. Rajwa, P., *et al*. Association of Negative Followup Biopsy and Reclassification during Active Surveillance of Prostate Cancer: A Systematic Review and Meta-Analysis. J Urol, 2021. 205: 1559.
https://pubmed.ncbi.nlm.nih.gov/33683937/

836. Klotz, L., *et al*. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol, 2010. 28: 126.
https://pubmed.ncbi.nlm.nih.gov/19917860/

837. Ross, A.E., *et al*. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol, 2010. 28: 2810.
https://pubmed.ncbi.nlm.nih.gov/20439642/

838. Thomsen, F.B., *et al*. Association between PSA kinetics and cancer-specific mortality in patients with localised prostate cancer: analysis of the placebo arm of the SPCG-6 study. Ann Oncol, 2016. 27: 460.
https://pubmed.ncbi.nlm.nih.gov/26681677/

839. Liu, J.L., *et al*. Advances in the selection of patients with prostate cancer for active surveillance. Nat Rev Urol, 2021. 18: 197.
https://pubmed.ncbi.nlm.nih.gov/33623103/

840. McLeod, D.G., *et al*. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int, 2006. 97: 247.
https://pubmed.ncbi.nlm.nih.gov/16430622/

841. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol, 1997. 79: 235.
https://pubmed.ncbi.nlm.nih.gov/9052476/

842. Enikeev, D., *et al*. Active Surveillance for Intermediate-Risk Prostate Cancer: Systematic Review and Meta-analysis of Current Protocols and Outcomes. Clin Genitourin Cancer, 2020. 18: e739.
https://pubmed.ncbi.nlm.nih.gov/32768356/

843. Baboudjian, M., *et al*. Active Surveillance for Intermediate-risk Prostate Cancer: A Systematic Review, Meta-analysis, and Metaregression. Eur Urol Oncol, 2022. 5: 617.
https://pubmed.ncbi.nlm.nih.gov/35934625/

844. Morash, C., *et al*. Active surveillance for the management of localized prostate cancer: Guideline recommendations. Can Urol Assoc J, 2015. 9: 171.
https://pubmed.ncbi.nlm.nih.gov/26225165/

845. Musunuru, H.B., *et al*. Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. J Urol, 2016. 196: 1651.
https://pubmed.ncbi.nlm.nih.gov/27569437/

846. Raldow, A.C., *et al*. Risk Group and Death From Prostate Cancer: Implications for Active Surveillance in Men With Favorable Intermediate-Risk Prostate Cancer. JAMA Oncol, 2015. 1: 334.
https://pubmed.ncbi.nlm.nih.gov/26181182/

847. Luo, X., *et al*. Prostatectomy Versus Observation for Localized Prostate Cancer: A Meta-Analysis. Scand J Surg, 2021. 110: 78.
https://pubmed.ncbi.nlm.nih.gov/31662032/

848. Studer, U.E., *et al*. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol, 2008. 53: 941.
https://pubmed.ncbi.nlm.nih.gov/18191322/

849. James, N.D., *et al*. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet, 2016. 387: 1163.
https://pubmed.ncbi.nlm.nih.gov/26719232/

850. Krauss, D., *et al*. Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys, 2011. 80: 1064.
https://pubmed.ncbi.nlm.nih.gov/20584576/

851. Kupelian, P.A., *et al*. Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. Int J Radiat Oncol Biol Phys, 2008. 71: 16.
https://pubmed.ncbi.nlm.nih.gov/17996382/

852. Nabid, A., *et al*. Optimizing Treatment in Intermediate-Risk Prostate Cancer: Secondary Analysis of a Randomized Phase 3 Trial. Int J Radiat Oncol Biol Phys, 2021. 111: 732.
https://pubmed.ncbi.nlm.nih.gov/33901566/

853. King, M.T., *et al*. Low dose rate brachytherapy for primary treatment of localized prostate cancer: A systemic review and executive summary of an evidence-based consensus statement. Brachytherapy, 2021. 20: 1114.
https://pubmed.ncbi.nlm.nih.gov/34509378/

854. Joniau, S., *et al*. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol, 2015. 67: 157.
https://pubmed.ncbi.nlm.nih.gov/24486307/

855. Donohue, J.F., *et al*. Poorly differentiated prostate cancer treated with radical prostatectomy: long-term outcome and incidence of pathological downgrading. J Urol, 2006. 176: 991.
https://pubmed.ncbi.nlm.nih.gov/16890678/

856. Nguyen, D.D., *et al*. Systematic Review of Time to Definitive Treatment for Intermediate Risk and High Risk Prostate Cancer: Are Delays Associated with Worse Outcomes? J Urol, 2021. 205: 1263.
https://pubmed.ncbi.nlm.nih.gov/33443458/

857. Bianco, F.J., Jr., *et al*. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology, 2005. 66: 83.
https://pubmed.ncbi.nlm.nih.gov/16194712/

858. Walz, J., *et al*. A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. J Clin Oncol, 2007. 25: 3576.
https://pubmed.ncbi.nlm.nih.gov/17704404/

859. Eastham, J.A., *et al*. Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. J Urol, 2003. 170: 2292.
https://pubmed.ncbi.nlm.nih.gov/14634399/

860. Vickers, A.J., *et al*. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol, 2009. 10: 475.
https://pubmed.ncbi.nlm.nih.gov/19342300/

861. Trinh, Q.D., *et al*. A systematic review of the volume-outcome relationship for radical prostatectomy. Eur Urol, 2013. 64: 786.
https://pubmed.ncbi.nlm.nih.gov/23664423/

862. Joniau, S., *et al*. Pretreatment tables predicting pathologic stage of locally advanced prostate cancer. Eur Urol, 2015. 67: 319.
https://pubmed.ncbi.nlm.nih.gov/24684960/

863. Loeb, S., *et al*. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology, 2007. 69: 1170.
https://pubmed.ncbi.nlm.nih.gov/17572209/

864. Carver, B.S., *et al*. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. J Urol, 2006. 176: 564.
https://pubmed.ncbi.nlm.nih.gov/16813890/

865. Freedland, S.J., *et al*. Radical prostatectomy for clinical stage T3a disease. Cancer, 2007. 109: 1273.
https://pubmed.ncbi.nlm.nih.gov/17315165/

866. Joniau, S., *et al*. Radical prostatectomy in very high-risk localized prostate cancer: long-term outcomes and outcome predictors. Scand J Urol Nephrol, 2012. 46: 164.
https://pubmed.ncbi.nlm.nih.gov/22364377/

867. Johnstone, P.A., *et al*. Radical prostatectomy for clinical T4 prostate cancer. Cancer, 2006. 106: 2603.
https://pubmed.ncbi.nlm.nih.gov/16700037/

868. Marra, G., *et al*. Management of Patients with Node-positive Prostate Cancer at Radical Prostatectomy and Pelvic Lymph Node Dissection: A Systematic Review. Eur Urol Oncol, 2020. 3: 565.
https://pubmed.ncbi.nlm.nih.gov/32933887/

869. Roach, M., *et al*. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol, 2018. 19: 1504.
https://pubmed.ncbi.nlm.nih.gov/30316827/

870. Murthy, V., *et al*. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. J Clin Oncol, 2021. 39: 1234.
https://pubmed.ncbi.nlm.nih.gov/33497252/

871. Murthy, V., *et al*. Late toxicity and quality of life with prostate only or whole pelvic radiation therapy in high risk prostate cancer (POP-RT): A randomised trial. Radiother Oncol, 2020. 145: 71.
https://pubmed.ncbi.nlm.nih.gov/31923712/

872. Studer, U.E., *et al*. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol, 2006. 24: 1868.
https://pubmed.ncbi.nlm.nih.gov/16622261/

873. Moris, L., *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.
https://pubmed.ncbi.nlm.nih.gov/32146018/

874. Gongora, M., *et al*. Characteristics of Patients in SPCG-15-A Randomized Trial Comparing Radical Prostatectomy with Primary Radiotherapy plus Androgen Deprivation Therapy in Men with Locally Advanced Prostate Cancer. Eur Urol Open Sci, 2022. 41: 63.
https://pubmed.ncbi.nlm.nih.gov/35813256/

875. Yossepowitch, O., *et al*. Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. J Urol, 2007. 178: 493.
https://pubmed.ncbi.nlm.nih.gov/17561152/

876. Bastian, P.J., *et al*. Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10. Cancer, 2006. 107: 1265.
https://pubmed.ncbi.nlm.nih.gov/16900523/

877. Surgery Versus Radiotherapy for Locally Advanced Prostate Cancer (SPCG-15). ClinicalTrials: NCT02102477. 2014. Access date December 2022.
https://clinicaltrials.gov/ct2/show/NCT02102477

878. Chang, K., *et al*. Comparison of two adjuvant hormone therapy regimens in patients with high-risk localized prostate cancer after radical prostatectomy: primary results of study CU1005. Asian J Androl, 2016. 18: 452.
https://pubmed.ncbi.nlm.nih.gov/26323560/

879. 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.
https://pubmed.ncbi.nlm.nih.gov/20875089/

880. 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.
https://pubmed.ncbi.nlm.nih.gov/20299147/

881. Zwergel, U., *et al*. Outcome of prostate cancer patients with initial PSA> or =20 ng/ml undergoing radical prostatectomy. Eur Urol, 2007. 52: 1058.
https://pubmed.ncbi.nlm.nih.gov/17418938/

882. Magheli, A., *et al*. Importance of tumor location in patients with high preoperative prostate specific antigen levels (greater than 20 ng/ml) treated with radical prostatectomy. J Urol, 2007. 178: 1311.
https://pubmed.ncbi.nlm.nih.gov/17698095/

883.   Ward, J.F., *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.
https://pubmed.ncbi.nlm.nih.gov/15794776/

884.   Ventimiglia, E., *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.
https://pubmed.ncbi.nlm.nih.gov/31200844/

885.   Tward, J.D., *et al*. Radiation therapy for clinically node-positive prostate adenocarcinoma is correlated with improved overall and prostate cancer-specific survival. Pract Radiat Oncol, 2013. 3: 234.
https://pubmed.ncbi.nlm.nih.gov/24674370/

886.   Lin, C.C., *et al*. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. J Natl Cancer Inst, 2015. 107: djv119.
https://pubmed.ncbi.nlm.nih.gov/25957435/

887.   Seisen, T., *et al*. Efficacy of Local Treatment in Prostate Cancer Patients with Clinically Pelvic Lymph Node-positive Disease at Initial Diagnosis. Eur Urol, 2017. 73: 452.
https://pubmed.ncbi.nlm.nih.gov/28890245/

888.   James, N.D., *et al*. Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer: Data From Patients in the Control Arm of the STAMPEDE Trial. JAMA Oncol, 2016. 2: 348.
https://pubmed.ncbi.nlm.nih.gov/26606329/

889.   Rusthoven, C.G., *et al*. The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. Int J Radiat Oncol Biol Phys, 2014. 88: 1064.
https://pubmed.ncbi.nlm.nih.gov/24661660/

890.   Moschini, M., *et al*. Outcomes for Patients with Clinical Lymphadenopathy Treated with Radical Prostatectomy. Eur Urol, 2016. 69: 193.
https://pubmed.ncbi.nlm.nih.gov/26264160/

891.   Fischer-Valuck, B.W., *et al*. Overall survival comparison between androgen deprivation therapy (ADT) plus external beam radiation therapy (EBRT) vs ADT plus EBRT with brachytherapy boost in clinically node-positive prostate cancer. Brachytherapy, 2020. 19: 557.
https://pubmed.ncbi.nlm.nih.gov/32624405/

892.   James, N.D., *et al*. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med, 2017. 377: 338.
https://pubmed.ncbi.nlm.nih.gov/28578639/

893.   Fizazi, K., *et al*. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol, 2015. 16: 787.
https://pubmed.ncbi.nlm.nih.gov/26028518/

894.   Vale, C.L., *et al*. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol, 2016. 17: 243.
https://pubmed.ncbi.nlm.nih.gov/26718929/

895.   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.
https://pubmed.ncbi.nlm.nih.gov/34953525/

896.   Bryant, A.K., *et al*. Definitive Radiation Therapy and Survival in Clinically Node-Positive Prostate Cancer. Int J Radiat Oncol Biol Phys, 2018. 101: 1188.
https://pubmed.ncbi.nlm.nih.gov/29891203/

897.   Sarkar, R.R., *et al*. Association between Radical Prostatectomy and Survival in Men with Clinically Node-positive Prostate Cancer. Eur Urol Oncol, 2019. 2: 584.
https://pubmed.ncbi.nlm.nih.gov/31411995/

898.   Würnschimmel, C., *et al*. Radical prostatectomy for localized prostate cancer: 20-year oncological outcomes from a German high-volume center. Urol Oncol, 2021. 39: 830.e17.
https://pubmed.ncbi.nlm.nih.gov/34092484/

899.   Bader, P., *et al*. Is a limited lymph node dissection an adequate staging procedure for prostate cancer? J Urol, 2002. 168: 514.
https://pubmed.ncbi.nlm.nih.gov/12131300/

900. Briganti, A., *et al*. Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol, 2009. 55: 261.
https://pubmed.ncbi.nlm.nih.gov/18838212/

901. Schumacher, M.C., *et al*. Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. Eur Urol, 2008. 54: 344.
https://pubmed.ncbi.nlm.nih.gov/18511183/

902. Abdollah, F., *et al*. More extensive pelvic lymph node dissection improves survival in patients with node-positive prostate cancer. Eur Urol, 2015. 67: 212.
https://pubmed.ncbi.nlm.nih.gov/24882672/

903. Pound, C.R., *et al*. Natural history of progression after PSA elevation following radical prostatectomy. JAMA, 1999. 281: 1591.
https://pubmed.ncbi.nlm.nih.gov/10235151/

904. Aus, G., *et al*. Prognostic factors and survival in node-positive (N1) prostate cancer-a prospective study based on data from a Swedish population-based cohort. Eur Urol, 2003. 43: 627.
https://pubmed.ncbi.nlm.nih.gov/12767363/

905. Cheng, L., *et al*. Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer, 2001. 91: 66.
https://pubmed.ncbi.nlm.nih.gov/11148561/

906. Seiler, R., *et al*. Removal of limited nodal disease in patients undergoing radical prostatectomy: long-term results confirm a chance for cure. J Urol, 2014. 191: 1280.
https://pubmed.ncbi.nlm.nih.gov/24262495/

907. Passoni, N.M., *et al*. Prognosis of patients with pelvic lymph node (LN) metastasis after radical prostatectomy: value of extranodal extension and size of the largest LN metastasis. BJU Int, 2014. 114: 503.
https://pubmed.ncbi.nlm.nih.gov/24053552/

908. Daneshmand, S., *et al*. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol, 2004. 172: 2252.
https://pubmed.ncbi.nlm.nih.gov/15538242/

909. Touijer, K.A., *et al*. Long-term outcome of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. Eur Urol, 2014. 65: 20.
https://pubmed.ncbi.nlm.nih.gov/23619390/

910. Spratt, D.E., *et al*. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. J Clin Oncol, 2017. 35: 1991.
https://pubmed.ncbi.nlm.nih.gov/28358655/

911. Jairath, N.K., *et al*. A Systematic Review of the Evidence for the Decipher Genomic Classifier in Prostate Cancer. Eur Urol, 2021. 79: 374.
https://pubmed.ncbi.nlm.nih.gov/33293078/

912. Wiegel, T., *et al*. Adjuvant Radiotherapy Versus Wait-and-See After Radical Prostatectomy: 10-year Follow-up of the ARO 96-02/AUO AP 09/95 Trial. Eur Urol, 2014. 66: 243.
https://pubmed.ncbi.nlm.nih.gov/24680359/

913. Thompson, I.M., *et al*. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol, 2009. 181: 956.
https://pubmed.ncbi.nlm.nih.gov/19167731/

914. Bolla, M., *et al*. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet, 2012. 380: 2018.
https://pubmed.ncbi.nlm.nih.gov/23084481/

915. Hackman, G., *et al*. Randomised Trial of Adjuvant Radiotherapy Following Radical Prostatectomy Versus Radical Prostatectomy Alone in Prostate Cancer Patients with Positive Margins or Extracapsular Extension. Eur Urol, 2019. 76: 586.
https://pubmed.ncbi.nlm.nih.gov/31375279/

916. Fossati, N., *et al*. Long-term Impact of Adjuvant Versus Early Salvage Radiation Therapy in pT3N0 Prostate Cancer Patients Treated with Radical Prostatectomy: Results from a Multi-institutional Series. Eur Urol, 2017. 71: 886.
https://pubmed.ncbi.nlm.nih.gov/27484843/

917. Buscariollo, D.L., *et al*. Long-term results of adjuvant versus early salvage postprostatectomy radiation: A large single-institutional experience. Pract Radiat Oncol, 2017. 7: e125.
https://pubmed.ncbi.nlm.nih.gov/28274403/

918. Hwang, W.L., *et al*. Comparison Between Adjuvant and Early-Salvage Postprostatectomy Radiotherapy for Prostate Cancer With Adverse Pathological Features. JAMA Oncol, 2018. 4: e175230.
https://pubmed.ncbi.nlm.nih.gov/29372236/

919. Parker, C.C., *et al*. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet, 2020. 396: 1413.
https://pubmed.ncbi.nlm.nih.gov/33002429/

920. Kneebone, A., *et al*. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol, 2020. 21: 1331.
https://pubmed.ncbi.nlm.nih.gov/33002437/

921. Sargos, P., *et al*. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. Lancet Oncol, 2020. 21: 1341.
https://pubmed.ncbi.nlm.nih.gov/33002438/

922. Vale, C.L., *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.
https://pubmed.ncbi.nlm.nih.gov/33002431/

923. Tilki, D., *et al*. Timing of radiotherapy after radical prostatectomy. Lancet, 2020. 396: 1374.
https://pubmed.ncbi.nlm.nih.gov/33002430/

924. Ghadjar, P., *et al*. Postoperative radiotherapy in prostate cancer. Lancet, 2021. 397: 1623.
https://pubmed.ncbi.nlm.nih.gov/33933203/

925. Tilki, D., *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.
https://pubmed.ncbi.nlm.nih.gov/34086480/

926. Iversen, P., *et al*. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int, 2010. 105: 1074.
https://pubmed.ncbi.nlm.nih.gov/22129214/

927. Ahlgren, G.M., *et al*. Docetaxel Versus Surveillance After Radical Prostatectomy for High-risk Prostate Cancer: Results from the Prospective Randomised, Open-label Phase 3 Scandinavian Prostate Cancer Group 12 Trial. Eur Urol, 2018. 73: 870.
https://pubmed.ncbi.nlm.nih.gov/29395502/

928. Schweizer, M.T., *et al*. Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. Cancer, 2013. 119: 3610.
https://pubmed.ncbi.nlm.nih.gov/23943299/

929. Ghavamian, R., *et al*. Radical retropubic prostatectomy plus orchiectomy versus orchiectomy alone for pTxN+ prostate cancer: a matched comparison. J Urol, 1999. 161: 1223.
https://pubmed.ncbi.nlm.nih.gov/10081874/

930. Messing, E.M., *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.
https://pubmed.ncbi.nlm.nih.gov/16750497/

931. Abdollah, F., *et al*. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol, 2014. 32: 3939.
https://pubmed.ncbi.nlm.nih.gov/25245445/

932. Tilki, D., *et al*. Adjuvant Versus Early Salvage Radiation Therapy After Radical Prostatectomy for pN1 Prostate Cancer and the Risk of Death. J Clin Oncol, 2022. 40: 2186.
https://pubmed.ncbi.nlm.nih.gov/35290082/

933. Abdollah, F., *et al*. Impact of Adjuvant Radiotherapy in Node-positive Prostate Cancer Patients: The Importance of Patient Selection. Eur Urol, 2018. 74: 253.
https://pubmed.ncbi.nlm.nih.gov/29720348/

934. Gupta, M., *et al*. Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. BJU Int, 2019. 123: 252.
https://pubmed.ncbi.nlm.nih.gov/29626845/

935. Tilki, D., *et al*. Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. BJU Int, 2017. 119: 717.
https://pubmed.ncbi.nlm.nih.gov/27743493/

936. Mandel, P., *et al*. Long-term oncological outcomes in patients with limited nodal disease undergoing radical prostatectomy and pelvic lymph node dissection without adjuvant treatment. World J Urol, 2017. 35: 1833.
https://pubmed.ncbi.nlm.nih.gov/28828530/

937. Kimura, S., *et al*. Prognostic Significance of Prostate-Specific Antigen Persistence after Radical Prostatectomy: A Systematic Review and Meta-Analysis. Cancers (Basel), 2021. 13: 948.
https://pubmed.ncbi.nlm.nih.gov/33668270/

938. Ploussard, G., *et al*. Management of Persistently Elevated Prostate-specific Antigen After Radical Prostatectomy: A Systematic Review of the Literature. Eur Urol Oncol, 2021. 4: 150.
https://pubmed.ncbi.nlm.nih.gov/33574012/

939. Moreira, D.M., *et al*. Natural history of persistently elevated prostate specific antigen after radical prostatectomy: results from the SEARCH database. J Urol, 2009. 182: 2250.
https://pubmed.ncbi.nlm.nih.gov/19758614/

940. Moreira, D.M., *et al*. Definition and preoperative predictors of persistently elevated prostate-specific antigen after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. BJU Int, 2010. 105: 1541.
https://pubmed.ncbi.nlm.nih.gov/19912191/

941. Spratt, D.E., *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.
https://pubmed.ncbi.nlm.nih.gov/29233664/

942. Preisser, F., *et al*. Persistent Prostate-Specific Antigen After Radical Prostatectomy and Its Impact on Oncologic Outcomes. Eur Urol, 2019. 76: 106.
https://pubmed.ncbi.nlm.nih.gov/30772034/

943. Xiang, C., *et al*. Prediction of Biochemical Recurrence Following Radiotherapy among Patients with Persistent PSA after Radical Prostatectomy: A Single-Center Experience. Urol Int, 2018. 101: 47.
https://pubmed.ncbi.nlm.nih.gov/29627830/

944. Rogers, C.G., *et al*. Natural history of disease progression in patients who fail to achieve an undetectable prostate-specific antigen level after undergoing radical prostatectomy. Cancer, 2004. 101: 2549.
https://pubmed.ncbi.nlm.nih.gov/15470681/

945. Perera, M., *et al*. Sensitivity, Specificity, and Predictors of Positive 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol, 2016. 70: 926.
https://pubmed.ncbi.nlm.nih.gov/27363387/

946. Farolfi, A., *et al*. (68)Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA <0.5 ng/ml. Efficacy and impact on treatment strategy. Eur J Nucl Med Mol Imaging, 2019. 46: 11.
https://pubmed.ncbi.nlm.nih.gov/29905907/

947. Ceci, F., *et al*. (68)Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy. Eur J Nucl Med Mol Imaging, 2019. 46: 31.
https://pubmed.ncbi.nlm.nih.gov/30350010/

948. Rauscher, I., *et al*. Efficacy, Predictive Factors, and Prediction Nomograms for (68)Ga-labeled Prostate-specific Membrane Antigen-ligand Positron-emission Tomography/Computed Tomography in Early Biochemical Recurrent Prostate Cancer After Radical Prostatectomy. Eur Urol, 2018. 73: 656.
https://pubmed.ncbi.nlm.nih.gov/29358059/

949. Wondergem, M., *et al*. Early lesion detection with (18)F-DCFPyL PET/CT in 248 patients with biochemically recurrent prostate cancer. Eur J Nucl Med Mol Imaging, 2019. 46: 1911.
https://pubmed.ncbi.nlm.nih.gov/31230088/

950. Mena, E., *et al*. Clinical impact of PSMA-based (18)F-DCFBC PET/CT imaging in patients with biochemically recurrent prostate cancer after primary local therapy. Eur J Nucl Med Mol Imaging, 2018. 45: 4.
https://pubmed.ncbi.nlm.nih.gov/28894899/

951. Habl, G., *et al*. (68) Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: Individualized medicine or new standard in salvage treatment. Prostate, 2017. 77: 920.
https://pubmed.ncbi.nlm.nih.gov/28317152/

952. Schmidt-Hegemann, N.S., *et al*. Outcome after PSMA PET/CT based radiotherapy in patients with biochemical persistence or recurrence after radical prostatectomy. Radiat Oncol, 2018. 13: 37.
https://pubmed.ncbi.nlm.nih.gov/29499730/

953. Farolfi, A., *et al*. (68)Ga-PSMA-11 Positron Emission Tomography Detects Residual Prostate Cancer after Prostatectomy in a Multicenter Retrospective Study. J Urol, 2019. 202: 1174.
https://pubmed.ncbi.nlm.nih.gov/31233369/

954. Meijer, D., *et al*. Biochemical Persistence of Prostate-Specific Antigen After Robot-Assisted Laparoscopic Radical Prostatectomy: Tumor Localizations Using PSMA PET/CT Imaging. J Nucl Med, 2021. 62: 961.
https://pubmed.ncbi.nlm.nih.gov/33158904/

955. Bartkowiak, D., *et al*. The impact of prostate-specific antigen persistence after radical prostatectomy on the efficacy of salvage radiotherapy in patients with primary N0 prostate cancer. BJU Int, 2019. 124: 785.
https://pubmed.ncbi.nlm.nih.gov/31220400/

956. Wiegel, T., *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.
https://pubmed.ncbi.nlm.nih.gov/25445556/

957. Choo, R., *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.
https://pubmed.ncbi.nlm.nih.gov/19211197/

958. Gandaglia, G., *et al*. Impact of Postoperative Radiotherapy in Men with Persistently Elevated Prostate-specific Antigen After Radical Prostatectomy for Prostate Cancer: A Long-term Survival Analysis. Eur Urol, 2017. 72: 910.
https://pubmed.ncbi.nlm.nih.gov/28622831/

959. Garcia-Barreras, S., *et al*. Predictive factors and the important role of detectable prostate-specific antigen for detection of clinical recurrence and cancer-specific mortality following robot-assisted radical prostatectomy. Clin Transl Oncol, 2018. 20: 1004.
https://pubmed.ncbi.nlm.nih.gov/29243074/

960. Lohm, G., *et al*. Salvage radiotherapy in patients with persistently detectable PSA or PSA rising from an undetectable range after radical prostatectomy gives comparable results. World J Urol, 2013. 31: 423.
https://pubmed.ncbi.nlm.nih.gov/22460203/

961. Ploussard, G., *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.
https://pubmed.ncbi.nlm.nih.gov/24270970/

962. Fossati, N., *et al*. Impact of Early Salvage Radiation Therapy in Patients with Persistently Elevated or Rising Prostate-specific Antigen After Radical Prostatectomy. Eur Urol, 2018. 73: 436.
https://pubmed.ncbi.nlm.nih.gov/28779974/

963. Guerif, S.G., *et al*. The acute toxicity results of the GETUG-AFU 22 study: A multicenter randomized phase II trial comparing the efficacy of a short hormone therapy in combination with radiotherapy to radiotherapy alone as a salvage treatment for patients with detectable PSA after radical prostatectomy. J Clin Oncol, 2017. 35: 16.
https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.6_suppl.16

964. Arlen, P.M., *et al*. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. J Urol, 2008. 179: 2181.
https://pubmed.ncbi.nlm.nih.gov/18423743/

965. Vickers, A.J., *et al*. PSA Velocity and Doubling Time in Diagnosis and Prognosis of Prostate Cancer. Br J Med Surg Urol, 2012. 5: 162.
https://pubmed.ncbi.nlm.nih.gov/22712027/

966. O'Brien, M.F., *et al*. Pretreatment prostate-specific antigen (PSA) velocity and doubling time are associated with outcome but neither improves prediction of outcome beyond pretreatment PSA alone in patients treated with radical prostatectomy. J Clin Oncol, 2009. 27: 3591.
https://pubmed.ncbi.nlm.nih.gov/19506163/

967.   Heidenreich, A. Identification of high-risk prostate cancer: role of prostate-specific antigen, PSA doubling time, and PSA velocity. Eur Urol, 2008. 54: 976.
https://pubmed.ncbi.nlm.nih.gov/18640768/

968.   Ramirez, M.L., *et al*. Current applications for prostate-specific antigen doubling time. Eur Urol, 2008. 54: 291.
https://pubmed.ncbi.nlm.nih.gov/18439749/

969.   Vickers, A.J., *et al*. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. J Clin Oncol, 2009. 27: 398.
https://pubmed.ncbi.nlm.nih.gov/19064972/

970.   Lee, A.K., *et al*. Utility of prostate-specific antigen kinetics in addition to clinical factors in the selection of patients for salvage local therapy. J Clin Oncol, 2005. 23: 8192.
https://pubmed.ncbi.nlm.nih.gov/16278472/

971.   Campbell, S.R., *et al*. Integrating Prostate-specific Antigen Kinetics into Contemporary Predictive Nomograms of Salvage Radiotherapy After Radical Prostatectomy. Eur Urol Oncol, 2022. 5: 304.
https://pubmed.ncbi.nlm.nih.gov/34016556/

972.   Smith, M.R., *et al*. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol, 2005. 23: 2918.
https://pubmed.ncbi.nlm.nih.gov/15860850/

973.   Amling, C.L., *et al*. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol, 2001. 165: 1146.
https://pubmed.ncbi.nlm.nih.gov/11257657/

974.   Toussi, A., *et al*. Standardizing the Definition of Biochemical Recurrence after Radical Prostatectomy-What Prostate Specific Antigen Cut Point Best Predicts a Durable Increase and Subsequent Systemic Progression? J Urol, 2016. 195: 1754.
https://pubmed.ncbi.nlm.nih.gov/26721226/

975.   Stephenson, A.J., *et al*. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol, 2006. 24: 3973.
https://pubmed.ncbi.nlm.nih.gov/16921049/

976.   Roach, M., 3rd, *et al*. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys, 2006. 65: 965.
https://pubmed.ncbi.nlm.nih.gov/16798415/

977.   Van den Broeck, T., *et al*. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol, 2019. 75: 967.
https://pubmed.ncbi.nlm.nih.gov/30342843/

978.   Jackson, W.C., *et al*. Intermediate Endpoints After Postprostatectomy Radiotherapy: 5-Year Distant Metastasis to Predict Overall Survival. Eur Urol, 2018. 74: 413.
https://pubmed.ncbi.nlm.nih.gov/29306514/

979.   Choueiri, T.K., *et al*. Impact of postoperative prostate-specific antigen disease recurrence and the use of salvage therapy on the risk of death. Cancer, 2010. 116: 1887.
https://pubmed.ncbi.nlm.nih.gov/20162710/

980.   Freiberger, C., *et al*. Long-term prognostic significance of rising PSA levels following radiotherapy for localized prostate cancer - focus on overall survival. Radiat Oncol, 2017. 12: 98.
https://pubmed.ncbi.nlm.nih.gov/28615058/

981.   Royce, T.J., *et al*. Surrogate End Points for All-Cause Mortality in Men With Localized Unfavorable-Risk Prostate Cancer Treated With Radiation Therapy vs Radiation Therapy Plus Androgen Deprivation Therapy: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol, 2017. 3: 652.
https://pubmed.ncbi.nlm.nih.gov/28097317/

982.   Tilki, D., *et al*. External Validation of the European Association of Urology Biochemical Recurrence Risk Groups to Predict Metastasis and Mortality After Radical Prostatectomy in a European Cohort. Eur Urol, 2019. 75: 896.
https://pubmed.ncbi.nlm.nih.gov/30955970/

983.   Zagars, G.K., *et al*. Kinetics of serum prostate-specific antigen after external beam radiation for clinically localized prostate cancer. Radiother Oncol, 1997. 44: 213.
https://pubmed.ncbi.nlm.nih.gov/9380819/

984.   Rouviere, O., *et al*. Imaging of prostate cancer local recurrences: why and how? Eur Radiol, 2010. 20: 1254.
https://pubmed.ncbi.nlm.nih.gov/19921202/

985. Beresford, M.J., et al. A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. Clin Oncol (R Coll Radiol), 2010. 22: 46.
https://pubmed.ncbi.nlm.nih.gov/19948393/

986. Gomez, P., et al. Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int, 2004. 94: 299.
https://pubmed.ncbi.nlm.nih.gov/15291855/

987. Kane, C.J., et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology, 2003. 61: 607.
https://pubmed.ncbi.nlm.nih.gov/12639656/

988. Evangelista, L., et al. Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. Clin Nucl Med, 2013. 38: 305.
https://pubmed.ncbi.nlm.nih.gov/23486334/

989. Fanti, S., et al. PET/CT with (11)C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. Eur J Nucl Med Mol Imaging, 2016. 43: 55.
https://pubmed.ncbi.nlm.nih.gov/26450693/

990. Fuccio, C., et al. Role of 11C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. Ann Nucl Med, 2010. 24: 485.
https://pubmed.ncbi.nlm.nih.gov/20544323/

991. Fuccio, C., et al. Role of 11C-choline PET/CT in the re-staging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy. Eur J Radiol, 2012. 81: e893.
https://pubmed.ncbi.nlm.nih.gov/22621862/

992. Treglia, G., et al. Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: a meta-analysis. Clin Chem Lab Med, 2014. 52: 725.
https://pubmed.ncbi.nlm.nih.gov/24310773/

993. Castellucci, P., et al. Early Biochemical Relapse After Radical Prostatectomy: Which Prostate Cancer Patients May Benefit from a Restaging 11C-Choline PET/CT Scan Before Salvage Radiation Therapy? J Nucl Med, 2014. 55: 1424.
https://pubmed.ncbi.nlm.nih.gov/24935990/

994. Mitchell, C.R., et al. Operational characteristics of (11)c-choline positron emission tomography/ computerized tomography for prostate cancer with biochemical recurrence after initial treatment. J Urol, 2013. 189: 1308.
https://pubmed.ncbi.nlm.nih.gov/23123372/

995. Soyka, J.D., et al. Clinical impact of 18F-choline PET/CT in patients with recurrent prostate cancer. Eur J Nucl Med Mol Imaging, 2012. 39: 936.
https://pubmed.ncbi.nlm.nih.gov/22415598/

996. Ceci, F., et al. Impact of 11C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. Eur J Nucl Med Mol Imaging, 2014. 41: 2222.
https://pubmed.ncbi.nlm.nih.gov/25182750/

997. Beer, A.J., et al. Radionuclide and hybrid imaging of recurrent prostate cancer. Lancet Oncol, 2011. 12: 181.
https://pubmed.ncbi.nlm.nih.gov/20599424/

999. Beheshti, M., et al. Detection of bone metastases in patients with prostate cancer by 18F fluorocholine and 18F fluoride PET-CT: a comparative study. Eur J Nucl Med Mol Imaging, 2008. 35: 1766.
https://pubmed.ncbi.nlm.nih.gov/18465129/

999. Songmen, S., et al. Axumin Positron Emission Tomography: Novel Agent for Prostate Cancer Biochemical Recurrence. J Clin Imaging Sci, 2019. 9: 49.
https://pubmed.ncbi.nlm.nih.gov/31819826/

1000. U.S. Food & Drug Adminstration. FDA approves new diagnostic imaging agent to detect recurrent prostate cancer - axumin. 2016. Access date December 2022.
https://www.fda.gov/news-events/press-announcements/fda-approves-new-diagnostic-imaging-agent-detect-recurrent-prostate-cancer

1001. European Medicine Agency. Axumin 2017. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/axumin

1002. Nanni, C., et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging, 2016. 43: 1601.
https://pubmed.ncbi.nlm.nih.gov/26960562/

1003. Bach-Gansmo, T., *et al*. Multisite Experience of the Safety, Detection Rate and Diagnostic Performance of Fluciclovine ((18)F) Positron Emission Tomography/Computerized Tomography Imaging in the Staging of Biochemically Recurrent Prostate Cancer. J Urol, 2017. 197: 676.
https://pubmed.ncbi.nlm.nih.gov/27746282/

1004. Abiodun-Ojo, O.A., *et al*. Salvage Radiotherapy Management Decisions in Postprostatectomy Patients with Recurrent Prostate Cancer Based on (18)F-Fluciclovine PET/CT Guidance. J Nucl Med, 2021. 62: 1089.
https://pubmed.ncbi.nlm.nih.gov/33517323/

1005. Morigi, J.J., *et al*. Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med, 2015. 56: 1185.
https://pubmed.ncbi.nlm.nih.gov/26112024/

1006. Afshar-Oromieh, A., *et al*. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging, 2014. 41: 11.
https://pubmed.ncbi.nlm.nih.gov/24072344/

1007. Caroli, P., *et al*. (68)Ga-PSMA PET/CT in patients with recurrent prostate cancer after radical treatment: prospective results in 314 patients. Eur J Nucl Med Mol Imaging, 2018. 45: 2035.
https://pubmed.ncbi.nlm.nih.gov/29922948/

1008. Fendler, W.P., *et al*. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncol, 2019. 5: 856.
https://pubmed.ncbi.nlm.nih.gov/30920593/

1009. Morris, M.J., *et al*. Diagnostic Performance of (18)F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res, 2021. 27: 3674.
https://pubmed.ncbi.nlm.nih.gov/33622706/

1010. Giesel, F.L., *et al*. Intraindividual Comparison of (18)F-PSMA-1007 and (18)F-DCFPyL PET/CT in the Prospective Evaluation of Patients with Newly Diagnosed Prostate Carcinoma: A Pilot Study. J Nucl Med, 2018. 59: 1076.
https://pubmed.ncbi.nlm.nih.gov/29269569/

1011. Eiber, M., *et al*. Whole-body MRI including diffusion-weighted imaging (DWI) for patients with recurring prostate cancer: technical feasibility and assessment of lesion conspicuity in DWI. J Magn Reson Imaging, 2011. 33: 1160.
https://pubmed.ncbi.nlm.nih.gov/21509875/

1012. Zacho, H.D., *et al*. Prospective comparison of (68)Ga-PSMA PET/CT, (18)F-sodium fluoride PET/CT and diffusion weighted-MRI at for the detection of bone metastases in biochemically recurrent prostate cancer. Eur J Nucl Med Mol Imaging, 2018. 45: 1884.
https://pubmed.ncbi.nlm.nih.gov/29876619/

1013. Renard-Penna, R., *et al*. Targeting Local Recurrence After Surgery With MRI Imaging for Prostate Cancer in the Setting of Salvage Radiation Therapy. Front Oncol, 2022. 12: 775387.
https://pubmed.ncbi.nlm.nih.gov/35242702/

1014. Song, W., *et al*. Prognostic factors after salvage radiotherapy alone in patients with biochemical recurrence after radical prostatectomy. Int J Urol, 2016. 23: 56.
https://pubmed.ncbi.nlm.nih.gov/26502086/

1015. Sharma, V., *et al*. Multiparametric Magnetic Resonance Imaging Is an Independent Predictor of Salvage Radiotherapy Outcomes After Radical Prostatectomy. Eur Urol, 2018. 73: 879.
https://pubmed.ncbi.nlm.nih.gov/29195777/

1016. Achard, V., *et al*. Recurrent prostate cancer after radical prostatectomy: restaging performance of 18F-choline hybrid PET/MRI. Med Oncol, 2019. 36: 67.
https://pubmed.ncbi.nlm.nih.gov/31190232/

1017. Luiting, H.B., *et al*. Use of gallium-68 prostate-specific membrane antigen positron-emission tomography for detecting lymph node metastases in primary and recurrent prostate cancer and location of recurrence after radical prostatectomy: an overview of the current literature. BJU Int, 2020. 125: 206.
https://pubmed.ncbi.nlm.nih.gov/31680398/

1018. Boreta, L., *et al*. Location of Recurrence by Gallium-68 PSMA-11 PET Scan in Prostate Cancer Patients Eligible for Salvage Radiotherapy. Urology, 2019. 129: 165.
https://pubmed.ncbi.nlm.nih.gov/30928607/

1019. Guberina, N., *et al*. Whole-Body Integrated [(68)Ga]PSMA-11-PET/MR Imaging in Patients with Recurrent Prostate Cancer: Comparison with Whole-Body PET/CT as the Standard of Reference. Mol Imaging Biol, 2020. 22: 788.
https://pubmed.ncbi.nlm.nih.gov/31482413/

1020. Metser, U., *et al*. The Contribution of Multiparametric Pelvic and Whole-Body MRI to Interpretation of (18)F-Fluoromethylcholine or (68)Ga-HBED-CC PSMA-11 PET/CT in Patients with Biochemical Failure After Radical Prostatectomy. J Nucl Med, 2019. 60: 1253.
https://pubmed.ncbi.nlm.nih.gov/30902875/

1021. Freitag, M.T., *et al*. Local recurrence of prostate cancer after radical prostatectomy is at risk to be missed in (68)Ga-PSMA-11-PET of PET/CT and PET/MRI: comparison with mpMRI integrated in simultaneous PET/MRI. Eur J Nucl Med Mol Imaging, 2017. 44: 776.
https://pubmed.ncbi.nlm.nih.gov/27988802/

1022. Jani, A.B., *et al*. (18)F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. Lancet, 2021. 397: 1895.
https://pubmed.ncbi.nlm.nih.gov/33971152/

1023. Donati, O.F., *et al*. Multiparametric prostate MR imaging with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? Radiology, 2013. 268: 440.
https://pubmed.ncbi.nlm.nih.gov/23481164/

1024. Abd-Alazeez, M., *et al*. Multiparametric MRI for detection of radiorecurrent prostate cancer: added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. Prostate Cancer Prostatic Dis, 2015. 18: 128.
https://pubmed.ncbi.nlm.nih.gov/25644248/

1025. Alonzo, F., *et al*. Detection of locally radio-recurrent prostate cancer at multiparametric MRI: Can dynamic contrast-enhanced imaging be omitted? Diagn Interv Imaging, 2016. 97: 433.
https://pubmed.ncbi.nlm.nih.gov/26928245/

1026. Dinis Fernandes, C., *et al*. Quantitative 3T multiparametric MRI of benign and malignant prostatic tissue in patients with and without local recurrent prostate cancer after external-beam radiation therapy. J Magn Reson Imaging, 2019. 50: 269.
https://pubmed.ncbi.nlm.nih.gov/30585368/

1027. Dinis Fernandes, C., *et al*. Quantitative 3-T multi-parametric MRI and step-section pathology of recurrent prostate cancer patients after radiation therapy. Eur Radiol, 2019. 29: 4160.
https://pubmed.ncbi.nlm.nih.gov/30421016/

1028. Rasing, M., *et al*. Value of Targeted Biopsies and Combined PSMA PET/CT and mp-MRI Imaging in Locally Recurrent Prostate Cancer after Primary Radiotherapy. Cancers (Basel), 2022. 14: 781.
https://pubmed.ncbi.nlm.nih.gov/35159048/

1029. Boorjian, S.A., *et al*. Radiation therapy after radical prostatectomy: impact on metastasis and survival. J Urol, 2009. 182: 2708.
https://pubmed.ncbi.nlm.nih.gov/19836762/

1030. Kneebone, A., *et al*. A Phase III Multi-Centre Randomised Trial comparing adjuvant versus early salvage Radiotherapy following a Radical Prostatectomy: Results of the TROG 08.03 and ANZUP "RAVES" Trial. Int J Radiat Oncol Biol Phys, 2019. 105: S37.
https://www.redjournal.org/article/S0360-3016(19)31291-X/fulltext

1031. Stish, B.J., *et al*. Improved Metastasis-Free and Survival Outcomes With Early Salvage Radiotherapy in Men With Detectable Prostate-Specific Antigen After Prostatectomy for Prostate Cancer. J Clin Oncol, 2016. 34: 3864.
https://pubmed.ncbi.nlm.nih.gov/27480153/

1032. Pfister, D., *et al*. Early salvage radiotherapy following radical prostatectomy. Eur Urol, 2014. 65: 1034.
https://pubmed.ncbi.nlm.nih.gov/23972524/

1033. Siegmann, A., *et al*. Salvage radiotherapy after prostatectomy - what is the best time to treat? Radiother Oncol, 2012. 103: 239.
https://pubmed.ncbi.nlm.nih.gov/22119375/

1034. Ohri, N., *et al*. Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. Eur J Cancer, 2012. 48: 837.
https://pubmed.ncbi.nlm.nih.gov/21945099/

1035. Wiegel, T., *et al*. Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome--results of a retrospective study. Int J Radiat Oncol Biol Phys, 2009. 73: 1009.
https://pubmed.ncbi.nlm.nih.gov/18963539/

1036. Trock, B.J., *et al*. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA, 2008. 299: 2760.
https://pubmed.ncbi.nlm.nih.gov/18560003/

1037. Sweeney, C., *et al*. The Development of Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP). J Natl Cancer Inst, 2015. 107: djv261.
https://pubmed.ncbi.nlm.nih.gov/26409187/

1038. Xie, W., *et al*. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. J Clin Oncol, 2017. 35: 3097.
https://pubmed.ncbi.nlm.nih.gov/28796587/

1039. Bartkowiak, D., *et al*. Prostate-specific antigen after salvage radiotherapy for postprostatectomy biochemical recurrence predicts long-term outcome including overall survival. Acta Oncol, 2018. 57: 362.
https://pubmed.ncbi.nlm.nih.gov/28816074/

1040. Soto, D.E., *et al*. Concurrent androgen deprivation therapy during salvage prostate radiotherapy improves treatment outcomes in high-risk patients. Int J Radiat Oncol Biol Phys, 2012. 82: 1227.
https://pubmed.ncbi.nlm.nih.gov/21549519/

1041. Tendulkar, R.D., *et al*. Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy. J Clin Oncol, 2016. 34: 3648.
https://pubmed.ncbi.nlm.nih.gov/27528718/

1042. Jackson, W.C., *et al*. Combining prostate-specific antigen nadir and time to nadir allows for early identification of patients at highest risk for development of metastasis and death following salvage radiation therapy. Pract Radiat Oncol, 2014. 4: 99.
https://pubmed.ncbi.nlm.nih.gov/24890350/

1043. Shipley, W., *et al*. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. N Eng J Med, 2017. 376: 417.
https://www.nejm.org/doi/full/10.1056/NEJMoa1607529

1044. Carrie, C., *et al*. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol, 2019. 20: 1740.
https://pubmed.ncbi.nlm.nih.gov/31629656/

1045. Pollack, A., *et al*. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet, 2022. 399: 1886.
https://pubmed.ncbi.nlm.nih.gov/35569466/

1046. Ramey, S.J., *et al*. Multi-institutional Evaluation of Elective Nodal Irradiation and/or Androgen Deprivation Therapy with Postprostatectomy Salvage Radiotherapy for Prostate Cancer. Eur Urol, 2018. 74: 99.
https://pubmed.ncbi.nlm.nih.gov/29128208/

1047. Dess, R.T., *et al*. Association of Presalvage Radiotherapy PSA Levels After Prostatectomy With Outcomes of Long-term Antiandrogen Therapy in Men With Prostate Cancer. JAMA Oncol, 2020. 6: 735.
https://pubmed.ncbi.nlm.nih.gov/32215583/

1048. Spratt, D.E., *et al*. A Systematic Review and Framework for the Use of Hormone Therapy with Salvage Radiation Therapy for Recurrent Prostate Cancer. Eur Urol, 2018. 73: 156.
https://pubmed.ncbi.nlm.nih.gov/28716370/

1049. Michalski, J.M., *et al*. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys, 2010. 76: 361.
https://pubmed.ncbi.nlm.nih.gov/19394158/

1050. Malone, S., *et al*. Postoperative radiotherapy for prostate cancer: a comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy IMRT. Int J Radiat Oncol Biol Phys, 2012. 84: 725.
https://pubmed.ncbi.nlm.nih.gov/22444999/

1051. Robin, S., *et al*. Prostate Bed Delineation Guidelines for Postoperative Radiation Therapy: On Behalf Of The Francophone Group of Urological Radiation Therapy. Int J Radiat Oncol Biol Phys, 2021. 109: 1243.
https://pubmed.ncbi.nlm.nih.gov/33186618/

1052. Pisansky, T.M., *et al*. Salvage Radiation Therapy Dose Response for Biochemical Failure of Prostate Cancer After Prostatectomy-A Multi-Institutional Observational Study. Int J Radiat Oncol Biol Phys, 2016. 96: 1046.
https://pubmed.ncbi.nlm.nih.gov/27745980/

1053. King, C.R. The dose-response of salvage radiotherapy following radical prostatectomy: A systematic review and meta-analysis. Radiother Oncol, 2016. 121: 199.
https://pubmed.ncbi.nlm.nih.gov/27863963/

1054. Fossati, N., *et al*. Assessing the Optimal Timing for Early Salvage Radiation Therapy in Patients with Prostate-specific Antigen Rise After Radical Prostatectomy. Eur Urol, 2016. 69: 728.
https://pubmed.ncbi.nlm.nih.gov/26497924/

1055. Abugharib, A., *et al*. Very Early Salvage Radiotherapy Improves Distant Metastasis-Free Survival. J Urol, 2017. 197: 662.
https://pubmed.ncbi.nlm.nih.gov/27614333/

1056. Fiorino, C., *et al*. Predicting the 5-Year Risk of Biochemical Relapse After Postprostatectomy Radiation Therapy in >/=PT2, pN0 Patients With a Comprehensive Tumor Control Probability Model. Int J Radiat Oncol Biol Phys, 2016. 96: 333.
https://pubmed.ncbi.nlm.nih.gov/27497691/

1076. Qi, X., *et al*. Toxicity and Biochemical Outcomes of Dose-Intensified Postoperative Radiation Therapy for Prostate Cancer: Results of a Randomized Phase III Trial. Int J Radiat Oncol Biol Phys, 2020. 106: 282.
https://pubmed.ncbi.nlm.nih.gov/31669564/

1058. Ghadjar, P., *et al*. Acute Toxicity and Quality of Life After Dose-Intensified Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: First Results of the Randomized Trial SAKK 09/10. J Clin Oncol, 2015. 33: 4158.
https://pubmed.ncbi.nlm.nih.gov/26527774/

1059. Ghadjar, P., *et al*. Impact of dose intensified salvage radiation therapy on urinary continence recovery after radical prostatectomy: Results of the randomized trial SAKK 09/10. Radiother Oncol, 2018. 126: 257.
https://pubmed.ncbi.nlm.nih.gov/29103826/

1060. Goenka, A., *et al*. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. Eur Urol, 2011. 60: 1142.
https://pubmed.ncbi.nlm.nih.gov/21855208/

1061. Ost, P., *et al*. High-dose salvage intensity-modulated radiotherapy with or without androgen deprivation after radical prostatectomy for rising or persisting prostate-specific antigen: 5-year results. Eur Urol, 2011. 60: 842.
https://pubmed.ncbi.nlm.nih.gov/21514039/

1062. Roach, P.J., *et al*. The Impact of (68)Ga-PSMA PET/CT on Management Intent in Prostate Cancer: Results of an Australian Prospective Multicenter Study. J Nucl Med, 2018. 59: 82.
https://pubmed.ncbi.nlm.nih.gov/28646014/

1063. Emmett, L., *et al*. Treatment Outcomes from (68)Ga-PSMA PET/CT-Informed Salvage Radiation Treatment in Men with Rising PSA After Radical Prostatectomy: Prognostic Value of a Negative PSMA PET. J Nucl Med, 2017. 58: 1972.
https://pubmed.ncbi.nlm.nih.gov/28747524/

1064. Meijer, D., *et al*. Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Is Associated with Improved Oncological Outcome in Men Treated with Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer. Eur Urol Oncol, 2022. 5: 146.
https://pubmed.ncbi.nlm.nih.gov/35074282/

1065. Ghadjar, P., *et al*. Dose-intensified Versus Conventional-dose Salvage Radiotherapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: The SAKK 09/10 Randomized Phase 3 Trial. Eur Urol, 2021. 80: 306.
https://pubmed.ncbi.nlm.nih.gov/34140144/

1066. Steuber, T., *et al*. Standard of Care Versus Metastases-directed Therapy for PET-detected Nodal Oligorecurrent Prostate Cancer Following Multimodality Treatment: A Multi-institutional Case-control Study. Eur Urol Focus, 2019. 5: 1007.
https://pubmed.ncbi.nlm.nih.gov/29530632/

1067.   De Bleser, E., *et al*. Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. Eur Urol, 2019. 76: 732.
https://pubmed.ncbi.nlm.nih.gov/31331782/

1068.   Suardi, N., *et al*. Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. Eur Urol, 2015. 67: 299.
https://pubmed.ncbi.nlm.nih.gov/24571959/

1069.   Tilki, D., *et al*. Salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy. J Urol, 2015. 193: 484.
https://pubmed.ncbi.nlm.nih.gov/25180792/

1070.   Fossati, N., *et al*. Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis. Eur Urol, 2019. 75: 176.
https://pubmed.ncbi.nlm.nih.gov/30301694/

1071.   Ploussard, G., *et al*. Salvage Lymph Node Dissection for Nodal Recurrent Prostate Cancer: A Systematic Review. Eur Urol, 2019. 76: 493.
https://pubmed.ncbi.nlm.nih.gov/30391078/

1072.   Ost, P., *et al*. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. Eur Urol, 2015. 67: 852.
https://pubmed.ncbi.nlm.nih.gov/25240974/

1073.   Rischke, H.C., *et al*. Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only. Strahlenther Onkol, 2015. 191: 310.
https://pubmed.ncbi.nlm.nih.gov/25326142/

1074.   Bravi, C.A., *et al*. Long-term Outcomes of Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer After Radical Prostatectomy: Not as Good as Previously Thought. Eur Urol, 2020. 78: 661.
https://pubmed.ncbi.nlm.nih.gov/32624288/

1075.   Knipper, S., *et al*. Cohort Study of Oligorecurrent Prostate Cancer Patients: Oncological Outcomes of Patients Treated with Salvage Lymph Node Dissection via Prostate-specific Membrane Antigen-radioguided Surgery. Eur Urol, 2023. 83: 62.
https://pubmed.ncbi.nlm.nih.gov/35718637/

1076.   Valle, L.F., *et al*. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur Urol, 2021. 80: 280.
https://pubmed.ncbi.nlm.nih.gov/33309278/

1077.   Gontero, P., *et al*. Salvage Radical Prostatectomy for Recurrent Prostate Cancer: Morbidity and Functional Outcomes from a Large Multicenter Series of Open versus Robotic Approaches. J Urol, 2019. 202: 725.
https://pubmed.ncbi.nlm.nih.gov/31075058/

1078.   Chade, D.C., *et al*. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol, 2012. 61: 961.
https://pubmed.ncbi.nlm.nih.gov/22280856/

1079.   Marra, G., *et al*. Oncological outcomes of salvage radical prostatectomy for recurrent prostate cancer in the contemporary era: A multicenter retrospective study. Urol Oncol, 2021. 39: 296.e21.
https://pubmed.ncbi.nlm.nih.gov/33436329/

1080.   Chade, D.C., *et al*. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. Eur Urol, 2011. 60: 205.
https://pubmed.ncbi.nlm.nih.gov/21420229/

1081.   Mandel, P., *et al*. Salvage radical prostatectomy for recurrent prostate cancer: verification of European Association of Urology guideline criteria. BJU Int, 2016. 117: 55.
https://pubmed.ncbi.nlm.nih.gov/25711672/

1082.   Ogaya-Pinies, G., *et al*. Salvage robotic-assisted radical prostatectomy: oncologic and functional outcomes from two high-volume institutions. World J Urol, 2019. 37: 1499.
https://pubmed.ncbi.nlm.nih.gov/30006908/

1083.   Gotto, G.T., *et al*. Impact of prior prostate radiation on complications after radical prostatectomy. J Urol, 2010. 184: 136.
https://pubmed.ncbi.nlm.nih.gov/20478594/

1084. Ginsburg, K.B., *et al*. Avoidance of androgen deprivation therapy in radiorecurrent prostate cancer as a clinically meaningful endpoint for salvage cryoablation. Prostate, 2017. 77: 1446.
https://pubmed.ncbi.nlm.nih.gov/28856702/

1085. Spiess, P.E., *et al*. A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer. BJU Int, 2010. 106: 194.
https://pubmed.ncbi.nlm.nih.gov/19922545/

1086. Li, R., *et al*. The Effect of Androgen Deprivation Therapy Before Salvage Whole-gland Cryoablation After Primary Radiation Failure in Prostate Cancer Treatment. Urology, 2015. 85: 1137.
https://pubmed.ncbi.nlm.nih.gov/25799176/

1087. Kovac, E., *et al*. Five-Year Biochemical Progression-Free Survival Following Salvage Whole-Gland Prostate Cryoablation: Defining Success with Nadir Prostate-Specific Antigen. J Endourol, 2016. 30: 624.
https://pubmed.ncbi.nlm.nih.gov/26915721/

1088. Ahmad, I., *et al*. Prostate gland lengths and iceball dimensions predict micturition functional outcome following salvage prostate cryotherapy in men with radiation recurrent prostate cancer. PLoS One, 2013. 8: e69243.
https://pubmed.ncbi.nlm.nih.gov/23950886/

1089. Pisters, L.L., *et al*. Salvage prostate cryoablation: initial results from the cryo on-line data registry. J Urol, 2008. 180: 559.
https://pubmed.ncbi.nlm.nih.gov/18554664/

1090. Henríquez López, I., *et al*. Salvage brachytherapy for locally-recurrent prostate cancer after radiation therapy: A comparison of efficacy and toxicity outcomes with high-dose rate and low-dose rate brachytherapy. Radiother Oncol, 2019. 141: 156.
https://pubmed.ncbi.nlm.nih.gov/31570236/

1091. Crook, J.M., *et al*. A Prospective Phase 2 Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer After External Beam Radiation Therapy (NRG Oncology/ RTOG-0526). Int J Radiat Oncol Biol Phys, 2019. 103: 335.
https://pubmed.ncbi.nlm.nih.gov/30312717/

1092. Smith, W.H., *et al*. Salvage low dose rate brachytherapy for prostate cancer recurrence following definitive external beam radiation therapy. Radiother Oncol, 2021. 155: 42.
https://pubmed.ncbi.nlm.nih.gov/33075391/

1093. Łyczek, J., *et al*. HDR brachytherapy as a solution in recurrences of locally advanced prostate cancer. J Contemp Brachyther, 2009. 1: 105.
https://pubmed.ncbi.nlm.nih.gov/27795720/

1094. Pasquier, D., *et al*. Salvage Stereotactic Body Radiation Therapy for Local Prostate Cancer Recurrence After Radiation Therapy: A Retrospective Multicenter Study of the GETUG. Int J Radiat Oncol Biol Phys, 2019. 105: 727.
https://pubmed.ncbi.nlm.nih.gov/31344433/

1095. Fuller, D., *et al*. Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT. Int J Radiat Oncol Biol Phys, 2020. 106: 291.
https://pubmed.ncbi.nlm.nih.gov/31629838/

1096. Bergamin, S., *et al*. Interim Results of a Prospective Prostate-Specific Membrane Antigen-Directed Focal Stereotactic Reirradiation Trial for Locally Recurrent Prostate Cancer. Int J Radiat Oncol Biol Phys, 2020. 108: 1172.
https://pubmed.ncbi.nlm.nih.gov/32659332/

1097. Crouzet, S., *et al*. Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients. BJU Int, 2017. 119: 896.
https://pubmed.ncbi.nlm.nih.gov/28063191/

1098. Murat, F.J., *et al*. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol, 2009. 55: 640.
https://pubmed.ncbi.nlm.nih.gov/18508188/

1099. Kanthabalan, A., *et al*. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU Int, 2017. 120: 246.
https://pubmed.ncbi.nlm.nih.gov/28258616/

1000. Jones, T.A., *et al*. High Intensity Focused Ultrasound for Radiorecurrent Prostate Cancer: A North American Clinical Trial. J Urol, 2018. 199: 133.
https://pubmed.ncbi.nlm.nih.gov/28652121/

1101.   van den Bergh, R.C., *et al*. Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review. Eur Urol, 2016. 69: 802.
https://pubmed.ncbi.nlm.nih.gov/26691493/

1102.   Duchesne, G.M., *et al*. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol, 2016. 17: 727.
https://pubmed.ncbi.nlm.nih.gov/27155740/

1103.   Siddiqui, S.A., *et al*. Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: a matched cohort study. J Urol, 2008. 179: 1830.
https://pubmed.ncbi.nlm.nih.gov/18353378/

1104.   Boorjian, S.A., *et al*. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol, 2011. 59: 893.
https://pubmed.ncbi.nlm.nih.gov/21388736/

1105.   Crook, J.M., *et al*. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med, 2012. 367: 895.
https://pubmed.ncbi.nlm.nih.gov/22931259/

1106.   Levine, G.N., *et al*. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. Circulation, 2010. 121: 833.
https://pubmed.ncbi.nlm.nih.gov/20124128/

1107.   O'Farrell, S., *et al*. Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer. J Clin Oncol, 2015. 33: 1243.
https://pubmed.ncbi.nlm.nih.gov/25732167/

1108.   James, N.D., *et al*. Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol, 2015. 67: 1028.
https://pubmed.ncbi.nlm.nih.gov/25301760/

1109.   Glass, T.R., *et al*. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol, 2003. 169: 164.
https://pubmed.ncbi.nlm.nih.gov/12478127/

1110.   Gravis, G., *et al*. Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: Validation of the Glass Model and Development of a Novel Simplified Prognostic Model. Eur Urol, 2015. 68: 196.
https://pubmed.ncbi.nlm.nih.gov/25277272/

1111.   Gravis, G., *et al*. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol, 2016. 70: 256.
https://pubmed.ncbi.nlm.nih.gov/26610858/

1112.   Sweeney, C.J., *et al*. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med, 2015. 373: 737.
https://pubmed.ncbi.nlm.nih.gov/26244877/

1113.   Kyriakopoulos, C.E., *et al*. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol, 2018. 36: 1080.
https://pubmed.ncbi.nlm.nih.gov/29384722/

1114.   Gravis, G., *et al*. Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies. Eur Urol, 2018. 73: 847.
https://pubmed.ncbi.nlm.nih.gov/29475737/

1115.   Parker, C.C., *et al*. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet, 2018. 392: 2353.
https://pubmed.ncbi.nlm.nih.gov/30355464/

1116.   Francini, E., *et al*. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). Prostate, 2018. 78: 889.
https://pubmed.ncbi.nlm.nih.gov/29707790/

1117.   Hussain, M., *et al*. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol, 2006. 24: 3984.
https://pubmed.ncbi.nlm.nih.gov/16921051/

1118.   Harshman, L.C., *et al*. Seven-Month Prostate-Specific Antigen Is Prognostic in Metastatic Hormone-Sensitive Prostate Cancer Treated With Androgen Deprivation With or Without Docetaxel. J Clin Oncol, 2018. 36: 376.
https://pubmed.ncbi.nlm.nih.gov/29261442/

1119.   Davey, P., *et al*. Cardiovascular risk profiles of GnRH agonists and antagonists: real-world analysis from UK general practice. World J Urol, 2021. 39: 307.
https://pubmed.ncbi.nlm.nih.gov/32979057/

1120.   Boland, J., *et al*. Cardiovascular Toxicity of Androgen Deprivation Therapy. Curr Cardiol Rep, 2021. 23: 109.
https://pubmed.ncbi.nlm.nih.gov/34216282/

1121.   Kunath, F., *et al*. Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev, 2014. 6: CD009266.
https://pubmed.ncbi.nlm.nih.gov/24979481/

1122.   Niraula, S., *et al*. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. J Clin Oncol, 2013. 31: 2029.
https://pubmed.ncbi.nlm.nih.gov/23630216/

1123.   Botrel, T.E., *et al*. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. BMC Urol, 2014. 14: 9.
https://pubmed.ncbi.nlm.nih.gov/24460605/

1124.   Tsai, H.T., *et al*. Efficacy of intermittent androgen deprivation therapy vs conventional continuous androgen deprivation therapy for advanced prostate cancer: a meta-analysis. Urology, 2013. 82: 327.
https://pubmed.ncbi.nlm.nih.gov/23896094/

1125.   Brungs, D., *et al*. Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. Prostate Cancer Prostatic Dis, 2014. 17: 105.
https://pubmed.ncbi.nlm.nih.gov/24686773/

1126.   Magnan, S., *et al*. Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Oncol, 2015. 1: 1261.
https://pubmed.ncbi.nlm.nih.gov/26378418/

1127.   Hussain, M., *et al*. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med, 2013. 368: 1314.
https://pubmed.ncbi.nlm.nih.gov/23550669/

1128.   Kunath, F., *et al*. Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer. Cochrane Database Syst Rev, 2019. 6: CD003506.
https://pubmed.ncbi.nlm.nih.gov/31194882/

1129.   Walsh, P.C. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. J Urol, 1997. 158: 1623.
https://pubmed.ncbi.nlm.nih.gov/9302187/

1130.   Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet, 2000. 355: 1491.
https://pubmed.ncbi.nlm.nih.gov/10801170/

1131.   Schmitt, B., *et al*. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev, 2000: CD001526.
https://pubmed.ncbi.nlm.nih.gov/10796804/

1132.   Davis, I.D., *et al*. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med, 2019. 381: 121.
https://pubmed.ncbi.nlm.nih.gov/31157964/

1133.   Gu, W., *et al*. Rezvilutamide versus bicalutamide in combination with androgen-deprivation therapy in patients with high-volume, metastatic, hormone-sensitive prostate cancer (CHART): a randomised, open-label, phase 3 trial. Lancet Oncol, 2022. 23: 1249.
https://pubmed.ncbi.nlm.nih.gov/36075260/

1134. Gravis, G., et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol, 2013. 14: 149.
https://pubmed.ncbi.nlm.nih.gov/23306100/

1135. Clarke, N.W., et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol, 2019. 30: 1992.
https://pubmed.ncbi.nlm.nih.gov/31560068/

1136. Smith, T.J., et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol, 2015. 33: 3199.
https://pubmed.ncbi.nlm.nih.gov/26169616/

1137. Sathianathen, N.J., et al. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. Cochrane Database Syst Rev, 2018. 10: CD012816.
https://pubmed.ncbi.nlm.nih.gov/30320443/

1138. Rydzewska, L.H.M., et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. Eur J Cancer, 2017. 84: 88.
https://pubmed.ncbi.nlm.nih.gov/28800492/

1139. Hoyle, A.P., et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. Eur Urol, 2019. 76: 719.
https://pubmed.ncbi.nlm.nih.gov/31447077/

1140. Armstrong, A.J., et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol, 2022. 40: 1616.
https://pubmed.ncbi.nlm.nih.gov/35420921/

1141. Chi, K.N., et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol, 2021. 39: 2294.
https://pubmed.ncbi.nlm.nih.gov/33914595/

1142. Sweeney, C.J., et al. Overall Survival of Men with Metachronous Metastatic Hormone-sensitive Prostate Cancer Treated with Enzalutamide and Androgen Deprivation Therapy. Eur Urol, 2021. 80: 275.
https://pubmed.ncbi.nlm.nih.gov/34030924/

1143. Fizazi, K., et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2×2 factorial design. Lancet, 2022. 399: 1695.
https://pubmed.ncbi.nlm.nih.gov/35405085/

1144. Fizazi, K., et al. A phase 3 trial with a 2x2 factorial design of abiraterone acetate plus prednisone and/or local radiotherapy in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): First results of PEACE-1. J Clin Oncol, 2021. 39: 5000.
https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.5000

1145. Smith, M.R., et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med, 2022. 386: 1132.
https://pubmed.ncbi.nlm.nih.gov/35179323/

1146. Marchioni, M., et al. New Antiandrogen Compounds Compared to Docetaxel for Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis. J Urol, 2020. 203: 751.
https://pubmed.ncbi.nlm.nih.gov/31689158/

1147. Sathianathen, N.J., et al. Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. Eur Urol, 2020. 77: 365.
https://pubmed.ncbi.nlm.nih.gov/31679970/

1148. Boeve, L.M.S., et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol, 2019. 75: 410.
https://pubmed.ncbi.nlm.nih.gov/30266309/

1149. Parker, C.C., et al. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. PLoS Med, 2022. 19: e1003998.
https://pubmed.ncbi.nlm.nih.gov/35671327/

1150. Ali, A., *et al*. Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol, 2021. 7: 555.
https://pubmed.ncbi.nlm.nih.gov/33599706/

1151. Burdett, S., *et al*. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. Eur Urol, 2019. 76: 115.
https://pubmed.ncbi.nlm.nih.gov/30826218/

1152. Ost, P., *et al*. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. J Clin Oncol, 2018. 36: 446.
https://pubmed.ncbi.nlm.nih.gov/29240541/

1153. Phillips, R., *et al*. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncol, 2020. 6: 650.
https://pubmed.ncbi.nlm.nih.gov/32215577/

1154. Deek, M.P., *et al*. Long-Term Outcomes and Genetic Predictors of Response to Metastasis-Directed Therapy Versus Observation in Oligometastatic Prostate Cancer: Analysis of STOMP and ORIOLE Trials. J Clin Oncol, 2022: Jco2200644.
https://pubmed.ncbi.nlm.nih.gov/36001857/

1155. Glicksman, R.M., *et al*. Curative-intent Metastasis-directed Therapies for Molecularly-defined Oligorecurrent Prostate Cancer: A Prospective Phase II Trial Testing the Oligometastasis Hypothesis. Eur Urol, 2021. 80: 374.
https://pubmed.ncbi.nlm.nih.gov/33685838/

1156. Battaglia, A., *et al*. Novel Insights into the Management of Oligometastatic Prostate Cancer: A Comprehensive Review. Eur Urol Oncol, 2019. 2: 174.
https://pubmed.ncbi.nlm.nih.gov/31017094/

1157. Connor, M.J., *et al*. Targeting Oligometastasis with Stereotactic Ablative Radiation Therapy or Surgery in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review of Prospective Clinical Trials. Eur Urol Oncol, 2020. 3: 582.
https://pubmed.ncbi.nlm.nih.gov/32891600/

1158. Marvaso, G., *et al*. Oligorecurrent Prostate Cancer and Stereotactic Body Radiotherapy: Where Are We Now? A Systematic Review and Meta-analysis of Prospective Studies. Eur Urol Open Sci, 2021. 27: 19.
https://pubmed.ncbi.nlm.nih.gov/34337513/

1159. Devos, G., *et al*. Oncological Outcomes of Metastasis-Directed Therapy in Oligorecurrent Prostate Cancer Patients Following Radical Prostatectomy. Cancers (Basel), 2020. 12: 2271.
https://pubmed.ncbi.nlm.nih.gov/32823690/

1160. Eisenhauer, E.A., *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45: 228.
https://pubmed.ncbi.nlm.nih.gov/19097774/

1161. U.S. Food and Drug Administration. FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers. 2020. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-liquid-biopsy-ngs-companion-diagnostic-test-multiple-cancers-and-biomarkers

1162. Lotan, T.L., *et al*. Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers. I. Molecular Biomarkers in Prostate Cancer. Am J Surg Pathol, 2020. 44: e15.
https://pubmed.ncbi.nlm.nih.gov/32044806/

1163. Dienstmann, R., *et al*. Standardized decision support in next generation sequencing reports of somatic cancer variants. Mol Oncol, 2014. 8: 859.
https://pubmed.ncbi.nlm.nih.gov/24768039/

1164. Li, M.M., *et al*. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn, 2017. 19: 4.
https://pubmed.ncbi.nlm.nih.gov/27993330/

1165. Hussain, M., *et al*. LBA12_PRPROfound: Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations. Ann Oncol, 2019. 30: Suppl 5, v881.
https://www.annalsofoncology.org/article/S0923-7534(19)60399-6/pdf

1166. de Bono, J., *et al*. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med, 2020. 382: 2091.
https://pubmed.ncbi.nlm.nih.gov/32343890/

1167. Hussain, M., *et al*. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med, 2020. 383: 2345.
https://pubmed.ncbi.nlm.nih.gov/32955174/

1168. U.S. Food & Drug Administration. Pembrolizumab (KEYTRUDA). 2016. Access date December 2022.
https://www.fda.gov/drugs/resources-information-approved-drugs/pembrolizumab-keytruda-checkpoint-inhibitor

1169. de Wit, R., *et al*. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med, 2019. 381: 2506.
https://pubmed.ncbi.nlm.nih.gov/31566937/

1170. Loriot, Y., *et al*. Prior long response to androgen deprivation predicts response to next-generation androgen receptor axis targeted drugs in castration resistant prostate cancer. Eur J Cancer, 2015. 51: 1946.
https://pubmed.ncbi.nlm.nih.gov/26208462/

1171. Smith, M.R., *et al*. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer, 2011. 117: 2077.
https://pubmed.ncbi.nlm.nih.gov/21523719/

1172. Crawford, E.D., *et al*. Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology, 2014. 83: 664.
https://pubmed.ncbi.nlm.nih.gov/24411213/

1173. Fendler, W.P., *et al*. Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer. Clin Cancer Res, 2019. 25: 7448.
https://pubmed.ncbi.nlm.nih.gov/31511295/

1174. Hussain, M., *et al*. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med, 2018. 378: 2465.
https://pubmed.ncbi.nlm.nih.gov/29949494/

1175. Smith, M.R., *et al*. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med, 2018. 378: 1408.
https://pubmed.ncbi.nlm.nih.gov/29420164/

1176. Fizazi, K., *et al*. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med, 2019. 380: 1235.
https://pubmed.ncbi.nlm.nih.gov/30763142/

1177. Fizazi, K., *et al*. Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide. N Engl J Med, 2020. 383: 1040.
https://pubmed.ncbi.nlm.nih.gov/32905676/

1178. Sternberg, C.N., *et al*. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med, 2020. 382: 2197.
https://pubmed.ncbi.nlm.nih.gov/32469184/

1179. Smith, M.R., *et al*. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol, 2021. 79: 150.
https://pubmed.ncbi.nlm.nih.gov/32907777/

1180. Hussain, M., *et al*. Effects of continued androgen-deprivation therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group report. J Clin Oncol, 1994. 12: 1868.
https://pubmed.ncbi.nlm.nih.gov/8083710/

1181. Taylor, C.D., *et al*. Importance of continued testicular suppression in hormone-refractory prostate cancer. J Clin Oncol, 1993. 11: 2167.
https://pubmed.ncbi.nlm.nih.gov/8229130/

1182. Ryan, C.J., *et al*. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med, 2013. 368: 138.
https://pubmed.ncbi.nlm.nih.gov/23228172/

1183. Ryan, C.J., *et al*. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol, 2015. 16: 152.
https://pubmed.ncbi.nlm.nih.gov/25601341/

1184. Roviello, G., *et al*. Targeting the androgenic pathway in elderly patients with castration-resistant prostate cancer: A meta-analysis of randomized trials. Medicine (Baltimore), 2016. 95: e4636.
https://pubmed.ncbi.nlm.nih.gov/27787354/

1185. Beer, T.M., *et al*. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med, 2014. 371: 424.
https://pubmed.ncbi.nlm.nih.gov/24881730/

1186. Graff, J.N., *et al*. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. Ann Oncol, 2016. 27: 286.
https://pubmed.ncbi.nlm.nih.gov/26578735/

1187. Evans, C.P., *et al*. The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer. Eur Urol, 2016. 70: 675.
https://pubmed.ncbi.nlm.nih.gov/27006332/

1188. Shore, N.D., *et al*. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol, 2016. 17: 153.
https://pubmed.ncbi.nlm.nih.gov/26774508/

1189. Beer, T.M., *et al*. Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. Eur Urol, 2017. 71: 151.
https://pubmed.ncbi.nlm.nih.gov/27477525/

1190. Tannock, I.F., *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med, 2004. 351: 1502.
https://pubmed.ncbi.nlm.nih.gov/15470213/

1191. Scher, H.I., *et al*. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol, 2016. 34: 1402.
https://pubmed.ncbi.nlm.nih.gov/26903579/

1192. Armstrong, A.J., *et al*. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res, 2010. 16: 203.
https://pubmed.ncbi.nlm.nih.gov/20008841/

1193. Italiano, A., *et al*. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. Eur Urol, 2009. 55: 1368.
https://pubmed.ncbi.nlm.nih.gov/18706755/

1194. Horgan, A.M., *et al*. Tolerability and efficacy of docetaxel in older men with metastatic castrate-resistant prostate cancer (mCRPC) in the TAX 327 trial. J Geriatr Oncol, 2014. 5: 119.
https://pubmed.ncbi.nlm.nih.gov/24495703/

1195. Kellokumpu-Lehtinen, P.L., *et al*. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. Lancet Oncol, 2013. 14: 117.
https://pubmed.ncbi.nlm.nih.gov/23294853/

1196. Kantoff, P.W., *et al*. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med, 2010. 363: 411.
https://pubmed.ncbi.nlm.nih.gov/20818862/

1197. Sweeney, C., *et al*. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. Lancet, 2021. 398: 131.
https://pubmed.ncbi.nlm.nih.gov/34246347/

1198. Clarke, N.W., *et al*. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evidence, 2022. 1: EVIDoa2200043.
https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200043

1199. Chi, K.N., *et al*. Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. J Clin Oncol, 2022. 40: 12.
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.6_suppl.012

1200. Petrylak, D.P., *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med, 2004. 351: 1513.
https://pubmed.ncbi.nlm.nih.gov/15470214/

1201. Berthold, D.R., *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol, 2008. 26: 242.
https://pubmed.ncbi.nlm.nih.gov/18182665/

1202. Rathkopf, D.E., *et al*. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol, 2014. 66: 815.
https://pubmed.ncbi.nlm.nih.gov/24647231/

1203. Small, E.J., *et al*. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol, 2006. 24: 3089.
https://pubmed.ncbi.nlm.nih.gov/16809734/

1204. de Bono, J.S., *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet, 2010. 376: 1147.
https://pubmed.ncbi.nlm.nih.gov/20888992/

1205. Sartor, A., *et al*. Cabazitaxel vs docetaxel in chemotherapy-naive (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA). J Clin Oncol 2016. 34: Abstract 5006.
https://ascopubs.org/doi/10.1200/JCO.2016.34.15_suppl.5006

1206. Eisenberger, M., *et al*. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m(2)) and the Currently Approved Dose (25 mg/m(2)) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer-PROSELICA. J Clin Oncol, 2017. 35: 3198.
https://pubmed.ncbi.nlm.nih.gov/28809610/

1207. Di Lorenzo, G., *et al*. Peg-filgrastim and cabazitaxel in prostate cancer patients. Anticancer Drugs, 2013. 24: 84.
https://pubmed.ncbi.nlm.nih.gov/23044721/

1208. de Bono, J.S., *et al*. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med, 2011. 364: 1995.
https://pubmed.ncbi.nlm.nih.gov/21612468/

1209. Fizazi, K., *et al*. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol, 2012. 13: 983.
https://pubmed.ncbi.nlm.nih.gov/22995653/

1210. Scher, H.I., *et al*. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med, 2012. 367: 1187.
https://pubmed.ncbi.nlm.nih.gov/22894553/

1211. Parker, C., *et al*. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med, 2013. 369: 213.
https://pubmed.ncbi.nlm.nih.gov/23863050/

1212. Hoskin, P., *et al*. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol, 2014. 15: 1397.
https://pubmed.ncbi.nlm.nih.gov/25439694/

1213. European Medicines Agency. EMA restricts use of prostate cancer medicine Xofigo. 2018. Access date December 2022.
https://www.ema.europa.eu/en/news/ema-restricts-use-prostate-cancer-medicine-xofigo

1214. Smith, M., *et al*. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol, 2019. 20: 408.
https://pubmed.ncbi.nlm.nih.gov/30738780/

1215. de Bono, J.S., *et al*. Subsequent Chemotherapy and Treatment Patterns After Abiraterone Acetate in Patients with Metastatic Castration-resistant Prostate Cancer: *Post Hoc* Analysis of COU-AA-302. Eur Urol, 2017. 71: 656.
https://pubmed.ncbi.nlm.nih.gov/27402060/

1216. Badrising, S., *et al*. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer, 2014. 120: 968.
https://pubmed.ncbi.nlm.nih.gov/24382803/

1217. Zhang, T., *et al*. Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. Expert Opin Pharmacother, 2015. 16: 473.
https://pubmed.ncbi.nlm.nih.gov/25534660/

1218.   Antonarakis, E.S., *et al*. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer.
         N Engl J Med, 2014. 371: 1028.
         https://pubmed.ncbi.nlm.nih.gov/25184630/

1219.   Attard, G., *et al*. Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-
         Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment.
         J Clin Oncol, 2018. 36: 2639.
         https://pubmed.ncbi.nlm.nih.gov/30028657/

1220.   Hofman, M.S., *et al*. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic
         castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet, 2021.
         397: 797.
         https://pubmed.ncbi.nlm.nih.gov/33581798/

1221.   Mateo, J., *et al*. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med,
         2015. 373: 1697.
         https://pubmed.ncbi.nlm.nih.gov/26510020/

1222.   Mateo, J., *et al*. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA
         repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet
         Oncol, 2020. 21: 162.
         https://pubmed.ncbi.nlm.nih.gov/31806540/

1223.   Serafini, A.N. Current status of systemic intravenous radiopharmaceuticals for the treatment of
         painful metastatic bone disease. Int J Radiat Oncol Biol Phys, 1994. 30: 1187.
         https://pubmed.ncbi.nlm.nih.gov/7525518/

1224.   Ballinger, J.R. Theranostic radiopharmaceuticals: established agents in current use. Br J Radiol,
         2018. 91: 20170969.
         https://pubmed.ncbi.nlm.nih.gov/29474096/

1225.   Emmett, L., *et al*. Lutetium (177) PSMA radionuclide therapy for men with prostate cancer: a review
         of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci, 2017. 64: 52.
         https://pubmed.ncbi.nlm.nih.gov/28303694/

1226.   Calopedos, R.J.S., *et al*. Lutetium-177-labelled anti-prostate-specific membrane antigen antibody
         and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review
         and meta-analysis. Prostate Cancer Prostatic Dis, 2017. 20: 352.
         https://pubmed.ncbi.nlm.nih.gov/28440324/

1227.   Hofman, M.S., *et al*. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic
         castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study.
         Lancet Oncol, 2018. 19: 825.
         https://pubmed.ncbi.nlm.nih.gov/29752180/

1228.   Emmett, L., *et al*. Results of a Prospective Phase 2 Pilot Trial of (177)Lu-PSMA-617 Therapy
         for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment
         Response and Patterns of Progression. Clin Genitourin Cancer, 2019. 17: 15.
         https://pubmed.ncbi.nlm.nih.gov/30425003/

1229.   Sartor, O., *et al*. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer.
         N Engl J Med, 2021. 385: 1091.
         https://pubmed.ncbi.nlm.nih.gov/34161051/

1230.   Sadaghiani, M.S., *et al*. (177) Lu-PSMA radioligand therapy effectiveness in metastatic castration-
         resistant prostate cancer: An updated systematic review and meta-analysis. Prostate, 2022. 82: 826.
         https://pubmed.ncbi.nlm.nih.gov/35286735/

1231.   Lee, D.Y., *et al*. Effects of (225)Ac-Labeled Prostate-Specific Membrane Antigen Radioligand
         Therapy in Metastatic Castration-Resistant Prostate Cancer: A Meta-Analysis. J Nucl Med, 2022.
         63: 840.
         https://pubmed.ncbi.nlm.nih.gov/34503960/

1232.   European Medicines Agency. Lynparza (olaparib). 2014. Access date December 2022.
         https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza

1233.   Abida, W., *et al*. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring
         a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol, 2020. 38: 3763.
         https://pubmed.ncbi.nlm.nih.gov/32795228/

1234.   U.S. Food and Drug Administration. FDA grants accelerated approval to rucaparib for BRCA-
         mutated metastatic castration-resistant prostate cancer. 2020. Access date December 2022.
         https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-
         approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate

1235.   Khalaf, D.J., *et al.* Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol, 2019. 20: 1730.
https://pubmed.ncbi.nlm.nih.gov/31727538/

1236.   Miyake, H., *et al.* Comparative Assessment of Efficacies Between 2 Alternative Therapeutic Sequences With Novel Androgen Receptor-Axis-Targeted Agents in Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer. Clin Genitourin Cancer, 2017. 15: e591.
https://pubmed.ncbi.nlm.nih.gov/28063845/

1237.   Terada, N., *et al.* Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: The Kyoto-Baltimore collaboration. Int J Urol, 2017. 24: 441.
https://pubmed.ncbi.nlm.nih.gov/28455853/

1238.   Azad, A.A., *et al.* Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. Eur Urol, 2015. 67: 23.
https://pubmed.ncbi.nlm.nih.gov/25018038/

1239.   Kobayashi, T., *et al.* Sequential Use of Androgen Receptor Axis-targeted Agents in Chemotherapy-naive Castration-resistant Prostate Cancer: A Multicenter Retrospective Analysis With 3-Year Follow-up. Clin Genitourin Cancer, 2020. 18: e46.
https://pubmed.ncbi.nlm.nih.gov/31759831/

1240.   Komura, K., *et al.* Comparison of Radiographic Progression-Free Survival and PSA Response on Sequential Treatment Using Abiraterone and Enzalutamide for Newly Diagnosed Castration-Resistant Prostate Cancer: A Propensity Score Matched Analysis from Multicenter Cohort. J Clin Med, 2019. 8.
https://pubmed.ncbi.nlm.nih.gov/31430900/

1241.   Matsubara, N., *et al.* Abiraterone Followed by Enzalutamide Versus Enzalutamide Followed by Abiraterone in Chemotherapy-naive Patients With Metastatic Castration-resistant Prostate Cancer. Clin Genitourin Cancer, 2018. 16: 142.
https://pubmed.ncbi.nlm.nih.gov/29042308/

1242.   Maughan, B.L., *et al.* Comparing Sequencing of Abiraterone and Enzalutamide in Men With Metastatic Castration-Resistant Prostate Cancer: A Retrospective Study. Prostate, 2017. 77: 33.
https://pubmed.ncbi.nlm.nih.gov/27527643/

1243.   de Bono, J.S., *et al.* Antitumour Activity and Safety of Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer Previously Treated with Abiraterone Acetate Plus Prednisone for ≥24 weeks in Europe. Eur Urol, 2018. 74: 37.
https://pubmed.ncbi.nlm.nih.gov/28844372/

1244.   Mori, K., *et al.* Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis, 2020. 23: 539.
https://pubmed.ncbi.nlm.nih.gov/32152435/

1245.   Lavaud, P., *et al.* Anticancer Activity and Tolerance of Treatments Received Beyond Progression in Men Treated Upfront with Androgen Deprivation Therapy With or Without Docetaxel for Metastatic Castration-naïve Prostate Cancer in the GETUG-AFU 15 Phase 3 Trial. Eur Urol, 2018. 73: 696.
https://pubmed.ncbi.nlm.nih.gov/29074061/

1246.   Bahl, A., *et al.* Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol, 2013. 24: 2402.
https://pubmed.ncbi.nlm.nih.gov/23723295/

1247.   de Bono, J.S., *et al.* Final overall survival (OS) analysis of PROfound: Olaparib vs physician's choice of enzalutamide or abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations. Ann Oncol 2020. 31: S507.
https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/final-overall-survival-os-analysis-of-profound-olaparib-vs-physician-s-choice-of-enzalutamide-or-abiraterone-in-patients-pts-with-metastatic-c

1248.   Hofman, M.S., *et al.* TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603). J Clin Oncol, 2022. 40: 5000.
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.5000

1249.   Hager, S., *et al.* Anti-tumour activity of platinum compounds in advanced prostate cancer-a systematic literature review. Ann Oncol, 2016. 27: 975.
https://pubmed.ncbi.nlm.nih.gov/27052650/

1250.   Corn, P.G., *et al*. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1-2 trial. Lancet Oncol, 2019. 20: 1432.
https://pubmed.ncbi.nlm.nih.gov/31515154/

1251.   Aparicio, A.M., *et al*. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res, 2013. 19: 3621.
https://pubmed.ncbi.nlm.nih.gov/23649003/

1252.   Mota, J.M., *et al*. Platinum-Based Chemotherapy in Metastatic Prostate Cancer With DNA Repair Gene Alterations. JCO Precis Oncol, 2020. 4: 355.
https://pubmed.ncbi.nlm.nih.gov/32856010/

1253.   Schmid, S., *et al*. Activity of Platinum-Based Chemotherapy in Patients With Advanced Prostate Cancer With and Without DNA Repair Gene Aberrations. JAMA Netw Open, 2020. 3: e2021692.
https://pubmed.ncbi.nlm.nih.gov/33112397/

1254.   Gillessen, S., *et al*. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol, 2015. 26: 1589.
https://pubmed.ncbi.nlm.nih.gov/26041764/

1255.   Saad, F., *et al*. Prostate-specific Antigen Progression in Enzalutamide-treated Men with Nonmetastatic Castration-resistant Prostate Cancer: Any Rise in Prostate-specific Antigen May Require Closer Monitoring. Eur Urol, 2020. 78: 847.
https://pubmed.ncbi.nlm.nih.gov/33010985/

1256.   Aggarwal, R., *et al*. Heterogeneous Flare in Prostate-specific Membrane Antigen Positron Emission Tomography Tracer Uptake with Initiation of Androgen Pathway Blockade in Metastatic Prostate Cancer. Eur Urol Oncol, 2018. 1: 78.
https://pubmed.ncbi.nlm.nih.gov/31100231/

1257.   Payne, H., *et al*. Prostate-specific antigen: an evolving role in diagnosis, monitoring, and treatment evaluation in prostate cancer. Urol Oncol, 2011. 29: 593.
https://pubmed.ncbi.nlm.nih.gov/20060331/

1258.   Pezaro, C.J., *et al*. Visceral disease in castration-resistant prostate cancer. Eur Urol, 2014. 65: 270.
https://pubmed.ncbi.nlm.nih.gov/24295792/

1259.   Ohlmann, C., *et al*. Second-line chemotherapy with docetaxel for prostate-specific antigen relapse in men with hormone refractory prostate cancer previously treated with docetaxel based chemotherapy. Eur Urol Suppl 2006. 5: abstract #289.
https://ascopubs.org/doi/abs/10.1200/jco.2005.23.16_suppl.46821259.

1260.   Gillessen, S., *et al*. Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. Eur Urol, 2020. 77: 508.
https://pubmed.ncbi.nlm.nih.gov/32001144/

1261.   Rao, K., *et al*. Uro-oncology multidisciplinary meetings at an Australian tertiary referral centre--impact on clinical decision-making and implications for patient inclusion. BJU Int, 2014. 114 Suppl 1: 50.
https://pubmed.ncbi.nlm.nih.gov/25070295/

1262.   Cereceda, L.E., *et al*. Management of vertebral metastases in prostate cancer: a retrospective analysis in 119 patients. Clin Prostate Cancer, 2003. 2: 34.
https://pubmed.ncbi.nlm.nih.gov/15046682/

1263.   Chaichana, K.L., *et al*. Outcome following decompressive surgery for different histological types of metastatic tumors causing epidural spinal cord compression. Clinical article. J Neurosurg Spine, 2009. 11: 56.
https://pubmed.ncbi.nlm.nih.gov/19569942/

1264.   Hoskin, P., *et al*. A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. J Natl Cancer Inst, 2015. 107: djv197.
https://pubmed.ncbi.nlm.nih.gov/26242893/

1265.   Frankel, B.M., *et al*. Percutaneous vertebral augmentation: an elevation in adjacent-level fracture risk in kyphoplasty as compared with vertebroplasty. Spine J, 2007. 7: 575.
https://pubmed.ncbi.nlm.nih.gov/17905320/

1266.   Dutka, J., *et al*. Time of survival and quality of life of the patients operatively treated due to pathological fractures due to bone metastases. Ortop Traumatol Rehabil, 2003. 5: 276.
https://pubmed.ncbi.nlm.nih.gov/18034018/

1267.   Frankel, B.M., *et al*. Segmental polymethylmethacrylate-augmented pedicle screw fixation in patients with bone softening caused by osteoporosis and metastatic tumor involvement: a clinical evaluation. Neurosurgery, 2007. 61: 531.
https://pubmed.ncbi.nlm.nih.gov/17881965/

1268.   Lawton, A.J., *et al*. Assessment and Management of Patients With Metastatic Spinal Cord Compression: A Multidisciplinary Review. J Clin Oncol, 2019. 37: 61.
https://pubmed.ncbi.nlm.nih.gov/30395488/

1269.   Saad, F., *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst, 2002. 94: 1458.
https://pubmed.ncbi.nlm.nih.gov/12359855/

1270.   Fizazi, K., *et al*. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet, 2011. 377: 813.
https://pubmed.ncbi.nlm.nih.gov/21353695/

1271.   Smith, M.R., *et al*. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet, 2012. 379: 39.
https://pubmed.ncbi.nlm.nih.gov/22093187/

1272.   Marco, R.A., *et al*. Functional and oncological outcome of acetabular reconstruction for the treatment of metastatic disease. J Bone Joint Surg Am, 2000. 82: 642.
https://pubmed.ncbi.nlm.nih.gov/10819275/

1273.   Stopeck, A.T., *et al*. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer, 2016. 24: 447.
https://pubmed.ncbi.nlm.nih.gov/26335402/

1274.   Aapro, M., *et al*. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol, 2008. 19: 420.
https://pubmed.ncbi.nlm.nih.gov/17906299/

1275.   Medication-Related Osteonecrosis of the Jaws, ed. S. Otto. 2015, Berlin Heidelberg.

1276.   European Medicine Agency. Xgeva. 2019. Access date December 2022.
https://www.ema.europa.eu/en/medicines/human/EPAR/xgeva

1277.   Stopeck, A.T., *et al*. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol, 2010. 28: 5132.
https://pubmed.ncbi.nlm.nih.gov/21060033/

1278.   Body, J.J., *et al*. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. Eur J Cancer, 2015. 51: 1812.
https://pubmed.ncbi.nlm.nih.gov/26093811/

1279.   Rice, S.M., *et al*. Depression and Prostate Cancer: Examining Comorbidity and Male-Specific Symptoms. Am J Mens Health, 2018. 12: 1864.
https://pubmed.ncbi.nlm.nih.gov/29957106/

1280.   van Stam, M.A., *et al*. Prevalence and correlates of mental health problems in prostate cancer survivors: A case-control study comparing survivors with general population peers. Urol Oncol, 2017. 35: 531 e1.
https://pubmed.ncbi.nlm.nih.gov/28457651/

1281.   Horwitz, E.M., *et al*. Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: a multi-institutional pooled analysis. J Urol, 2005. 173: 797.
https://pubmed.ncbi.nlm.nih.gov/15711272/

1282.   Stamey, T.A., *et al*. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol, 1989. 141: 1076.
https://pubmed.ncbi.nlm.nih.gov/2468795/

1283.   Jackson, W.C., *et al*. Impact of Biochemical Failure After Salvage Radiation Therapy on Prostate Cancer-specific Mortality: Competition Between Age and Time to Biochemical Failure. Eur Urol Oncol, 2018. 1: 276.
https://pubmed.ncbi.nlm.nih.gov/31100248/

1284.   Grivas, N., *et al*. Ultrasensitive prostate-specific antigen level as a predictor of biochemical progression after robot-assisted radical prostatectomy: Towards risk adapted follow-up. J Clin Lab Anal, 2019. 33: e22693.
https://pubmed.ncbi.nlm.nih.gov/30365194/

1285. Shen, S., *et al*. Ultrasensitive serum prostate specific antigen nadir accurately predicts the risk of early relapse after radical prostatectomy. J Urol, 2005. 173: 777.
https://pubmed.ncbi.nlm.nih.gov/15711268/

1286. Zakaria, A.S., *et al*. Detectable Prostate-specific antigen value between 0.01 and 0.1 ng/ml following robotic-assisted radical prostatectomy (RARP): does it correlate with future biochemical recurrence? World J Urol, 2021. 39: 1853.
https://pubmed.ncbi.nlm.nih.gov/32696130/

1287. Teeter, A.E., *et al*. Does Early Prostate Specific Antigen Doubling Time after Radical Prostatectomy, Calculated Prior to Prostate Specific Antigen Recurrence, Correlate with Prostate Cancer Outcomes? A Report from the SEARCH Database Group. J Urol, 2018. 199: 713.
https://pubmed.ncbi.nlm.nih.gov/28870860/

1288. Seikkula, H., *et al*. Role of ultrasensitive prostate-specific antigen in the follow-up of prostate cancer after radical prostatectomy. Urol Oncol, 2015. 33: 16.e1.
https://pubmed.ncbi.nlm.nih.gov/25456996/

1289. Lonergan, P.E., *et al*. Natural history of an immediately detectable PSA following radical prostatectomy in a contemporary cohort. Prostate, 2021. 81: 1009.
https://pubmed.ncbi.nlm.nih.gov/34288004/

1290. Ray, M.E., *et al*. PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: a multi-institutional analysis. Int J Radiat Oncol Biol Phys, 2006. 64: 1140.
https://pubmed.ncbi.nlm.nih.gov/16198506/

1291. Oefelein, M.G., *et al*. The incidence of prostate cancer progression with undetectable serum prostate specific antigen in a series of 394 radical prostatectomies. J Urol, 1995. 154: 2128.
https://pubmed.ncbi.nlm.nih.gov/7500474/

1292. Doneux, A., *et al*. The utility of digital rectal examination after radical radiotherapy for prostate cancer. Clin Oncol (R Coll Radiol), 2005. 17: 172.
https://pubmed.ncbi.nlm.nih.gov/15901001/

1293. Chaplin, B.J., *et al*. Digital rectal examination is no longer necessary in the routine follow-up of men with undetectable prostate specific antigen after radical prostatectomy: the implications for follow-up. Eur Urol, 2005. 48: 906.
https://pubmed.ncbi.nlm.nih.gov/16126322/

1294. Warren, K.S., *et al*. Is routine digital rectal examination required for the followup of prostate cancer? J Urol, 2007. 178: 115.
https://pubmed.ncbi.nlm.nih.gov/17499293/

1295. Beesley, L.J., *et al*. Individual and Population Comparisons of Surgery and Radiotherapy Outcomes in Prostate Cancer Using Bayesian Multistate Models. JAMA Netw Open, 2019. 2: e187765.
https://pubmed.ncbi.nlm.nih.gov/30707231/

1296. Marshall, C.H., *et al*. Timing of Androgen Deprivation Treatment for Men with Biochemical Recurrent Prostate Cancer in the Context of Novel Therapies. J Urol, 2021. 206: 623.
https://pubmed.ncbi.nlm.nih.gov/34003011/

1297. Loblaw, A., *et al*. Follow-up Care for Survivors of Prostate Cancer - Clinical Management: a Program in Evidence-Based Care Systematic Review and Clinical Practice Guideline. Clin Oncol (R Coll Radiol), 2017. 29: 711.
https://pubmed.ncbi.nlm.nih.gov/28928084/

1298. Thorstenson, A., *et al*. Incidence of fractures causing hospitalisation in prostate cancer patients: results from the population-based PCBaSe Sweden. Eur J Cancer, 2012. 48: 1672.
https://pubmed.ncbi.nlm.nih.gov/22386317/

1299. Franck Lissbrant, I., *et al*. Set-up and preliminary results from the Patient-overview Prostate Cancer. Longitudinal registration of treatment of advanced prostate cancer in the National Prostate Cancer Register of Sweden. Scand J Urol, 2020. 54: 227.
https://pubmed.ncbi.nlm.nih.gov/32363988/

1300. Saad, F., *et al*. Testosterone Breakthrough Rates during Androgen Deprivation Therapy for Castration Sensitive Prostate Cancer. J Urol, 2020. 204: 416.
https://pubmed.ncbi.nlm.nih.gov/32096678/

1301. Rouleau, M., *et al*. Discordance between testosterone measurement methods in castrated prostate cancer patients. Endocr Connect, 2019.
https://pubmed.ncbi.nlm.nih.gov/30673630/

1302. Morote, J., *et al*. Serum Testosterone Levels in Prostate Cancer Patients Undergoing Luteinizing Hormone-Releasing Hormone Agonist Therapy. Clin Genitourin Cancer, 2018. 16: e491.
https://pubmed.ncbi.nlm.nih.gov/29198640/

1303. Long, M.E., *et al*. Decreased testosterone recovery after androgen deprivation therapy for prostate cancer. Can J Urol, 2021. 28: 10738.
https://pubmed.ncbi.nlm.nih.gov/34378507/

1304. Nascimento, B., *et al*. Testosterone Recovery Profiles After Cessation of Androgen Deprivation Therapy for Prostate Cancer. J Sex Med, 2019. 16: 872.
https://pubmed.ncbi.nlm.nih.gov/31080102/

1305. Beer, T.M., *et al*. Hepatic effects assessed by review of safety data in enzalutamide castration-resistant prostate cancer (CRPC) trials. J Clin Oncol, 2018. 36: 199.
https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.6_suppl.199

1306. Yanagisawa, T., *et al*. Abiraterone acetate versus nonsteroidal antiandrogen with androgen deprivation therapy for high-risk metastatic hormone-sensitive prostate cancer. Prostate, 2022. 82: 3.
https://pubmed.ncbi.nlm.nih.gov/34559410/

1307. Daniell, H.W. Osteoporosis due to androgen deprivation therapy in men with prostate cancer. Urology, 2001. 58: 101.
https://pubmed.ncbi.nlm.nih.gov/11502461/

1308. Beer, T.M., *et al*. The prognostic value of hemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: A multivariate analysis of Southwest Oncology Group Study 8894. Cancer, 2006. 107: 489.
https://pubmed.ncbi.nlm.nih.gov/16804926/

1309. Ebbinge, M., *et al*. Clinical and prognostic significance of changes in haemoglobin concentration during 1 year of androgen-deprivation therapy for hormone-naïve bone-metastatic prostate cancer. BJU Int, 2018. 122: 583.
https://pubmed.ncbi.nlm.nih.gov/29611275/

1310. Sini, C., *et al*. Dose-volume effects for pelvic bone marrow in predicting hematological toxicity in prostate cancer radiotherapy with pelvic node irradiation. Radiother Oncol, 2016. 118: 79.
https://pubmed.ncbi.nlm.nih.gov/26702990/

1311. Turner, P.G., *et al*. Toxicity and Efficacy of Concurrent Androgen Deprivation Therapy, Pelvic Radiotherapy, and Radium-223 in Patients with *De Novo* Metastatic Hormone-Sensitive Prostate Cancer. Clin Cancer Res, 2021. 27: 4549.
https://pubmed.ncbi.nlm.nih.gov/34187853/

1312. Iacovelli, R., *et al*. The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer. Clin Genitourin Cancer, 2018. 16: e645.
https://pubmed.ncbi.nlm.nih.gov/29339044/

1313. Rizzo, A., *et al*. Risk of cardiovascular toxicities and hypertension in nonmetastatic castration-resistant prostate cancer patients treated with novel hormonal agents: a systematic review and meta-analysis. Expert Opin Drug Metab Toxicol, 2021. 17: 1237.
https://pubmed.ncbi.nlm.nih.gov/34407702/

1314. Gong, J., *et al*. Reduced Cardiorespiratory Fitness and Increased Cardiovascular Mortality After Prolonged Androgen Deprivation Therapy for Prostate Cancer. JACC CardioOncol, 2020. 2: 553.
https://pubmed.ncbi.nlm.nih.gov/34396266/

1315. Lopes, R.D., *et al*. Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Prostate Cancer: The Primary Results of the PRONOUNCE Randomized Trial. Circulation, 2021. 144: 1295.
https://pubmed.ncbi.nlm.nih.gov/34459214/

1316. Attard, G., *et al*. Assessment of the Safety of Glucocorticoid Regimens in Combination With Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer: A Randomized, Open-label Phase 2 Study. JAMA Oncol, 2019. 5: 1159.
https://pubmed.ncbi.nlm.nih.gov/31246234/

1317. James, N., *et al*. TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer. Health Technol Assess, 2016. 20: 1.
https://pubmed.ncbi.nlm.nih.gov/27434595/

1318. Ng, H.S., *et al*. Development of comorbidities in men with prostate cancer treated with androgen deprivation therapy: an Australian population-based cohort study. Prostate Cancer Prostatic Dis, 2018. 21: 403.
https://pubmed.ncbi.nlm.nih.gov/29720722/

1319. Kanis, J.A., *et al*. Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. Osteoporos Int, 2008. 19: 1395.
https://pubmed.ncbi.nlm.nih.gov/18751937/

1320. Cianferotti, L., *et al*. The prevention of fragility fractures in patients with non-metastatic prostate cancer: a position statement by the international osteoporosis foundation. Oncotarget, 2017. 8: 75646.
https://pubmed.ncbi.nlm.nih.gov/29088899/

1321. Rubin, K.H., *et al*. Comparison of different screening tools (FRAX®, OST, ORAI, OSIRIS, SCORE and age alone) to identify women with increased risk of fracture. A population-based prospective study. Bone, 2013. 56: 16.
https://pubmed.ncbi.nlm.nih.gov/23669650/

1322. Conde, F.A., *et al*. Risk factors for male osteoporosis. Urol Oncol, 2003. 21: 380.
https://pubmed.ncbi.nlm.nih.gov/14670549/

1323. Hamdy, R.C., *et al*. Algorithm for the management of osteoporosis. South Med J, 2010. 103: 1009.
https://pubmed.ncbi.nlm.nih.gov/20818296/

1324. Higano, C.S. Bone loss and the evolving role of bisphosphonate therapy in prostate cancer. Urol Oncol, 2003. 21: 392.
https://pubmed.ncbi.nlm.nih.gov/14670551/

1325. Sharma, A., *et al*. A prospective longitudinal study to evaluate bone health, implication of FRAX tool and impact on quality of life (FACT-P) in advanced prostate cancer patients. Am J Clin Exp Urol, 2021. 9: 211.
https://pubmed.ncbi.nlm.nih.gov/34327260/

1326. Edmunds, K., *et al*. Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. Support Care Cancer, 2020. 28: 2079.
https://pubmed.ncbi.nlm.nih.gov/31912360/

1327. Edmunds, K., *et al*. The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer: a rapid review. Support Care Cancer, 2020. 28: 5661.
https://pubmed.ncbi.nlm.nih.gov/32699997/

1328. Thomas, H.R., *et al*. Association Between Androgen Deprivation Therapy and Patient-reported Depression in Men With Recurrent Prostate Cancer. Clin Genitourin Cancer, 2018. 16: 313.
https://pubmed.ncbi.nlm.nih.gov/29866496/

1329. Hoogland, A.I., *et al*. Systemic inflammation and symptomatology in patients with prostate cancer treated with androgen deprivation therapy: Preliminary findings. Cancer, 2021. 127: 1476.
https://pubmed.ncbi.nlm.nih.gov/33378113/

1330. Gonzalez, B.D., *et al*. Course and Predictors of Cognitive Function in Patients With Prostate Cancer Receiving Androgen-Deprivation Therapy: A Controlled Comparison. J Clin Oncol, 2015. 33: 2021.
https://pubmed.ncbi.nlm.nih.gov/25964245/

1331. Duthie, C.J., *et al*. Maintenance of sexual activity following androgen deprivation in males. Crit Rev Oncol Hematol, 2020. 153: 103064.
https://pubmed.ncbi.nlm.nih.gov/32712517/

1332. Miller, P.D., *et al*. Prostate specific antigen and bone scan correlation in the staging and monitoring of patients with prostatic cancer. Br J Urol, 1992. 70: 295.
https://pubmed.ncbi.nlm.nih.gov/1384920/

1333. Bryce, A.H., *et al*. Patterns of Cancer Progression of Metastatic Hormone-sensitive Prostate Cancer in the ECOG3805 CHAARTED Trial. Eur Urol Oncol, 2020. 3: 717.
https://pubmed.ncbi.nlm.nih.gov/32807727/

1334. Padhani, A.R., *et al*. Rationale for Modernising Imaging in Advanced Prostate Cancer. Eur Urol Focus, 2017. 3: 223.
https://pubmed.ncbi.nlm.nih.gov/28753774/

1335. Lecouvet, F.E., *et al*. Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: a review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer, 2014. 50: 2519.
https://pubmed.ncbi.nlm.nih.gov/25139492/

1336. Ulmert, D., *et al*. A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the Bone Scan Index. Eur Urol, 2012. 62: 78.
https://pubmed.ncbi.nlm.nih.gov/22306323/

1337. Padhani, A.R., *et al*. METastasis Reporting and Data System for Prostate Cancer: Practical Guidelines for Acquisition, Interpretation, and Reporting of Whole-body Magnetic Resonance Imaging-based Evaluations of Multiorgan Involvement in Advanced Prostate Cancer. Eur Urol, 2017. 71: 81.
https://pubmed.ncbi.nlm.nih.gov/27317091/

1338. Trabulsi, E.J., *et al*. Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline. J Clin Oncol, 2020. 38: 1963.
https://pubmed.ncbi.nlm.nih.gov/31940221/

1339. Bourke, L., *et al*. Survivorship and improving quality of life in men with prostate cancer. Eur Urol, 2015. 68: 374.
https://pubmed.ncbi.nlm.nih.gov/25941049/

1340. Prashar, J., *et al*. Supportive care needs of men with prostate cancer: A systematic review update. Eur J Cancer Care (Engl), 2022. 31: e13541.
https://pubmed.ncbi.nlm.nih.gov/35038783/

1341. Resnick, M.J., *et al*. Prostate cancer survivorship care guideline: American Society of Clinical Oncology Clinical Practice Guideline endorsement. J Clin Oncol, 2015. 33: 1078.
https://pubmed.ncbi.nlm.nih.gov/25667275/

1342. Yiannopoulou, K.G., *et al*. Cognitive and Psychological Impacts of Different Treatment Options for Prostate Cancer: A Critical Analysis. Curr Urol, 2020. 14: 169.
https://pubmed.ncbi.nlm.nih.gov/33488334/

1343. Venderbos, L.D.F., *et al*. Europa Uomo Patient Reported Outcome Study (EUPROMS): Descriptive Statistics of a Prostate Cancer Survey from Patients for Patients. Eur Urol Focus, 2021. 7: 987.
https://pubmed.ncbi.nlm.nih.gov/33281109/

1344. Downing, A., *et al*. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. Lancet Oncol, 2019. 20: 436.
https://pubmed.ncbi.nlm.nih.gov/30713036/

1345. Luckenbaugh, A.N., *et al*. Association between Treatment for Localized Prostate Cancer and Mental Health Outcomes. J Urol, 2022. 207: 1029.
https://pubmed.ncbi.nlm.nih.gov/34978488/

1346. Carlsson, S., *et al*. Surgery-related complications in 1253 robot-assisted and 485 open retropubic radical prostatectomies at the Karolinska University Hospital, Sweden. Urology, 2010. 75: 1092.
https://pubmed.ncbi.nlm.nih.gov/20022085/

1347. Ficarra, V., *et al*. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol, 2009. 55: 1037.
https://pubmed.ncbi.nlm.nih.gov/19185977/

1348. Rabbani, F., *et al*. Comprehensive standardized report of complications of retropubic and laparoscopic radical prostatectomy. Eur Urol, 2010. 57: 371.
https://pubmed.ncbi.nlm.nih.gov/19945779/

1349. Resnick, M.J., *et al*. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med, 2013. 368: 436.
https://pubmed.ncbi.nlm.nih.gov/23363497/

1350. Parekh, A., *et al*. Reduced penile size and treatment regret in men with recurrent prostate cancer after surgery, radiotherapy plus androgen deprivation, or radiotherapy alone. Urology, 2013. 81: 130.
https://pubmed.ncbi.nlm.nih.gov/23273077/

1351. Msezane, L.P., *et al*. Bladder neck contracture after robot-assisted laparoscopic radical prostatectomy: evaluation of incidence and risk factors and impact on urinary function. J Endourol, 2008. 22: 377.
https://pubmed.ncbi.nlm.nih.gov/18095861/

1352. Chiong, E., *et al*. Port-site hernias occurring after the use of bladeless radially expanding trocars. Urology, 2010. 75: 574.
https://pubmed.ncbi.nlm.nih.gov/19854489/

1353. Haglind, E., *et al*. Corrigendum re: "Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial" [Eur Urol 2015;68:216-25]. Eur Urol, 2017. 72: e81.
https://pubmed.ncbi.nlm.nih.gov/28552613/

1354. Park, B., *et al*. Comparison of oncological and functional outcomes of pure versus robotic-assisted laparoscopic radical prostatectomy performed by a single surgeon. Scand J Urol, 2013. 47: 10.
https://pubmed.ncbi.nlm.nih.gov/22835035/

1355. Alder, R., *et al*. Incidence of Inguinal Hernia after Radical Prostatectomy: A Systematic Review and Meta-Analysis. J Urol, 2020. 203: 265.
https://pubmed.ncbi.nlm.nih.gov/31039101/

1356. Fernando, H., *et al*. Incidence, Predictive Factors and Preventive Measures for Inguinal Hernia following Robotic and Laparoscopic Radical Prostatectomy: A Systematic Review. J Urol, 2019. 201: 1072.
https://pubmed.ncbi.nlm.nih.gov/30730406/

1357.   Donovan, J.L., *et al*. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med, 2016. 375: 1425.
https://pubmed.ncbi.nlm.nih.gov/27626365/

1358.   Barocas, D.A., *et al*. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. JAMA, 2017. 317: 1126.
https://pubmed.ncbi.nlm.nih.gov/28324093/

1359.   Wallis, C.J., *et al*. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ, 2016. 352: i851.
https://pubmed.ncbi.nlm.nih.gov/26936410/

1360.   Budaus, L., *et al*. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol, 2012. 61: 112.
https://pubmed.ncbi.nlm.nih.gov/22001105/

1361.   Nguyen, P.L., *et al*. Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them. Eur Urol, 2014: 67(5):825.
https://pubmed.ncbi.nlm.nih.gov/25097095/

1362.   Donovan, K.A., *et al*. Psychological effects of androgen-deprivation therapy on men with prostate cancer and their partners. Cancer, 2015. 121: 4286.
https://pubmed.ncbi.nlm.nih.gov/26372364/

1363.   Cherrier, M.M., *et al*. Cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. Psychooncology, 2009. 18: 237.
https://pubmed.ncbi.nlm.nih.gov/18636420/

1364.   Alibhai, S.M., *et al*. Effects of long-term androgen deprivation therapy on cognitive function over 36 months in men with prostate cancer. Cancer, 2017. 123: 237.
https://pubmed.ncbi.nlm.nih.gov/27583806/

1365.   Herr, H.W., *et al*. Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. J Urol, 2000. 163: 1743.
https://pubmed.ncbi.nlm.nih.gov/10799173/

1366.   Potosky, A.L., *et al*. Quality-of-life outcomes after primary androgen deprivation therapy: results from the Prostate Cancer Outcomes Study. J Clin Oncol, 2001. 19: 3750.
https://pubmed.ncbi.nlm.nih.gov/11533098/

1367.   Walker, L.M., *et al*. Luteinizing hormone--releasing hormone agonists: a quick reference for prevalence rates of potential adverse effects. Clin Genitourin Cancer, 2013. 11: 375.
https://pubmed.ncbi.nlm.nih.gov/23891497/

1368.   Elliott, S., *et al*. Androgen deprivation therapy for prostate cancer: recommendations to improve patient and partner quality of life. J Sex Med, 2010. 7: 2996.
https://pubmed.ncbi.nlm.nih.gov/20626600/

1369.   Iversen, P., *et al*. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. J Urol, 2000. 164: 1579.
https://pubmed.ncbi.nlm.nih.gov/11025708/

1370.   Iversen, P., *et al*. Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. BJU Int, 2001. 87: 47.
https://pubmed.ncbi.nlm.nih.gov/11121992/

1371.   Boccardo, F., *et al*. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study. J Clin Oncol, 1999. 17: 2027.
https://pubmed.ncbi.nlm.nih.gov/10561254/

1372.   Irani, J., *et al*. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. Lancet Oncol, 2010. 11: 147.
https://pubmed.ncbi.nlm.nih.gov/19963436/

1373.   Sloan, J.A., *et al*. Methodologic lessons learned from hot flash studies. J Clin Oncol, 2001. 19: 4280.
https://pubmed.ncbi.nlm.nih.gov/11731510/

1374.   Moraska, A.R., *et al*. Gabapentin for the management of hot flashes in prostate cancer survivors: a longitudinal continuation Study-NCCTG Trial N00CB. J Support Oncol, 2010. 8: 128.
https://pubmed.ncbi.nlm.nih.gov/20552926/

1375.   Frisk, J., *et al*. Two modes of acupuncture as a treatment for hot flushes in men with prostate cancer--a prospective multicenter study with long-term follow-up. Eur Urol, 2009. 55: 156.
https://pubmed.ncbi.nlm.nih.gov/18294761/

1376.   Smith, M.R., *et al*. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol, 2006. 175: 136.
https://pubmed.ncbi.nlm.nih.gov/16406890/

1377. Cree, M., *et al*. Mortality and institutionalization following hip fracture. J Am Geriatr Soc, 2000. 48: 283.
https://pubmed.ncbi.nlm.nih.gov/10733054/

1378. Compston, J.E., *et al*. Osteoporosis. Lancet, 2019. 393: 364.
https://pubmed.ncbi.nlm.nih.gov/30696576/

1379. Saylor, P.J., *et al*. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol, 2009. 181: 1998.
https://pubmed.ncbi.nlm.nih.gov/19286225/

1380. Gonnelli, S., *et al*. Obesity and fracture risk. Clin Cases Miner Bone Metab, 2014. 11: 9.
https://pubmed.ncbi.nlm.nih.gov/25002873/

1381. Sieber, P.R., *et al*. Bicalutamide 150 mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. J Urol, 2004. 171: 2272.
https://pubmed.ncbi.nlm.nih.gov/15126801/

1382. Wadhwa, V.K., *et al*. Bicalutamide monotherapy preserves bone mineral density, muscle strength and has significant health-related quality of life benefits for osteoporotic men with prostate cancer. BJU Int, 2011. 107: 1923.
https://pubmed.ncbi.nlm.nih.gov/20950306/

1383. Higano, C., *et al*. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Urology, 2004. 64: 1182.
https://pubmed.ncbi.nlm.nih.gov/15596194/

1384. Nobes, J.P., *et al*. A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. BJU Int, 2012. 109: 1495.
https://pubmed.ncbi.nlm.nih.gov/21933330/

1385. Grundy, S.M., *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation, 2005. 112: 2735.
https://pubmed.ncbi.nlm.nih.gov/16157765/

1386. Braga-Basaria, M., *et al*. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol, 2006. 24: 3979.
https://pubmed.ncbi.nlm.nih.gov/16921050/

1387. Cheung, A.S., *et al*. Muscle and bone effects of androgen deprivation therapy: current and emerging therapies. Endocr Relat Cancer, 2014. 21: R371.
https://pubmed.ncbi.nlm.nih.gov/25056176/

1388. Smith, M.R., *et al*. Sarcopenia during androgen-deprivation therapy for prostate cancer. J Clin Oncol, 2012. 30: 3271.
https://pubmed.ncbi.nlm.nih.gov/22649143/

1389. Saigal, C.S., *et al*. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer, 2007. 110: 1493.
https://pubmed.ncbi.nlm.nih.gov/17657815/

1390. Lu-Yao, G., *et al*. Changing patterns in competing causes of death in men with prostate cancer: a population based study. J Urol, 2004. 171: 2285.
https://pubmed.ncbi.nlm.nih.gov/15126804/

1391. Keating, N.L., *et al*. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst, 2010. 102: 39.
https://pubmed.ncbi.nlm.nih.gov/19996060/

1392. Efstathiou, J.A., *et al*. Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. Eur Urol, 2008. 54: 816.
https://pubmed.ncbi.nlm.nih.gov/18243498/

1393. Jones, C.U., *et al*. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med, 2011. 365: 107.
https://pubmed.ncbi.nlm.nih.gov/21751904/

1394. Butler, S.S., *et al*. Risk of cardiovascular mortality with androgen deprivation therapy in prostate cancer: A secondary analysis of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Controlled Trial. Cancer, 2021. 127: 2213.
https://pubmed.ncbi.nlm.nih.gov/33905530/

1395. Nguyen, P.L., *et al*. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA, 2011. 306: 2359.
https://pubmed.ncbi.nlm.nih.gov/22147380/

1396. Bourke, L., *et al*. Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness? Br J Cancer, 2013. 108: 9.
https://pubmed.ncbi.nlm.nih.gov/23321508/

1397. Blankfield, R.P. Androgen deprivation therapy for prostate cancer and cardiovascular death. JAMA, 2012. 307: 1252; author reply 1252.
https://pubmed.ncbi.nlm.nih.gov/22453560/

1398. Bosco, C., *et al*. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol, 2015. 68: 386.
https://pubmed.ncbi.nlm.nih.gov/25484142/

1399. Nguyen, P.L., *et al*. Influence of androgen deprivation therapy on all-cause mortality in men with high-risk prostate cancer and a history of congestive heart failure or myocardial infarction. Int J Radiat Oncol Biol Phys, 2012. 82: 1411.
https://pubmed.ncbi.nlm.nih.gov/21708431/

1400. Tsai, H.K., *et al*. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst, 2007. 99: 1516.
https://pubmed.ncbi.nlm.nih.gov/17925537/

1401. Tisseverasinghe, S., *et al*. Should Prostate Cancer Patients With History of Cardiovascular Events Be Preferentially Treated With Luteinizing Hormone-Releasing Hormone Antagonists? J Clin Oncol, 2022. 40: 4173.
https://pubmed.ncbi.nlm.nih.gov/35862876/

1402. Gilbert, S.E., *et al*. Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer. Br J Cancer, 2016. 114: 401.
https://pubmed.ncbi.nlm.nih.gov/26766737/

1403. Wilding, S., *et al*. Cancer-related symptoms, mental well-being, and psychological distress in men diagnosed with prostate cancer treated with androgen deprivation therapy. Qual Life Res, 2019. 28: 2741.
https://pubmed.ncbi.nlm.nih.gov/31115843/

1404. Bourke, L., *et al*. Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol, 2015: 69:693.
https://pubmed.ncbi.nlm.nih.gov/26632144/

1405. Meng, F., *et al*. Stroke related to androgen deprivation therapy for prostate cancer: a meta-analysis and systematic review. BMC Cancer, 2016. 16: 180.
https://pubmed.ncbi.nlm.nih.gov/26940836/

1406. Nead, K.T., *et al*. Androgen Deprivation Therapy and Future Alzheimer's Disease Risk. J Clin Oncol, 2016. 34: 566.
https://pubmed.ncbi.nlm.nih.gov/26644522/

1407. Bennett, D., *et al*. Factors influencing job loss and early retirement in working men with prostate cancer-findings from the population-based Life After Prostate Cancer Diagnosis (LAPCD) study. J Cancer Surviv, 2018. 12: 669.
https://pubmed.ncbi.nlm.nih.gov/30058009/

1408. James, C., *et al*. Fear of cancer recurrence and PSA anxiety in patients with prostate cancer: a systematic review. Support Care Cancer, 2022. 30: 5577.
https://pubmed.ncbi.nlm.nih.gov/35106656/

1409. Mundle, R., *et al*. The effectiveness of psychological intervention for depression, anxiety, and distress in prostate cancer: a systematic review of literature. Prostate Cancer Prostatic Dis, 2021. 24: 674.
https://pubmed.ncbi.nlm.nih.gov/33750905/

1410. Borji, M., *et al*. Positive Effects of Cognitive Behavioral Therapy on Depression, Anxiety and Stress of Family Caregivers of Patients with Prostate Cancer: A Randomized Clinical Trial. Asian Pac J Cancer Prev, 2017. 18: 3207.
https://pubmed.ncbi.nlm.nih.gov/29281868/

1411. Bourke, L., *et al*. A qualitative study evaluating experiences of a lifestyle intervention in men with prostate cancer undergoing androgen suppression therapy. Trials, 2012. 13: 208.
https://pubmed.ncbi.nlm.nih.gov/23151126/

1412. Berruti, A., *et al*. Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline. J Urol, 2000. 164: 1248.
https://pubmed.ncbi.nlm.nih.gov/10992374/

1413. Carlin, B.I., *et al*. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. Cancer, 2000. 88: 2989.
https://pubmed.ncbi.nlm.nih.gov/10898342/

1414. Smith, D.P., *et al*. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. BMJ, 2009. 339: b4817.
https://pubmed.ncbi.nlm.nih.gov/19945997/

1415. Taylor, K.L., *et al*. Long-term disease-specific functioning among prostate cancer survivors and noncancer controls in the prostate, lung, colorectal, and ovarian cancer screening trial. J Clin Oncol, 2012. 30: 2768.
https://pubmed.ncbi.nlm.nih.gov/22734029/

1416. Bhanvadia, S.K., *et al*. Financial Toxicity Among Patients with Prostate, Bladder, and Kidney Cancer: A Systematic Review and Call to Action. Eur Urol Oncol, 2021. 4: 396.
https://pubmed.ncbi.nlm.nih.gov/33820747/

1417. Ratti, M.M., *et al*. Standardising the Assessment of Patient-reported Outcome Measures in Localised Prostate Cancer. A Systematic Review. Eur Urol Oncol, 2022. 5: 153.
https://pubmed.ncbi.nlm.nih.gov/34785188/

1418. Groenvold, M., *et al*. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol, 1997. 50: 441.
https://pubmed.ncbi.nlm.nih.gov/9179103/

1419. van Andel, G., *et al*. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer, 2008. 44: 2418.
https://pubmed.ncbi.nlm.nih.gov/18774706/

1420. Cella, D.F., *et al*. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol, 1993. 11: 570.
https://pubmed.ncbi.nlm.nih.gov/8445433/

1421. Esper, P., *et al*. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology, 1997. 50: 920.
https://pubmed.ncbi.nlm.nih.gov/9426724/

1422. Wei, J.T., *et al*. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology, 2000. 56: 899.
https://pubmed.ncbi.nlm.nih.gov/11113727/

1423. Szymanski, K.M., *et al*. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology, 2010. 76: 1245.
https://pubmed.ncbi.nlm.nih.gov/20350762/

1424. Litwin, M.S., *et al*. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care, 1998. 36: 1002.
https://pubmed.ncbi.nlm.nih.gov/9674618/

1425. Giesler, R.B., *et al*. Assessing quality of life in men with clinically localized prostate cancer: development of a new instrument for use in multiple settings. Qual Life Res, 2000. 9: 645.
https://pubmed.ncbi.nlm.nih.gov/11236855/

1426. Hoffman, K.E., *et al*. Patient-Reported Outcomes Through 5 Years for Active Surveillance, Surgery, Brachytherapy, or External Beam Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer. JAMA, 2020. 323: 149.
https://pubmed.ncbi.nlm.nih.gov/31935027/

1427. Lantz, A., *et al*. Functional and Oncological Outcomes After Open Versus Robot-assisted Laparoscopic Radical Prostatectomy for Localised Prostate Cancer: 8-Year Follow-up. Eur Urol, 2021. 80: 650.
https://pubmed.ncbi.nlm.nih.gov/34538508/

1428. Fransson, P., *et al*. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. Lancet Oncol, 2021. 22: 235.
https://pubmed.ncbi.nlm.nih.gov/33444529/

1429. Aksnessæther, B.Y., *et al*. Second Cancers in Patients With Locally Advanced Prostate Cancer Randomized to Lifelong Endocrine Treatment With or Without Radical Radiation Therapy: Long-Term Follow-up of the Scandinavian Prostate Cancer Group-7 Trial. Int J Radiat Oncol Biol Phys, 2020. 106: 706.
https://pubmed.ncbi.nlm.nih.gov/31786279/

1430. Hunt, A.A., *et al*. Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer. Prostate Cancer Prostatic Dis, 2021. 24: 128.
https://pubmed.ncbi.nlm.nih.gov/32647352/

1431. Giberti, C., *et al*. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. World J Urol, 2009. 27: 607.
https://pubmed.ncbi.nlm.nih.gov/19455340/

1432. Giberti, C., *et al*. Robotic prostatectomy versus brachytherapy for the treatment of low risk prostate cancer. Can J Urol, 2017. 24: 8728.
https://pubmed.ncbi.nlm.nih.gov/28436359/

1433. Lardas, M., *et al*. Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review. Eur Urol, 2017. 72: 869.
https://pubmed.ncbi.nlm.nih.gov/28757301/

1434. Giesler, R.B., *et al*. Improving the quality of life of patients with prostate carcinoma: a randomized trial testing the efficacy of a nurse-driven intervention. Cancer, 2005. 104: 752.
https://pubmed.ncbi.nlm.nih.gov/15986401/

1435. Schumacher, O., *et al*. Effects of Exercise During Radiation Therapy on Physical Function and Treatment-Related Side Effects in Men With Prostate Cancer: A Systematic Review and Meta-Analysis. Int J Radiat Oncol Biol Phys, 2021. 111: 716.
https://pubmed.ncbi.nlm.nih.gov/34246737/

1436. Kang, D.W., *et al*. Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance: The ERASE Randomized Clinical Trial. JAMA Oncol, 2021. 7: 1487.
https://pubmed.ncbi.nlm.nih.gov/34410322/

1437. Shao, W., *et al*. The effects of exercise on body composition of prostate cancer patients receiving androgen deprivation therapy: An update systematic review and meta-analysis. PLoS One, 2022. 17: e0263918.
https://pubmed.ncbi.nlm.nih.gov/35167609/

1438. Anderson, C.A., *et al*. Conservative management for postprostatectomy urinary incontinence. Cochrane Database Syst Rev, 2015. 1: CD001843.
https://pubmed.ncbi.nlm.nih.gov/25602133/

1439. Chen, Y.C., *et al*. Surgical treatment for urinary incontinence after prostatectomy: A meta-analysis and systematic review. PLoS One, 2017. 12: e0130867.
https://pubmed.ncbi.nlm.nih.gov/28467435/

1440. Crivellaro, S., *et al*. Systematic review of surgical treatment of post radical prostatectomy stress urinary incontinence. Neurourol Urodyn, 2016. 35: 875.
https://pubmed.ncbi.nlm.nih.gov/26397171/

1441. Cornu, J.-N., *et al*. , EAU Guidelines on Non-neurogenic Male LUTS, 2023. In: EAU Guidelines published at the 38th EAU Annual Congress, Milan. EAU Guidelines Office, Arnhem, The Netherlands.
https://uroweb.org/guidelines/management-of-non-neurogenic-male-luts

1442. Skolarus, T.A., *et al*. Androgen-deprivation-associated bone disease. Curr Opin Urol, 2014. 24: 601.
https://pubmed.ncbi.nlm.nih.gov/25144145/

1443. Patel, H.R., *et al*. Effects of tadalafil treatment after bilateral nerve-sparing radical prostatectomy: quality of life, psychosocial outcomes, and treatment satisfaction results from a randomized, placebo-controlled phase IV study. BMC Urol, 2015. 15: 31.
https://pubmed.ncbi.nlm.nih.gov/25879460/

1444. Philippou, Y.A., *et al*. Penile rehabilitation for postprostatectomy erectile dysfunction. Cochrane Database Syst Rev, 2018. 10: CD012414.
https://pubmed.ncbi.nlm.nih.gov/30352488/

1445. Salonia, A., *et al*., EAU Guidelines on Sexual and Reproductive Health. In: EAU Guidelines published at the 38th EAU Annual Congress, Milan. EAU Guidelines Office, Arnhem, The Netherlands.
https://uroweb.org/guidelines/sexual-and-reproductive-health

1446. Dieperink, K.B., *et al*. The effects of multidisciplinary rehabilitation: RePCa-a randomised study among primary prostate cancer patients. Br J Cancer, 2013. 109: 3005.
https://pubmed.ncbi.nlm.nih.gov/24169342/

1447. Dieperink, K.B., *et al*. Long-term follow-up 3 years after a randomized rehabilitation study among radiated prostate cancer survivors. J Cancer Surviv, 2021. 15: 668.
https://pubmed.ncbi.nlm.nih.gov/33079329/

1448. Galvao, D.A., *et al*. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol, 2010. 28: 340.
https://pubmed.ncbi.nlm.nih.gov/19949016/

1449. Bourke, L., *et al*. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol, 2014. 65: 865.
https://pubmed.ncbi.nlm.nih.gov/Medline:24119318/

1450. Cella, D., *et al*. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health, 2009. 12: 124.
https://pubmed.ncbi.nlm.nih.gov/18647260/

1451. Galvão, D.A., *et al*. Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: modifying effects of exercise from a year-long randomized controlled trial. Prostate Cancer Prostatic Dis, 2021. 24: 758.
https://pubmed.ncbi.nlm.nih.gov/33558661/

1452. Lopez, P., *et al*. Resistance Exercise Dosage in Men with Prostate Cancer: Systematic Review, Meta-analysis, and Meta-regression. Med Sci Sports Exerc, 2021. 53: 459.
https://pubmed.ncbi.nlm.nih.gov/32890199/

1453. Nair-Shalliker, V., *et al*. Post-treatment levels of plasma 25- and 1,25-dihydroxy vitamin D and mortality in men with aggressive prostate cancer. Sci Rep, 2020. 10: 7736.
https://pubmed.ncbi.nlm.nih.gov/32385370/

1454. Grant, W.B. Review of Recent Advances in Understanding the Role of Vitamin D in Reducing Cancer Risk: Breast, Colorectal, Prostate, and Overall Cancer. Anticancer Res, 2020. 40: 491.
https://pubmed.ncbi.nlm.nih.gov/31892604/

1455. Coleman, R., *et al*. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol, 2020. 31: 1650.
https://pubmed.ncbi.nlm.nih.gov/32801018/

1456. Shapiro, C.L., *et al*. Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline. J Clin Oncol, 2019. 37: 2916.
https://pubmed.ncbi.nlm.nih.gov/31532726/

1457. Briot, K., *et al*. French recommendations for osteoporosis prevention and treatment in patients with prostate cancer treated by androgen deprivation. Joint Bone Spine, 2019. 86: 21.
https://pubmed.ncbi.nlm.nih.gov/30287350/

1458. Saylor, P.J., *et al*. Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a Cancer Care Ontario Guideline. J Clin Oncol, 2020. 38: 1736.
https://pubmed.ncbi.nlm.nih.gov/31990618/

1459. Brown, J.E., *et al*. Guidance for the assessment and management of prostate cancer treatment-induced bone loss. A consensus position statement from an expert group. J Bone Oncol, 2020. 25: 100311.
https://pubmed.ncbi.nlm.nih.gov/32995252/

1460. Smith, M.R., *et al*. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol, 2003. 169: 2008.
https://pubmed.ncbi.nlm.nih.gov/12771706/

1461. Michaelson, M.D., *et al*. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol, 2007. 25: 1038.
https://pubmed.ncbi.nlm.nih.gov/17369566/

1462. Migliorati, C.A., *et al*. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet Oncol, 2006. 7: 508.
https://pubmed.ncbi.nlm.nih.gov/16750501/

1463. Wadhwa, V.K., *et al*. Frequency of zoledronic acid to prevent further bone loss in osteoporotic patients undergoing androgen deprivation therapy for prostate cancer. BJU Int, 2010. 105: 1082.
https://pubmed.ncbi.nlm.nih.gov/19912210/

1464. Clemons, M., *et al*. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer, 2021. 142: 132.
https://pubmed.ncbi.nlm.nih.gov/33023785/

1465. Smith, M.R., *et al*. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med, 2009. 361: 745.
https://pubmed.ncbi.nlm.nih.gov/19671656/

1466. Chen, R.C., *et al*. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA, 2017. 317: 1141.
https://pubmed.ncbi.nlm.nih.gov/28324092/

1467. Sanda, M.G., *et al*. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol, 2018. 199: 683.
https://pubmed.ncbi.nlm.nih.gov/29203269/

1468. Makarov, D.V., *et al*. AUA White Paper on Implementation of Shared Decision Making into Urological Practice. Urol Pract, 2016. 3: 355.
https://www.sciencedirect.com/science/article/abs/pii/S2352077915002733

1469. Stiggelbout, A.M., *et al*. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns, 2015. 98: 1172.
https://pubmed.ncbi.nlm.nih.gov/26215573/

1470. Violette, P.D., *et al*. Decision aids for localized prostate cancer treatment choice: Systematic review and meta-analysis. CA Cancer J Clin, 2015. 65: 239.
https://pubmed.ncbi.nlm.nih.gov/25772796/

1471. Ramsey, S.D., *et al*. Unanticipated and underappreciated outcomes during management of local stage prostate cancer: a prospective survey. J Urol, 2010. 184: 120.
https://pubmed.ncbi.nlm.nih.gov/20478590/

1472. Connolly, T., *et al*. Regret in Decision Making. Curr Direct Psych Sci, 2002. 11: 212.
https://journals.sagepub.com/doi/10.1111/1467-8721.00203

1473. Maguire, R., *et al*. Expecting the worst? The relationship between retrospective and prospective appraisals of illness on quality of life in prostate cancer survivors. Psychooncology, 2018. 27: 1237.
https://pubmed.ncbi.nlm.nih.gov/29430755/

1474. Schroeck, F.R., *et al*. Satisfaction and regret after open retropubic or robot-assisted laparoscopic radical prostatectomy. Eur Urol, 2008. 54: 785.
https://pubmed.ncbi.nlm.nih.gov/18585849/

1475. Steentjes, L., *et al*. Factors associated with current and severe physical side-effects after prostate cancer treatment: What men report. Eur J Cancer Care (Engl), 2018. 27.
https://pubmed.ncbi.nlm.nih.gov/27726215/

1476. Orom, H., *et al*. What Is a "Good" Treatment Decision? Decisional Control, Knowledge, Treatment Decision Making, and Quality of Life in Men with Clinically Localized Prostate Cancer. Med Decis Making, 2016. 36: 714.
https://pubmed.ncbi.nlm.nih.gov/26957566/

1477. Davison, B.J., *et al*. Quality of life, sexual function and decisional regret at 1 year after surgical treatment for localized prostate cancer. BJU Int, 2007. 100: 780.
https://pubmed.ncbi.nlm.nih.gov/17578466/

1478. Wilding, S., *et al*. Decision regret in men living with and beyond nonmetastatic prostate cancer in the United Kingdom: A population-based patient-reported outcome study. Psychooncology, 2020. 29: 886.
https://pubmed.ncbi.nlm.nih.gov/32065691/

1479. Martínez-González, N.A., *et al*. Shared decision making for men facing prostate cancer treatment: a systematic review of randomized controlled trials. Patient Prefer Adherence, 2019. 13: 1153.
https://pubmed.ncbi.nlm.nih.gov/31413545/

1480. Menichetti, J., *et al*. Quality of life in active surveillance and the associations with decision-making-a literature review. Transl Androl Urol, 2018. 7: 160.
https://pubmed.ncbi.nlm.nih.gov/29594030/

1481. Ivlev, I., *et al*. Prostate Cancer Screening Patient Decision Aids: A Systematic Review and Meta-analysis. Am J Prev Med, 2018. 55: 896.
https://pubmed.ncbi.nlm.nih.gov/30337235/

1482. Kinsella, N., *et al*. A Single Educational Seminar Increases Confidence and Decreases Dropout from Active Surveillance by 5 Years After Diagnosis of Prostate Cancer. Eur Urol Oncol, 2019. 2: 464.
https://pubmed.ncbi.nlm.nih.gov/31277784/

1483.   Hoffman, R.M., *et al*. Selecting Active Surveillance: Decision Making Factors for Men with a Low-Risk Prostate Cancer. Med Decis Making, 2019. 39: 962.
https://pubmed.ncbi.nlm.nih.gov/31631745/
1484.   Berry, D.L., *et al*. Decision Support with the Personal Patient Profile-Prostate: A Multicenter Randomized Trial. J Urol, 2018. 199: 89.
https://pubmed.ncbi.nlm.nih.gov/28754540/
1485.   Campagna, J.P., *et al*. Prostate Cancer Survival Estimates by the General Public Using Unrestricted Internet Searches and Online Nomograms. Eur Urol Focus, 2020. 6: 959.
https://pubmed.ncbi.nlm.nih.gov/30723050/
1486.   de Freitas, H.M., *et al*. Patient Preferences for Metastatic Hormone-Sensitive Prostate Cancer Treatments: A Discrete Choice Experiment Among Men in Three European Countries. Adv Ther, 2019. 36: 318.
https://pubmed.ncbi.nlm.nih.gov/30617763/
1487.   Lorent, M., *et al*. Meta-analysis of predictive models to assess the clinical validity and utility for patient-centered medical decision making: application to the CAncer of the Prostate Risk Assessment (CAPRA). BMC Med Inform Decis Mak, 2019. 19: 2.
https://pubmed.ncbi.nlm.nih.gov/30616621/
1488.   Riikonen, J.M., *et al*. Decision Aids for Prostate Cancer Screening Choice: A Systematic Review and Meta-analysis. JAMA Intern Med, 2019. 179: 1072.
https://pubmed.ncbi.nlm.nih.gov/31233091/
1489.   Vromans, R.D., *et al*. Communicative aspects of decision aids for localized prostate cancer treatment - A systematic review. Urol Oncol, 2019. 37: 409.
https://pubmed.ncbi.nlm.nih.gov/31053529/

10.   CONFLICT OF INTEREST

All members of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/prostate-cancer/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11.   CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.