

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

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# 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, a pathologist 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): Prof.Dr. S. Fanti, Prof.Dr. O Rouvière and Dr. I.G. Schoots.

All radiotherapy 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. A.M. Henry, Prof.Dr. M.D. Mason and Prof.Dr. T. Wiegel.

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: <http://uroweb.org/guideline/prostatecancer/?type=panel>.

### 1.2.1 Acknowledgement

The PCa Guidelines Panel gratefully acknowledges the assistance and general guidance provided by Prof.Dr. M. Bolla, honorary member of the PCa Guidelines Panel.

## 1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions 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 2020 document presents a limited update of the 2019 PCa Guidelines publication.

### 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.

The following sections have been revised, or were added:

- Section 3.2.1 - Family history/genetics, has been updated resulting in a new recommendation.

### 5.1.3 Guidelines for screening and early detection

Recommendation for all patients	LE	Strength rating
Offer early PSA testing to well-informed men at elevated risk of having PCa: <ul style="list-style-type: none"><li>• men carrying <i>BRCA2</i> mutations &gt; 40 years of age.</li></ul>	2b	Strong

- Chapter 4 - Classification and staging systems, including two recommendations.

#### 4.4 Guideline for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Use the International Society of Urological Pathology (ISUP) 2014 system for grading of PCa.	Strong

- Section 5.2.4.2.7.3 - The role of risk-stratification, has been revised with the inclusion of a new table (Table 5.2.4.2: Impact of the PSA density on csPCa detection rates in patients with negative mpMRI findings) and amended recommendations.

##### 5.2.4.4 Guidelines for imaging in PCa detection

Introductory statement	LE
Systematic biopsy is an acceptable approach in case mpMRI is unavailable.	3

Recommendations for all patients	LE	Strength rating
Do not use mpMRI as an initial screening tool.	3	Strong
Adhere to PI-RADS guidelines for multiparametric magnetic resonance imaging (mpMRI) acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	3	Strong

- Section 5.3.2.3 - Prostate-specific membrane antigen-based PET/CT, has been completely revised.
- Section - 5.2.7.3 Tissue-based prognostic biomarker testing, includes the findings of a recently published multidisciplinary Guideline, resulting in one recommendation to be changed from 'Strong' to 'Weak'.

##### 5.2.2.6 Guidelines for risk-assessment of asymptomatic men

Recommendation	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination and a prostate-specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: <ul style="list-style-type: none"> <li>an additional serum or urine-based test.</li> </ul>	Weak

- Chapter 5.2 - Clinical diagnosis, in particular Section 5.2.6 - Prostate biopsy procedure, was amended resulting in an changed recommendation.

##### 5.2.8 Guidelines for the clinical diagnosis of prostate cancer

Recommendation for all patients	LE	Strength rating
Do not offer non-targeted transition zone sampling at initial biopsies due to low detection rates.	2b	Weak

- Section 6.1.2 - Radical prostatectomy, has been completely revised.
- Section 6.1.3.1.3 - Hypofractionation, was revised, also including a new table (Table 6.1.8: Selected trials on hypofractionation for intact localised PCa).
- Section 6.1.4 - Hormonal therapy, new Section 6.1.4.1.1.6.4 - Darolutamide, has been added.

- Section 6.2.1 - Treatment of low-risk disease; the findings of an international collaborative multi-stakeholder consensus project addressing the deferred treatment with curative intent for localised have been incorporated, resulting in several changes to the recommendations for this section.

New sections 6.2.1.1.3 - Imaging for treatment selection, 6.2.1.1.4 - Monitoring during active surveillance, and 6.2.1.1.5 - Active surveillance, when to change strategy, have been added. Due to the inclusion of new data, new sections and the findings of the international collaborative multi-stakeholder consensus project addressing the deferred treatment with curative intent for localised PCa, a number of recommendations were changed, and new recommendations have been added.

#### 6.2.1.4 Guidelines for the treatment of low-risk disease

Recommendations	Strength rating
<b>Active surveillance (AS)</b>	
Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong
If required perform mpMRI before a confirmatory biopsy.	Strong
Take both targeted biopsy (of any PI-RADS > 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
Perform digital rectal examination (DRE) every 12 months.	Strong
Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
During follow-up, if mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of prostate cancer progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
Counsel patients about the possibility of needing further treatment in the future.	Strong
<b>Other therapeutic options</b>	
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

- 6.2.2.4 - Other options for the primary treatment of intermediate-risk PCa (experimental therapies), has been revised.
- Section 6.2.3 - Treatment of high-risk localised disease; due to the inclusion of new data, a recommendation was revised.

#### 6.2.4.4 Guidelines for radical treatment of high-risk localised disease

Recommendation	Strength rating
<b>Radical Prostatectomy (RP)</b>	
Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong

- Section 6.2.4 - Treatment of locally-advanced prostate cancer, has been revised, also including a new section on the treatment of cN1 disease, resulting in a new recommendation:

6.2.4.5 Guidelines for radical treatment of locally-advanced disease

Recommendations	Strength rating
<b>Radiotherapeutic treatments</b>	
Offer long-term ADT for at least two years.	Weak
<b>Therapeutic options outside surgery and radiotherapy</b>	
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, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
Offer patients with cN1 disease a local treatment (either RP or external beam radiation therapy) plus long-term ADT.	Weak

- Section 6.2.5 - Adjuvant treatment after radical prostatectomy, due to the inclusion of new data, two recommendations were revised.

6.2.5.6 Guidelines for adjuvant treatment options after radical prostatectomy

Recommendations	Strength rating
Offer adjuvant external-beam radiation therapy to the surgical field to highly selected patients.	Strong
Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics: <ol style="list-style-type: none"> <li>Offer adjuvant ADT;</li> <li>Offer adjuvant ADT with additional radiotherapy;</li> <li>Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA &lt; 0.1 ng/mL and absence of extranodal extension.</li> </ol>	Weak

- Section 6.3.4 - The role of imaging in PSA-only recurrence, has been completely revised.
- Due to the inclusion of new data in the second-line treatment modalities, two recommendations have been added.

6.3.9 Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
<b>Recommendations for biochemical recurrence after radical prostatectomy</b>	
Offer PSA monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak

- Section 6.4 - Treatment of metastatic prostate cancer, has been considerably revised with additional data (including new Section - 6.4.4.2.2 - Combination with the new hormonal treatments [abiraterone, ezalutamide]) and the inclusion of a new table (Table 6.4.5: Results from the ENZAMET and TITAN studies), necessitating changes to the recommendations.

#### 6.4.9 Guidelines for the first-line treatment of 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
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
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 antagonists monotherapy to patients with M1 disease.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit for the regimen.	Strong
Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong

- Section 6.5 - Treatment; Castration-resistant PCa, has been updated, also including additional information general aspects (Section 6.5.1.2) and sequencing of drugs. New section 6.5.8 - Prostate-specific membrane antigen (PSMA) therapy, has been included. Recommendations were changed in sections:

#### 6.5.13 Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease

Recommendation	Strength rating
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong

#### 6.5.15 Guidelines for supportive care of castrate-resistant disease

These recommendations are in addition to appropriate systemic therapy.

Recommendation	Strength rating
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong

#### 6.5.16 Guidelines for non-metastatic castrate-resistant disease

Recommendations	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.	Strong

- Chapter 7 - Follow-up, aside from revised data, includes new section 7.2.6 - Disease progression during androgen deprivation therapy.
- Due to the inclusion of new publications, new recommendations were added to Chapter 8 - Quality of life outcomes in prostate cancer:

*8.3.2.1 Guidelines for quality of life in men undergoing systemic treatments*

<b>Recommendation</b>	<b>Strength rating</b>
Advise men on androgen deprivation therapy to maintain a healthy weight and diet, to stop smoking and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong

*8.3.2.1 Guidelines for quality of life in men undergoing systemic treatments*

<b>Recommendations</b>	<b>Strength rating</b>
Offer men starting on long-term androgen deprivation therapy dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Use the WHO FRAX tool to guide monitoring and treatment of bone mineral density in men on long term ADT.	Strong

## 2. METHODS

### 2.1 Data identification

For the 2020 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a comprehensive review of the GRADE forms [see definition below] and associated recommendation. Changes in recommendations were only considered on the basis of high level evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials [RCTs], and prospective comparative studies) published in the English language. A total of 223 additional references were added to the 2020 PCa Guidelines. Additional information can be found in the general Methodology section of this print, and online at the EAU website; <http://www.uroweb.org/guideline/>.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [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.

The results of an international collaborative multi-stakeholder consensus project addressing the deferred treatment with curative intent for localised PCa have been incorporated in the 2020 EAU-EANM-ESTRO-ESUR-SIOG PCa Guidelines update. The methodology used is presented in detail in the scientific publication [7].

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) and the European Association of Nuclear Medicine (EANM) 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 SRs will be included in the 2021 update of the PCa Guidelines:

- A SR on the deferred treatment with curative intent for localised PCa, explore heterogeneity of definitions, thresholds and criteria [8];
- A SR on progression criteria and quality of life (QoL) of patients diagnosed with PCa;
- A SR on the definition and the prognostic value of PSA persistence after radical prostatectomy (RP) 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;
- A SR on surgeon/hospital volume for RP in non-metastatic PCa;
- A SR comparing oncological outcomes for nerve-sparing RP vs. non-nerve-sparing surgery in non-metastatic PCa;
- A SR on patient- and tumour-related characteristics as prognostic factors for post-RP incontinence in non-metastatic PCa.

# 3. EPIDEMIOLOGY AND AETIOLOGY

## 3.1 Epidemiology

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [9]. The frequency of autopsy-detected PCa is roughly the same worldwide [10]. 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 [11].

The incidence of PCa diagnosis varies widely between different geographical areas, being 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), largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), whilst rates in Eastern and Southern Europe, which were low, have showed a steady increase [9, 10].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (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) [9].

## 3.2 Aetiology

### 3.2.1 Family history/genetics

Family history and racial/ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [12, 13]. Only a small subpopulation of men with PCa (~9%) has true hereditary disease. This is defined as three or more affected relatives or at least two relatives who have developed early-onset PCa (< 55 years) [13]. Hereditary PCa is associated with a 6 to 7-year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways [13, 14]. The probability of high-risk PCa at age 65 in men with their father and two brothers affected was 11.4% (vs. a population risk of 1.4%) in a Swedish population-based study [15].

Men with one first-degree relative diagnosed with PCa still suffer an increased risk (relative risk [RR]: 1.8) of developing PCa, and this increases further in men with a father and brother (RR: 5.51) or two brothers (RR: 7.71) diagnosed with PCa [16]. Ancestry-specific risk loci have been identified [17] and genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for PCa [18-20]. Of the underlying determinants of genomic diversity and mechanisms between genetic and environmental factors, much remains unknown. However, it is accepted that men of African descent show a higher incidence of PCa and generally have a more aggressive course of disease [21].

Germline mutations have also been increasingly identified amongst men with non-hereditary PCa. In metastatic PCa patients an incidence of 11.8% germline mutations was found in genes mediating DNA-repair processes [22]. Mutations were most commonly seen in *BRCA2* (5.35%), *ATM* (1.6%), *CHEK2* (1.9%), *BRCA1* (0.9%), and *PALB2* (0.4%). In 3,607 unselected PCa patients, 620 (17.2%) were found to have a pathogenic germline variant [23]. The percentage of *BRCA1/2* mutations in this study was 5.99%. Germline mutations in genes such as *BRCA1/2* and *HOXB13* have been associated with an increased risk of PCa and targeted genomic analysis of these genes could offer options to identify families at high risk [24, 25].

A prospective cohort study of male *BRCA1* and *BRCA2* carriers confirmed the association between *BRCA2* and aggressive PCa [26]. *BRCA* mutation carriers were reported to have a worse outcome when compared to non-carriers after local therapy [27]. The IMPACT study evaluates targeted PCa screening (annually, biopsy recommended if PSA > 3.0 ng/mL) using PSA in men aged 40-69 years with germline *BRCA1/2* mutations [28]. The authors found that 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. The influence of *BRCA1* mutations on PCa remains unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* non-carriers. Limitations of the IMPACT study include the lack of mpMRI data and targeted biopsies as it was initiated before that era.

### 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 [29]. Japanese men have a lower PCa risk compared to men from the Western world. However, as Japanese men move from Japan to California, their risk of PCa increases, approaching that of American men, implying a role of environmental or dietary factors [30]. However, currently there are no known effective preventative dietary or pharmacological interventions.

#### 3.2.2.1 Metabolic syndrome (MetS)

The single components of 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  $\geq 3$  components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60-0.82) [31, 32].

##### 3.2.2.1.1 Diabetes/metformin

On a 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) [33]. 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,  $p = 0.50$ ) [34]. The ongoing Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial assesses metformin use in advanced PCa [35].

##### 3.2.2.1.2 Cholesterol/statins

A meta-analysis of 14 large prospective studies did not show an association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of either overall PCa or high-grade PCa [36]. Results from the REDUCE study also did not show a preventive effect of statins on PCa risk [34].

##### 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,  $p = 0.042$ ) [37]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [38].

#### 3.2.2.2 Dietary factors

The association between a wide variety of dietary factors and PCa have been studied (Table 3.1).

**Table 3.1: Dietary factors that have been associated with PCa**

<b>Alcohol</b>	High alcohol intake, but also total abstinence from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [39]. A meta-analysis shows a dose-response relationship with PCa [40].
<b>Dairy</b>	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [41].
<b>Fat</b>	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [42]. A relation between intake of fried foods and risk of PCa may exist [43].
<b>Tomatoes (lycopenes/ carotenes)</b>	A trend towards a favourable effect of tomato intake (mainly cooked) and lycopenes on PCa incidence has been identified in meta-analyses [44, 45]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [46].
<b>Meat</b>	A meta-analysis did not show an association between red meat or processed meat consumption and PCa [47].
<b>Phytoestrogens</b>	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [48].
<b>Soy (phytoestrogens [isoflavones/ coumestans])</b>	Total soy food intake has been associated with reduced risk of PCa, but also with increased risk of advanced disease [49, 50].
<b>Vitamin D</b>	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 [51, 52].
<b>Vitamin E/Selenium</b>	Inverse associations of blood, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [53, 54]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [55].

### 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 (~25%, for ISUP grade 1 cancer only), this must be weighed against treatment-related side-effects as well as the potential small increased risk of high-grade PCa [56-58]. 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 [59]. 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 [60].

#### 3.2.2.4 *Other potential risk factors*

Balding was associated with a higher risk of PCa death [61]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31; 95% CI: 1.14-1.52) [62]. 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 [63]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24; 95% CI: 1.18-1.31) [64]. 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 [65]. Men positive for human papillomavirus-16 may be at increased risk [66].

A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [67] and self-reported acne [68]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa and mortality [69, 70].

Ultraviolet radiation exposure decreased the risk of PCa (hazard ratio [HR]: 0.91; 95% CI: 0.88-0.95) [71]. A review found a small but protective association of circumcision status with PCa [72]. Higher ejaculation frequency ( $\geq 21$  times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [73].

The associations with PCa identified to date lack evidence for causality. As a consequence there is no data to suggest effective preventative strategies.

### 3.2.3 Summary of evidence and guidelines for epidemiology and aetiology

Summary of evidence
Prostate cancer is a major health concern in men, with incidence mainly dependent on age.
Genetic factors are associated with risk of (aggressive) PCa.
A variety of exogenous/environmental factors may have an impact on PCa incidence and the risk of progression.
Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.
In hypogonadal men, testosterone supplements do not increase the risk of PCa.

Recommendation	Strength rating
No specific preventive or dietary measures are recommended to reduce the risk of developing prostate cancer.	Weak

## 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 the design of clinical trials on relatively homogeneous patient 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 2017 Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [74] and the EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, are used (Table 4.3) [75]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence after radical prostatectomy (RP) or external beam radiotherapy (EBRT).

**Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [74]**

<b>T - Primary Tumour (stage based on digital rectal examination [DRE] only)</b>	
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 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
<b>N - Regional (pelvic) Lymph Nodes<sup>1</sup></b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
<b>M - Distant Metastasis<sup>2</sup></b>	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

<sup>1</sup> Metastasis no larger than 0.2 cm can be designated pNmi.

<sup>2</sup> When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

Clinical T stage only refers to DRE findings; imaging findings are not considered in the TNM classification. Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCas after RP are pathological stage T2 and the current Union for International Cancer Control (UICC) no longer recognises pT2 substages [74].

#### **4.2 Gleason score and International Society of Urological Pathology 2014 grade**

The 2005 International Society of Urological Pathology (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 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. When a carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the GS. A GS ≤ 5 should not be given based on prostate biopsies [76, 77]. In addition to reporting of the carcinoma features for each biopsy, an overall (or global) GS based on the carcinoma-positive biopsies can be provided. The global GS takes into account the extent of each grade from all prostate biopsies. The 2014 ISUP endorsed grading system [77, 78] limits the number of PCa grades, ranging them from 1 to 5 (see Table 4.2), in order to:

1. align the PCa grading with the grading of other carcinomas;
2. eliminate the anomaly that the most highly differentiated PCas have a GS 6;
3. to further define the clinically highly significant distinction between GS 7(3+4) and 7(4+3) PCa [79].

**Table 4.2: International Society of Urological Pathology 2014 grades**

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

**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+
<b>Localised</b>			<b>Locally advanced</b>

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

### 4.3 Prognostic relevance of stratification

A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management. The adoption of the current ISUP grading system, defining the split-up of GS 7 cancers into ISUP grade 2 (primary Gleason grade 3) and ISUP grade 3 (primary Gleason grade 4) because of their distinct prognostic impact strengthens such a separation of the intermediate-risk group into a low-intermediate (ISUP grade 2) and high intermediate-risk (ISUP grade 3) group [78] (see Section 5.2.7.4.3).

Emerging clinical data support this distinction between favourable- and unfavourable-risk patient categories within the intermediate-risk group [79, 80].

### 4.4 Guideline for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Use the International Society of Urological Pathology (ISUP) 2014 system for grading of PCa.	Strong

## 5. DIAGNOSTIC EVALUATION

### 5.1 Screening and early detection

#### 5.1.1 Screening

Population or mass screening is defined as the 'systematic examination of asymptomatic men (at risk)' 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).

Prostate cancer mortality trends range widely from country to country in the industrialised world [81]. Mortality due to PCa has decreased in most Western nations but the magnitude of the reduction varies between countries. Currently, screening for PCa still remains one of the most controversial topics in the urological literature [82].

Initial widespread aggressive screening in USA was associated with a decrease in mortality [83]. In 2012 the US Preventive Services Task Force (USPSTF) released a recommendation against non-selective PSA screening [84], which was adopted in the 2013 AUA Guidelines [85] and resulted in a reduction in the use

of PSA for early detection [86]. While PCa mortality had decreased for two decades since the introduction of PSA [87], the incidence of advanced disease and, possibly, cancer-related mortality began to rise after 2012 [88]. Similarly, the reduction in the use of PSA testing was associated with higher rates of advanced disease at diagnosis (e.g., a 6% increase in the number of patients with metastatic PCa) [89-93]. Moreover, additional evidence suggests a long-term benefit of PSA in terms of reduction of cancer-specific mortality [94, 95].

In 2017 the USPSTF issued an updated statement suggesting that men aged 55-69 should be informed about the benefits and harms of PSA-based screening as this might be associated with a small survival benefit. The USPSTF has now upgraded this recommendation to a grade C [96], from a previous grade of 'D' [96-98]. The grade D recommendation remains in place for men over 70 years old. This represents a major switch from discouraging PSA-based screening (grade D) to offering screening to selected patients depending on individual circumstances.

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 a marginal survival benefit, at best, in the opportunistic screening regimen [99].

A Cochrane review published in 2013 [100], which has since been updated [101], presents the main overview to date. The findings of the updated publication (based on a literature search until April 3, 2013) are almost identical to the 2009 review:

- Screening is associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).
- Screening is associated with detection of more localised disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80, 95% CI: 0.73-0.87).
- From the results of 5 RCTs, randomising more than 341,000 men, no PCa-specific survival benefit was observed (RR: 1.00, 95% CI: 0.86-1.17). This was the main endpoint in all trials.
- From the results of four available RCTs, no overall survival (OS) benefit was observed (RR: 1.00, 95% CI: 0.96-1.03).

The diagnostic tool (i.e. biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [57, 58]. Increased diagnosis has historically led to over-treatment with associated side-effects. However, despite this, the impact on the patient's overall QoL is still unclear. At a population level screening has never been shown to be detrimental [102-104]. Nevertheless, all these findings have led to strong advice against systematic population-based screening in most countries, including those in Europe.

In case screening is considered, a single PSA test is not enough based on the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial. The CAP trial evaluated a single PSA screening vs. controls not undergoing PSA screening on PCa detection in men aged 50 to 69 years old. The single PSA screening intervention detected more low-risk PCa cases but had no significant effect on PCa mortality after a median follow-up of 10 years [105].

Since 2013, the European Randomized Study of Screening for Prostate Cancer (ERSPC) data have been updated with 16 years of follow up (see Table 5.1) [106]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen (NNS) and to treat is decreasing, and is now below the NNS observed in breast cancer trials [106, 107].

**Table 5.1: Follow-up data from the ERSPC study [106]**

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

### 5.1.2 Early detection

An individualised risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis. It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it [12, 108].

Men at elevated risk of having PCa are those > 50 years [109] or at age > 45 years with a family history of PCa (either paternal or maternal [110]) or of African descent [111, 112]. Men of African descent are more likely to be diagnosed with more advanced disease [113] and upgrade was more frequent after prostatectomy as compared to Caucasian men (49% vs. 26%) [114]. In 2014, as for breast cancer, a genetic abnormality associated with an increased risk has been shown prospectively i.e. *BRCA2* [115, 116]. Prostate-specific antigen screening in male *BRCA2* carriers detected more significant cancers at a younger age compared to non-mutation carriers [28].

In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years are also at increased risk of PCa metastasis or death from PCa several decades later [117, 118]. The long-term survival and QoL benefits of such an approach remain to be proven at a population level.

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 [119]. Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [120]. The optimal intervals for PSA testing and DRE follow-up are unknown as they varied between several prospective trials. A single PSA test in men between 50 and 69 years did not improve 10-year PCa-specific survival compared to standard care in a large RCT in a primary care setting [105]. A risk-adapted strategy might be a consideration, based on the initial PSA level. This could be every 2 years for those initially at risk, or postponed up to 8 to 10 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 [121]. An analysis of ERSPC data supports a recommendation for an 8-year screening interval in men with an initial PSA concentration < 1 µg/L; fewer than 1% of men with an initial PSA concentration < 1 µg/L were found to have a concentration above the biopsy threshold of 3 µg/L at 4-year follow-up; the cancer detection rate by 8 years was close to 1% [122]. 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; comorbidity is at least as important as age. A detailed review can be found in Section 5.4 'Evaluating health status and life expectancy' and in the SIOG Guidelines [123, 360].

Multiple tools are now available to determine the need for a biopsy to establish the diagnosis of a PCa, including imaging by MRI, if available (see Section 5.2.4). New biological markers such as *TMPRSS2-ERG* fusion, PCA3 [124, 125] or kallikreins as incorporated in the Phi or 4Kscore tests [126, 127] have been shown to add sensitivity and specificity on top of PSA, potentially avoiding unnecessary biopsies and lowering over-diagnosis (see Section 5.2.2.4). At this time there is too limited data to implement these markers into routine screening programmes.

Risk calculators 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. Several tools developed from cohort studies are available including:

- the PCPT cohort: PCPTRC 2.0 <http://myprostatecancerrisk.com/>;
- the ERSPC cohort: <http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators>; An updated version was presented in 2017 including prediction of low and high risk now also based on the ISUP grading system and presence of cribriform growth in histology [128].
- a local Canadian cohort: <https://sunnybrook.ca/content/?page=asure-calc> (among others).

Since none of these risk calculators has clearly shown superiority, it remains a personal decision as to which one to use [129].

### 5.1.3 Guidelines for screening and early detection

Recommendations	LE	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	3	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	3	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: <ul style="list-style-type: none"> <li>men &gt; 50 years of age;</li> <li>men &gt; 45 years of age and a family history of PCa;</li> <li>men of African descent &gt; 45 years of age;</li> <li>men carrying <i>BRCA2</i> mutations &gt; 40 years of age.</li> </ul>	2b	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: <ul style="list-style-type: none"> <li>men with a PSA level of &gt; 1 ng/mL at 40 years of age;</li> <li>men with a PSA level of &gt; 2 ng/mL at 60 years of age;</li> </ul> Postpone follow-up to 8 years in those not at risk.	3	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.	3	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

Most PCas are located in the peripheral zone and may be detected by DRE when the volume is  $\geq 0.2$  mL. In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [130]. A suspect DRE in patients with a PSA level  $\leq 2$  ng/mL has a positive predictive value (PPV) of 5-30% [131]. An abnormal DRE is associated with an increased risk of a higher ISUP grade and is an indication for biopsy [132, 133].

### 5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [134]. 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. As an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS) [135].

There are no agreed standards defined for measuring PSA [136]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [137]. Table 5.2.1 demonstrates the occurrence of GS  $\geq 7$  (or ISUP  $\geq$  grade 2) PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant (cs) PCa. The use of nomograms may help in predicting indolent PCa [138].

**Table 5.2.1: Risk of PCa in relation to low PSA values [137]**

PSA level (ng/mL)	Risk of PCa (%)	Risk of ISUP grade $\geq 2$ 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

#### 5.2.2.1 PSA density

Prostate-specific antigen density is the level of serum PSA divided by the prostate volume. The higher the PSA density, the more likely it is that the PCa is clinically significant (see Section 6.2.1 - Treatment of low-risk disease).

#### 5.2.2.2 PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [139];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [140].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treating PCa but have limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time [141]. These measurements do not provide additional information compared with PSA alone [142-145].

#### 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) [146]. Prostate cancer was detected in men with a PSA 4-10 ng/mL by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 ng/mL [147]. A systematic review including 14 studies found a pooled sensitivity of 70% in men with a PSA of 4-10 ng/mL [148]. 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 the light of novel serum tests.

#### 5.2.2.4 Additional serum testing

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 multicentre studies demonstrated that both the PHI and 4K score test out-performed f/t PSA PCa detection, with an improved prediction of clinically significant PCa in men with a PSA between 2-10 ng/mL [127, 149-151]. In a head-to-head comparison both tests performed equally [152].

#### 5.2.2.5 Urine tests: PCA3 marker/SelectMDX/Mi Prostate score (MiPS)/ExoDX

Prostate cancer gene 3 (PCA3) is a prostate-specific, non-coding microRNA (mRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available ProgenSA urine test for PCA3 is superior to total and percent-free PSA for the detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve (AUC) for positive biopsies [153-156].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts the ISUP grade [157]. Currently, the main indication for the ProgenSA test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain [158]. Wei *et al.* showed 42% sensitivity at a cut-off of 60 in the primary biopsy setting with a high specificity (91%) and a PPV of 80% suggesting that the assay may be used in the primary setting [159].

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 [160].

*TMPRSS2-ERG* fusion, a fusion of the trans-membrane protease serine 2 (*TMPRSS2*) and the *ERG* gene can be detected in 50% of PCAs [161]. When detection of *TMPRSS2-ERG* in urine was added to PCA3 expression and serum PSA (Mi(chigan)Prostate Score [MiPS]), cancer prediction improved [162]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [163, 164]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care. However, currently, both the MiPS-score and ExoDx assay are considered investigational.

In 6 head-to-head comparison studies of PCA3 and PHI, only Seisen *et al.* found a significant difference; PCA3 detected more cancers, but for the detection of significant disease, defined as ISUP grade  $\geq 2$ , more than three positive cores, or > 50% cancer involvement in any core, PHI proved superior [165]. Russo *et al.* suggested in their systematic review that, based on moderate quality data, PHI and the 4K panel had a high diagnostic accuracy and showed similar performance in predicting the detection of significant disease [166]. However, 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 [124]. 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 [167]. However, upfront multiparametric magnetic resonance imaging (mpMRI) is also likely to affect the utility of above-mentioned

biomarkers (see Section 5.2.4).

#### 5.2.2.6 Guidelines for risk-assessment of asymptomatic men

Recommendation	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination and a prostate-specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: <ul style="list-style-type: none"> <li>risk-calculator;</li> <li>imaging;</li> </ul>	Strong
<ul style="list-style-type: none"> <li>an additional serum or urine-based test.</li> </ul>	Weak

#### 5.2.3 Baseline biopsy

The need for prostate biopsy is based on PSA level and/or suspicious DRE and/or imaging (see Section 5.2.4). Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [168]. Risk stratification is a potential tool for reducing unnecessary biopsies [168].

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]) [169, 170]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [171].

Ultrasound (US)-guided biopsy is now the standard of care. Prostate biopsy is performed by either the transrectal or transperineal approach. Cancer detection rates, when performed without prior imaging with MRI, are comparable between the two approaches [172], however some evidence suggests reduced infection risk with the transperineal route (see Section 5.2.6.4). Rectal disinfection with povidone-iodine may be considered [173, 174].

Transurethral resection of the prostate should not be used as a tool for cancer detection [175].

#### 5.2.4 The role of imaging in clinical diagnosis

##### 5.2.4.1 Transrectal ultrasound and ultrasound-based techniques

Grey-scale TRUS is not reliable at detecting PCa [176] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [177]. Prostate HistoScanning™ provided inconsistent results across studies [178]. New sonographic modalities such as sonoelastography, contrast-enhanced US or high-resolution micro-ultrasound have given promising preliminary findings; either alone or combined in the so-called ‘multiparametric US’. However, these techniques are still limited by lack of standardisation, lack of large-scale evaluation and unclear results in transition zones [179-184].

##### 5.2.4.2 Multiparametric magnetic resonance imaging

###### 5.2.4.2.1 Multiparametric magnetic resonance imaging performance in detecting ISUP grade $\geq 2$ PCa

Correlation with RP specimens shows that mpMRI has good sensitivity for the detection and localisation of ISUP grade  $\geq 2$  cancers [185-187]. This was further confirmed in patients who underwent template biopsies. In a recent Cochrane meta-analysis which compared mpMRI to template biopsies ( $\geq 20$  cores) in biopsy-naïve and repeat-biopsy settings, mpMRI 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  $\geq 2$  cancers [188]. For ISUP grade  $\geq 3$  cancers, mpMRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87-0.99) and 0.35 (95% CI: 0.26-0.46), respectively.

###### 5.2.4.2.2 Multiparametric magnetic resonance imaging performance in detecting ISUP grade 1 PCa

Multiparametric 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 [185]. In series using template biopsy findings as the reference standard, mpMRI has a pooled sensitivity of 0.70 (95% CI: 0.59-0.80) and a pooled specificity of 0.27 (95% CI: 0.19-0.37) for identifying ISUP grade 1 cancers [188].

###### 5.2.4.2.3 Does targeted biopsy improve the detection of ISUP grade $\geq 2$ as compared to systematic 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 (MRI-TBx; median number of cores, 2-7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-TBx alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02-1.23) for ISUP grade  $\geq 2$  cancers and 1.20 (95% CI: 1.06-1.36) for ISUP grade  $\geq 3$  cancers, and therefore in favour of MRI-TBx [188]. However, the pooled detection ratios for ISUP grade  $\geq 2$  cancers and ISUP grade  $\geq 3$  cancers were 1.44 (95% CI: 1.19-1.75) and 1.64 (95% CI: 1.27-2.11), respectively, in patients with prior negative systematic biopsies, and only 1.05 (95% CI: 0.95-1.16) and 1.09 (95% CI: 0.94-

1.26) in biopsy-naïve patients.

Three prospective multicentre trials evaluated MRI-TBx in biopsy-naïve patients. In the Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION) trial, 500 biopsy-naïve patients were randomised to either MRI-TBx only or TRUS-guided systematic biopsy only. The detection rate of ISUP grade  $\geq 2$  cancers was significantly higher in men assigned to MRI-TBx (38%) than in those assigned to SBx (26%,  $p = 0.005$ , detection ratio 1.46) [189]. In the Assessment of Prostate MRI Before Prostate Biopsies (MRI-FIRST) trial, 251 biopsy-naïve patients underwent TRUS-guided systematic biopsy by an operator who was blinded to mpMRI findings, and MRI-TBx by another operator. MRI-TBx detected ISUP grade  $\geq 2$  cancers in a higher percentage of patients but the difference was not significant (32.3% vs. 29.9%,  $p = 0.38$ ; detection ratio: 1.08) [177]. However, MRI-TBx detected significantly more ISUP grade  $\geq 3$  cancers than systematic biopsy (19.9% vs. 15.1%,  $p = 0.0095$ ; detection ratio: 1.32). A similar trend for improved detection of ISUP grade  $\geq 3$  cancers by MRI-TBx was observed in the Cochrane analysis, however, it was not statistically significant (detection ratio 1.11 [0.88-1.40]) [188]. The Met Prostaat MRI Meer Mans (4M) study included 626 biopsy-naïve patients; all patients underwent systematic biopsy, and those with a positive mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] 3-5, 51%) underwent additional in-bore MRI-TBx. The results were close to those of the MRI-FIRST trial with a detection ratio for ISUP grade  $\geq 2$  cancers of 1.09 (detection rate: 25% for MRI-TBx vs. 23% for systematic biopsy) [190]. However, in this study, MRI-TBx and systematic biopsy detected an equal number of ISUP grade  $\geq 3$  cancers (11% vs. 12%; detection ratio: 0.92).

Thus, MRI-TBx significantly out-performs systematic biopsy for the detection of ISUP grade  $\geq 2$  in the repeat-biopsy setting. In biopsy-naïve patients, the difference appears to be less marked and not significant in all series, but it remains in favour of MRI-TBx in most studies.

#### 5.2.4.2.4 Does MRI-TBx reduce the detection of ISUP grade 1 PCa as compared to systematic biopsy?

In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy and MRI-TBx, 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-naïve patients [188]. In the PRECISION and 4M trials, the detection rate of ISUP grade 1 patients was significantly lower in the MRI-TBx 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) [189, 190]. In the MRI-FIRST trial, MRI-TBx 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) [177]. Consequently, MRI-TBx significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy.

#### 5.2.4.2.5 The added value of systematic and targeted biopsy

Magnetic resonance imaging-targeted biopsies can be used in two different diagnostic pathways: 1) the 'combined pathway', in which patients with a positive mpMRI undergo combined systematic and targeted biopsy, and patients with a negative mpMRI undergo systematic biopsy; 2) the 'MRI pathway', in which patients with a positive mpMRI undergo only MRI-TBx, and patients with a negative mpMRI are not biopsied at all.

Many studies evaluated combined systematic and targeted biopsy in the same patients and could therefore assess the absolute added value of each technique (i.e. the percentage of patients diagnosed by only one biopsy technique). Data from the Cochrane meta-analysis of these studies and from the MRI-FIRST and 4M trials suggest that the absolute added value of MRI-TBx for detecting ISUP grade  $\geq 2$  cancers is higher than that of systematic biopsy (see Table 5.2.4.1).

**Table 5.2.4.1: Absolute added values of targeted and systematic biopsies for ISUP grade  $\geq 2$  and  $\geq 3$  cancer detection**

ISUP grade		ISUP $\geq 2$			ISUP $\geq 3$		
		Cochrane meta-analysis* [188]	MRI-FIRST trial* [177]	4M trial [190]	Cochrane meta-analysis* [188]	MRI-FIRST trial* [177]	4M trial [190]
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)	-	-

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

In Table 5.2.4.1 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-TBx to systematic biopsy in biopsy-naïve patients increases the number of ISUP grade  $\geq 2$  and grade  $\geq 3$  PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-TBx increases detection of ISUP grade  $\geq 2$  and grade  $\geq 3$  PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naïve patients would miss approximately 16% of ISUP grade  $\geq 2$  PCa and 18% of ISUP grade  $\geq 3$  PCa. In the repeat-biopsy setting, it would miss approximately 10% of ISUP grade  $\geq 2$  PCa and 9% of ISUP grade  $\geq 3$  PCa.

#### 5.2.4.2.6 Number of biopsy procedures potentially avoided 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 positive mpMRI. In pooled studies on biopsy-naïve patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of  $\geq 3$  would have avoided 30% (95% CI: 23-38) of all biopsy procedures while missing 11% (95% CI: 6-18) of all detected ISUP grade  $\geq 2$  cancers (relative percentage) [188]. Increasing the threshold to  $\geq 4$  would have avoided 59% (95% CI: 43-78) of all biopsy procedures while missing 28% (95% CI: 14-48) of all detected ISUP grade  $\geq 2$  cancers [188]. Of note, the percentages of negative mpMRI (Likert/PI-RADS score  $\leq 2$ ) in MRI-FIRST, PRECISION and 4M were 21.1%, 28.9% and 49%, respectively [177, 189, 190].

#### 5.2.4.2.7 Other considerations

##### 5.2.4.2.7.1 Multiparametric magnetic resonance imaging reproducibility

Despite the use of the PIRADSV2 scoring system [191], mpMRI inter-reader reproducibility remains moderate at best [192, 193] which currently limits its broad use by non-dedicated radiologists. However, significant improvement in the accuracy of mpMRI and MRI-TBx can be observed over time, both in academic and community hospitals, especially after implementation of PIRADSV2 scoring and multidisciplinary meetings using pathological correlation and feedback [194-197]. An updated version of the PIRADS score (PIRADSV2.1) has been recently published to improve reader reproducibility [198], but it has not yet been fully evaluated. It is still too early to predict whether quantitative approaches and computer-aided diagnostic systems will improve the characterisation of lesions seen at mpMRI [199-201].

#### 5.2.4.2.7.2 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 undersampled by MRI-TBx). In two retrospective studies of 211 and 116 patients with a unilateral mpMRI lesion, targeted biopsy alone detected 73.5-85.5% of all csPCa (ISUP grade  $\geq 2$ ); combining MRI-TBx with systematic biopsy of the lobe with the MRI lesion detected 96-96.4% of all csPCas and combined targeted and systematic biopsy of the contralateral lobe only identified 81.6-92.7% of csPCAs [202, 203]. The difference may reflect targeting errors leading to undersampling of the tumour. Increasing the number of cores taken per target may partially compensate for guiding imprecision. In a retrospective study of 479 patients who underwent MRI-TBx with 4 cores per target that were sequentially labelled, the first 3 cores detected 95.1% of the csPCAs detected by the 4-core strategy [204]. In two other retrospective studies of 330 and 744 patients who underwent MRI-TBx with up to 5 cores per target, the one-core and 3-core sampling strategies detected respectively 63-75% and 90-93% of the ISUP grade  $\geq 2$  PCa detected by the 5-core strategy [205, 206]. These percentages are likely to be influenced by the lesion size and location, the prostate volume or the operator's experience, but no study has quantified the impact of these factors yet.

#### 5.2.4.2.7.3 Role of risk-stratification

The negative predictive value (NPV) of a diagnostic test decreases when the disease prevalence increases, i.e. when the *a priori* risk of the patient increases. Therefore, the excellent NPV reported for mpMRI in the literature may not apply to patients with a higher risk of disease [207] and evaluating the individual risk of csPCa is essential for interpreting mpMRI results. Prostate-specific antigen density (PSAD) is one of the strongest predictors of csPCa in risk-models and several studies found that PSAD and the PIRADS score were significant independent predictors of csPCa at biopsy [208, 209]. In patients with negative mpMRI findings (PIRADS 1-2), the risk of finding csPCa at subsequent SBx is usually  $\leq 10\%$  if the PSAD is  $< 0.15$  ng/mL/cc. In contrast, it is 27-40% if the PSAD is  $> 0.15$ - $0.20$  ng/mL/cc [190, 209-213] (Table 5.2.4.2).

Several groups have developed nomograms which combine mpMRI findings with simple clinical data as a tool to predict subsequent biopsy results. These nomograms require further validation, but in due time they may out-perform predictors such as the current risk calculators (e.g. ERSPC or PCPT) in the selection of patients who may benefit from systematic and/or MRI-TBx [214]. Combining mpMRI findings with the PCA3 score, the PHI density or the results of the Stockholm3 blood test may also improve risk stratification [215-217].

**Table 5.2.4.2: Impact of the PSA density on csPCa detection rates in patients with negative mpMRI findings**

Study	Study design	Population	Biopsy protocol	csPCa definition	csPCa detection rate
Washino (2017) [209]	Retrospective Single centre	n = 288 Biopsy naïve	SBx (14 cores) + cognitive TBx	ISUP ≥ 2 or MCCL ≥ 4 mm	<b>Whole cohort</b> (prevalence): 49%  <b>PIRADS 1-2:</b> 0% if PSAD < 0.15, 20% if PSAD = 0.15-0.29, 30% if PSAD ≥ 0.3
Distler (2017) [208]	Retrospective analysis of prospective database Single centre	n = 1,040 Biopsy naïve + prior negative biopsy	TTP (24 cores) + fusion TBx	ISUP ≥ 2	<b>Whole cohort</b> (prevalence): 43%  <b>PIRADS 1-2 / Whole cohort:</b> 11% if PSAD ≤ 0.15, 33% if PSAD > 0.15  <b>PIRADS 1-2 / prior negative biopsy:</b> 7% if PSAD ≤ 0.15, 27% if PSAD > 0.15
Hansen (2017) [210]	Retrospective Single centre	n = 514 Prior negative biopsy or AS for ISUP 1 PCa	TTP (24 cores) + fusion TBx	ISUP ≥ 2	<b>Whole cohort</b> (prevalence): 31%  <b>Likert 1-2:</b> 9% if PSAD ≤ 0.10, 9% if PSAD ≤ 0.2, 29% if PSAD > 0.2
Hansen (2018) [211]	Retrospective Multicentre	n = 807 Biopsy naïve	TTP + cognitive or fusion TBx	ISUP ≥ 2	<b>Whole cohort</b> (prevalence): 49%  <b>PIRADS 1-2:</b> 10% if PSAD < 0.10, 21% if PSAD = 0.1-0.2, 33% if PSAD > 0.2
Oishi (2019) [212]	Retrospective analysis of prospective database Single centre	n = 135 Biopsy naïve + prior negative biopsy + AS + Restaging <b>Only pts with negative MRI (PIRADS &lt; 2)</b>	SBx (12 cores)	ISUP ≥ 2	<b>Whole cohort</b> (prevalence): 18%  <b>PSAD &lt; 0.10:</b> 6% (overall pop), 15% (biopsy naïve), 0% (prior negative biopsy) <b>PSAD &lt; 0.15:</b> 10% (overall pop), 20% (biopsy naïve), 0% (prior negative biopsy) <b>PSAD &gt; 0.15:</b> 40% (overall pop), 29% (biopsy naïve), 29% (prior negative biopsy)
Boesen (2019) [213]	Retrospective analysis of prospective database Single centre	n = 808 Biopsy-naïve	SBx (10 cores) + fusion TBx	ISUP ≥ 2	<b>Whole cohort</b> (prevalence): 35%  <b>PIRADS 1-2:</b> 3% if PSAD < 0.10, 5% < 0.15, 5% if PSAD < 0.2, 32% if PSAD ≥ 0.2

Van der Leest (2019) [190]	Prospective Multicentre	n = 626 Biopsy naïve	TTP Bx (median 24 cores) + fusion TBx	ISUP ≥ 2	<b>Whole cohort</b> (prevalence): 30%  <b>PIRADS 1-2:</b> 1.3% if PSAD < 0.10, 2% if PSAD < 0.15
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*Retrosop.* = retrospective; *n* = number of patients; *SBx* = systematic transrectal biopsy; *TBx* = targeted biopsy; *TTP* = transperineal template biopsy; *PSAD* = PSA density; *ISUP* = international Society of Urological Pathology; *MCCL* = maximum cancer core length.

#### 5.2.4.3 Summary of evidence and practical considerations on pre-biopsy mpMRI

Magnetic resonance imaging-targeted biopsies substantially improve the detection of ISUP grade ≥ 2 PCa. This improvement is most notable in the repeat-biopsy setting, with marginal added value for systematic biopsies. It is less marked in biopsy-naïve patients in whom systematic biopsy retain a higher added value, at least for the detection of ISUP grade 2 cancers. Magnetic resonance imaging-targeted biopsies also detect significantly less ISUP grade 1 cancers than systematic biopsies.

The ‘MRI pathway’ is appealing since it could decrease the number of biopsy procedures, reduce the detection of low-grade PCa while maintaining (or even improving) the detection of csPCa, as compared to systematic biopsy. However, mpMRI findings must be interpreted in the light of the *a priori* risk of csPCa. Risk calculators or PSAD may help identify patients that can safely avoid biopsy in case of a negative mpMRI. Furthermore, without standardisation of mpMRI interpretation and of MRI-TBx technique the ‘MR pathway’ may lead to suboptimal care outside large-volume (expert) centres. Indeed, limitations of the ‘MR pathway’ are the moderate inter-reader reproducibility of mpMRI and the lack of standardisation of MRI-TBx, as well as the fact that MRI-TBx inter-operator reproducibility has not been evaluated. These caveats also apply to the systematic biopsy procedure. A substantial proportion of csPCa missed by the ‘MR pathway’ may be due to the imprecision of current targeting methods, and 3 to 5 biopsy cores per target may be needed to reduce the risk of missing or undersampling the lesion, even with US/MR fusion systems.

Finally, it must be emphasised that the ‘MR pathway’ has only been evaluated in patients in whom the risk of csPCa was judged high enough to deserve biopsy. Pre-biopsy mpMRI must not be used in patients who do not have an indication for prostate biopsy based on their family history and clinical and biochemical data. Because of its low specificity, mpMRI in very low-risk patients would result in an inflation of false-positive findings and subsequent unnecessary biopsies.

#### 5.2.4.4 Guidelines for imaging in PCa detection

<b>Introductory statement</b>	<b>LE</b>
Systematic biopsy is an acceptable approach in case mpMRI is unavailable.	3

<b>Recommendations for all patients</b>	<b>LE</b>	<b>Strength rating</b>
Do not use multiparametric magnetic resonance imaging (mpMRI) as an initial screening tool.	3	Strong
Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	3	Strong

<b>Recommendations in biopsy naïve patients</b>	<b>LE</b>	<b>Strength rating</b>
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	2a	Strong
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.	2a	Weak

<b>Recommendations in patients with prior negative biopsy</b>	<b>LE</b>	<b>Strength rating</b>
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	2a	Weak
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared shared decision making with the patient.	2a	Strong

### 5.2.5 Repeat biopsy

#### 5.2.5.1 Repeat biopsy after previously negative biopsy

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2.1 for risk estimates);
- suspicious DRE, 5-30% PCa risk [130, 131];
- atypical small acinar proliferation (i.e. atypical glands suspicious for cancer), 31-40% PCa risk on repeat biopsy [218, 219];
- extensive (multiple biopsy sites, i.e.  $\geq 3$ ) high-grade prostatic intraepithelial neoplasia (HGPIN), ~30% PCa risk [219, 220];
- a few atypical glands immediately adjacent to high-grade prostatic intraepithelial neoplasia (i.e. PINATYP), ~50% PCa risk [221];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade PCa [222];
- positive multiparametric MRI (mpMRI) findings (see Section 5.2.4.2).

##### 5.2.5.1.1 Tests to select men for a repeat biopsy

In men with an elevated risk of PCa with a prior negative biopsy, additional information may be gained by the ProgenSA-PCA3 and SelectMDX DRE urine tests, the serum 4Kscore and PHI tests or a tissue-based epigenetic test (ConfirmMDx). 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 [158]. 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 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 mpMRI 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 mpMRI before biopsy.

**Table 5.2.5.1: Description of additional investigational tests after a negative prostate biopsy\***

Name of test	Test substrate	Molecular	FDA approved
ProgenSA	DRE urine	lncRNA PCA3	Yes
SelectMDX	DRE urine	mRNA HOXC6, DLX1	No
PHI	Serum	Total, free and p2PSA	Yes
4Kscore Test	Serum/plasma	Total, free, intact PSA, hK2	No
ConfirmMDX	Benign prostate biopsy	Methylated APC, RASSF1 and GSTP1	No

\*Isolated high-grade prostatic intraepithelial neoplasia (PIN) in one or two biopsy sites is no longer an indication for repeat biopsy [224].

#### 5.2.5.2 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 [225]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention (10%) is a drawback [226].

### 5.2.6 Prostate biopsy procedure

#### 5.2.6.1 Sampling sites and number of cores

On baseline biopsies, where no prior imaging with mpMRI has been performed, or where mpMRI has not shown any suspicious lesion, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas identified by DRE; suspect areas on TRUS might be consideration for additional biopsies. Sextant biopsy is no longer considered adequate. At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc [227]. Ten to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive [228, 229].

Where mpMRI has shown a suspicious lesion MR-TBx can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature does not show a clear superiority of one technique over another [230-233]. A minimum of 3 cores are taken from each lesion (see Section 5.2.4.2.7.2).

#### 5.2.6.2 Antibiotics prior to biopsy

Oral or intravenous antibiotics are recommended. For transrectal biopsy, quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin [234]. Antibiotic prophylaxis showed a significant reduction in UTIs post biopsy. A 3-day antibiotic prophylaxis regimen provided no benefit over single-dose prophylaxis [235]. Increased quinolone resistance is associated with a rise in severe post-biopsy infection [236, 237]. Norwegian registry data show an increase in antibiotic resistance for both TMP-SMX and ciprofloxacin in recent years with an associated increase in 30-day mortality [238]. Risk factors for quinolone resistance include previous TRUS biopsy, a current indwelling catheter, and any of: urogenital infection, international travel or hospital admission within the previous 6 months. To minimise risk of severe infection due to quinolone resistant rectal flora, patients with any of these risk factors should be offered either TRUS biopsy with prior rectal swab culture or targeted antibiotic prophylaxis [173]. Rectal disinfection with povidone-iodine may be considered [173]. For transperineal biopsy, which avoids rectal flora, a single dose of intravenous cephazolin only is sufficient [239, 240]. A 2017 systematic review [172] found no significant difference between transrectal and transperineal biopsies with respect to infection while a more recent meta-analysis including 7 comparative studies showed in twice the number of patients a RR of 0.26 (0.14-0.48) for the risk of fever after transperineal biopsies compared to transrectal biopsies [241].

#### 5.2.6.3 Local anaesthesia prior to biopsy

Ultrasound-guided peri-prostatic block is recommended [242]. It is not important whether the depot is apical or basal. Intra-rectal instillation of local anaesthesia is inferior to peri-prostatic infiltration [243]. Local anaesthesia can also be used effectively for mpMRI-targeted transperineal biopsy [244]. Patients are placed in the lithotomy position. Bupivacaine is injected into the perineal skin and subcutaneous tissues, 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]). [241]. In a randomised comparison a combination of peri-prostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to peri-prostatic anaesthesia only [245]. Targeted biopsies can then be taken via a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [244, 246, 247].

#### 5.2.6.4 Complications

Complications of TRUS biopsy are listed in Table 5.2.3 [248]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [249]. Low-dose aspirin is no longer an absolute contraindication [250]. A systematic review found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haemospermia and urinary retention [251]. 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 [172].

**Table 5.2.6.1: Percentage of complications per TRUS biopsy session, irrespective of the number of cores**

Complications	Percentage of patients affected
Haemospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Epididymitis	0.7
Rectal bleeding > 2 days +/- surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

#### 5.2.6.5 Seminal vesicle biopsy

Indications for seminal vesicle (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20-25% [252]. A seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent radiotherapy (RT). Its added value compared with mpMRI is questionable.

#### 5.2.6.6 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to repeat biopsies [253].

#### 5.2.7 Pathology of prostate needle biopsies

##### 5.2.7.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [254]. To achieve optimal flattening and alignment, a maximum of three cores should be embedded per tissue cassette, and sponges or paper used to keep the cores stretched and flat [255, 256]. To optimise detection of small lesions, paraffin blocks should be cut at three levels and intervening unstained sections kept for immunohistochemistry [253].

##### 5.2.7.2 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 [257-259]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [257]. Table 5.2.7.1 lists the recommended terminology for reporting prostate biopsies [255].

**Table 5.2.7.1: Recommended terminology for reporting prostate biopsies [255]**

Recommended terminology	Strength rating
Benign/negative for malignancy; if appropriate, include a description	Strong
Active inflammation	
Granulomatous inflammation	
High-grade prostatic intraepithelial neoplasia (PIN)	
High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)	
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer	
Adenocarcinoma	
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 2014 grade [77]. A global ISUP grade comprising all 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 worse grade would be ISUP grade 4 (i.e. GS 8[4+4]). Recent publications demonstrated that global ISUP grade is somewhat superior in predicting prostatectomy ISUP grade [260] and biochemical recurrence (BCR) [261].

Intraductal carcinoma, lymphovascular invasion (LVI) and extraprostatic extension (EPE) must each be reported, if identified. More recently, expansile cribriform pattern of PCa as well as intraductal carcinoma in biopsies were identified as independent prognosticators of metastatic disease [262] and PCa-specific survival [263].

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP grade, tumour volume, surgical margins and pathologic stage in RP specimens and predict BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [264-266]. A pathology report should therefore provide both the proportion 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 [267]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [268] triggering immediate treatment vs. AS in patients with ISUP grade 1.

A prostate biopsy that does not contain glandular tissue should be reported as diagnostically inadequate. Mandatory elements to be reported for a carcinoma-positive prostate biopsy are:

- type of carcinoma;
- primary and secondary/worst Gleason grade (per biopsy site and global);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (at least per biopsy site);
- if present: EPE, seminal vesicle invasion, LVI, intraductal carcinoma/ciribriform pattern, peri-neural invasion;
- ISUP grade (global).

#### 5.2.7.3 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 [269].

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 clinically significant PCa requiring curative treatment, as well as for guidance of patient management after RP. In addition, a few studies showed that tissue biomarker tests and MRI findings independently improved the detection of clinically significant cancer in an AS setting, but it remains unclear which men would benefit of both tests. 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 at RP to decide on treatment intensification with hormonal therapy (HT).

#### 5.2.7.4 Histopathology of radical prostatectomy specimens

##### 5.2.7.4.1 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 detected 98% of PCa with an ISUP grade  $\geq 2$  with accurate staging in 96% of cases [270].

Ink the entire RP specimen 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. Fixation can be enhanced by injecting formalin, which provides more homogeneous fixation and sectioning after 24 hours [271]. 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 [76]. 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.

##### 5.2.7.4.1.1 Guidelines for processing prostatectomy specimens

Recommendations	LE	Strength rating
Ensure total embedding, by conventional (quadrant) or whole-mount sectioning.	3	Strong
Ink the entire surface before cutting, to evaluate the surgical margin.	3	Strong
Examine the apex and base separately, using the cone method with sagittal or radial sectioning.	3	Strong

#### 5.2.7.4.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.7.1). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.7.2). Synoptic reporting results in more transparent and complete pathology reporting [272].

**Table 5.2.7.1: Mandatory elements provided by the pathology report**

Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma.
Grading according to ISUP grade (or not applicable if therapy-related changes).
Presence of intraductal carcinoma.
Tumour (sub)staging and surgical margin status: location and extent of EPE, presence of bladder neck invasion, laterality of EPE or seminal vesicle invasion, location and extent of positive surgical margins.
Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.

**Table 5.2.7.2: Example checklist: reporting of prostatectomy specimens**

<b>Histopathological type</b>
Type of carcinoma, e.g. conventional acinar, or ductal
<b>Histological grade</b>
Primary (predominant) Gleason grade
Secondary Gleason grade
Tertiary Gleason grade (if applicable)
Global ISUP grade
Approximate percentage of Gleason grade 4 or 5
<b>Tumour quantitation (optional)</b>
Percentage of prostate involved
Size/volume of dominant tumour nodule
<b>Pathological staging (pTNM)</b>
<i>If extraprostatic extension is present:</i> indicate whether it is focal or extensive; specify sites; indicate whether there is seminal vesicle invasion.
<i>If applicable, regional lymph nodes:</i> location; number of nodes retrieved; number of nodes involved.
<b>Surgical margins</b>
<i>If carcinoma is present at the margin:</i> specify sites.
<b>Other</b>
Presence of lymphovascular/angio-invasion
Location of dominant tumour
Presence of intraductal carcinoma/cribriform architecture

#### 5.2.7.4.3 ISUP grade in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [77]. The ISUP grade is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [273].

The ISUP grade is based on the sum of the most and second-most dominant (in terms of volume) Gleason grade. ISUP grade 1 is any GS  $\leq$  6 (including < 5% Gleason grade 4). ISUP grades 2 and 3 represent carcinomas constituted of Gleason grade 3 and 4 components, with ISUP grade 2 when 50% of the carcinoma, or more, is Gleason grade 3 and ISUP grade 3 when the grade 4 component represents more than 50% of the carcinoma. ISUP grade 4 is largely composed of Gleason grade 4 and ISUP grade 5 of a combination of Gleason grade 4 and 5 or only Gleason grade 5. A global ISUP grade is given for multiple tumours, but a separate tumour focus with a higher ISUP grade should also be mentioned. Tertiary Gleason grade 5,

particularly if > 5% of the PCa volume, is an unfavourable prognostic indicator for BCR. The tertiary Gleason grade and its approximate proportion of the cancer volume should also be reported in addition to the global ISUP grade (see Section 4.2) [274].

#### 5.2.7.4.4 Definition of extraprostatic extension

Extraprostatic 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 [275].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [276] or extension as < 1 per high-power field (HPF) [277], whereas others measure the depth of extent in millimetres [278].

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 [279, 280] and should be recorded as EPE (pT3a). A positive margin at the bladder neck should be reported as EPE (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [281].

#### 5.2.7.4.5 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [277, 282-285]. Nevertheless, a cut-off of 0.5 mL is traditionally used to distinguish insignificant from clinically relevant cancer [282]. Improvement in prostatic radio-imaging allows more accurate pre-operative measurement of cancer volume. It is recommended that at least the diameter/volume of the dominant tumour nodule should be assessed, or a rough estimate of the percentage of cancer tissue provided [286].

#### 5.2.7.4.6 Surgical margin status

Surgical margin 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 [283] 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 [287].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [288]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [277]. However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [289], or number of blocks with positive margin involvement. Gleason score at the positive margin was found to correlate with outcome, and should be reported [245].

### 5.2.8 Guidelines for the clinical diagnosis of prostate cancer

Recommendations	LE	Strength rating
Perform transrectal prostate needle biopsies under antibiotic protection.	1b	Strong
Use a local anaesthetic by peri-prostatic infiltration for prostate needle biopsies.	1a	Strong
Do not offer non-targeted transition zone sampling at initial biopsies due to low detection rates.	2b	Weak
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	3	Strong

## 5.3 Diagnosis - Clinical Staging

The extent of PCa is evaluated by DRE and PSA, and may be supplemented with mpMRI, bone scanning and computed tomography (CT).

### 5.3.1 T-staging

The cT category used in the risk table only refers to the DRE finding. The imaging parameters and biopsy results for local staging are, so far, not part of the risk category stratification.

#### 5.3.1.1 TRUS

Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [290]. Some single-

centre studies reported good results in local staging using 3D TRUS or colour Doppler but these good results were not confirmed by large-scale studies [291, 292].

#### 5.3.1.2 *mpMRI*

T2-weighted imaging remains the most useful method for local staging on mpMRI. At 1.5 Tesla, mpMRI has good specificity but low sensitivity for detecting T3 stages. Pooled data from a meta-analysis for EPE, SVI, and overall stage T3, 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), respectively [293]. Multiparametric MRI cannot detect microscopic EPE. Its sensitivity increases with the radius of extension within peri-prostatic fat. In one study, the EPE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [294]. In another study, mpMRI sensitivity, specificity and accuracy for detecting pT3 stage were 40%, 95% and 76%, respectively, for focal (i.e. microscopic) EPE, and 62%, 95% and 88% for extensive EPE [295].

The use of high field strength (3 Tesla) or functional imaging in addition to T2-weighted imaging improves sensitivity for EPE or SVI detection [293], but the experience of the reader remains of paramount importance [296] and the inter-reader agreement remains moderate with kappa values ranging from 0.41 to 0.68 [297]. Multiparametric MRI, although not perfect for local staging, may improve the prediction of the pathological stage when combined with clinical data [298, 299]. Other MRI-derived parameters such as the tumour volume or the contact length of the tumour with the capsule [300-302], or the ISUP grade obtained through MRI-TBx [303] could further improve the local staging [303].

Given its low sensitivity for focal (microscopic) EPE, mpMRI is not recommended for local staging in low-risk patients [298, 304, 305]. However, mpMRI can still be useful for treatment planning.

#### 5.3.2 *N-staging*

##### 5.3.2.1 *Computed tomography (CT) and magnetic resonance imaging*

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 [306, 307]. Computed tomography and MRI sensitivity is less than 40% [308, 309]. Among 4,264 patients, 654 (15.3%) of whom had positive LNs at LND, CT was positive in only 105 patients (2.5%) [306]. In a multicentre database of 1,091 patients who underwent pelvic LN dissection, CT sensitivity and specificity were 8.8% and 98%, respectively [310]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade < 4 cancer, PSA < 20 ng/mL, or localised disease [311-313].

Diffusion-weighted MRI may detect metastases in normal-sized nodes, but a negative diffusion-weighted MRI cannot rule out the presence of LN metastases [307, 314].

##### 5.3.2.2 *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 [315]. 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 [316]. The sensitivity of choline PET/CT increases to 50% in patients at high risk and to 71% in patients at very high risk, in both cases out-performing contrast-enhanced CT [317]. However, comparisons between choline PET/CT and diffusion-weighted MRI yielded contradictory results, with PET/CT sensitivity found to be superior [318], similar [319, 320] or inferior [316] than that of diffusion-weighted MRI.

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).

##### 5.3.2.3 *Prostate-specific membrane antigen-based PET/CT*

<sup>68</sup>Ga- or <sup>18</sup>F-labelled prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT is increasingly used, because it provides excellent contrast-to-noise ratio, thereby improving the detectability of lesions. Prostate-specific membrane antigen is also an attractive target because of its specificity for prostate tissue, even if expression of PSMA in other non-prostatic malignancies, sarcoidosis or benign bone diseases, may cause incidental false-positive findings [321-324].

Recent assessment of PSMA PET/CT showed promising sensitivity for LN involvement, also suggesting that this modality may impact clinical decision making. From a meta-analysis of 37 articles, a subgroup analysis of 13 studies was performed in PCa patients prior to definitive therapy, using histological correlation as reference standard. The predictive ability of PSMA-PET imaging for primary staging was derived

from 5 studies. On a per-LN analysis, the pooled sensitivity and specificity were 75% and 99%, respectively. On a per-patient analysis, the pooled sensitivity and specificity were 77% and 97%, respectively [325]. Another prospective, multicentre validation of <sup>68</sup>Ga PSMA PET/CT in patients with newly diagnosed PCa and negative bone scan findings was recently published. In 103 eligible patients at increased risk for metastatic LNs prior to surgery, 97 eLNDs were performed, resulting in the identification of 85 LN metastases in 41 patients (42.3%). Positron emission tomography was positive in 17 patients, resulting in a per-patient-based sensitivity and specificity of 41.5% (95% CI: 26.7-57.8) and 90.9% (95% CI: 79.3-96.6), respectively. A treatment change occurred in 12.6% of patients [326].

Prostate-specific antigen may be a predictor of a positive PSMA PET scan. In the primary staging cohort from the meta-analysis [325], however, only 4 studies reported PSMA PET-positivity based on the PSA value, offering no robust estimates of positivity. The tracer uptake is also influenced by the ISUP grade and the PSA level. In a series of 90 patients with primary PCa, tumours with an ISUP grade between 1 and 3 showed significantly lower tracer uptake than tumours with an ISUP grade  $\geq$  4. Similarly, patients with PSA levels  $\geq$  10 ng/mL showed significantly higher uptake than those with PSA levels  $<$  10 ng/mL [327].

Comparison between PSMA PET/CT and mpMRI was recently performed in a systematic review and meta-analysis, including 13 studies ( $n = 1,597$ ) [328]. <sup>68</sup>Ga- was found to have a higher sensitivity and a comparable specificity for staging pre-operative LN metastases in intermediate- and high-risk PCa. The pooled sensitivity and specificity of <sup>68</sup>Ga-PSMA PET were 0.65 (95% CI: 0.49-0.79) and 0.94 (95% CI: 0.88-0.97), respectively, while the corresponding values of MRI were 0.41 (95% CI: 0.26-0.57) and 0.92 (95% CI: 0.86-0.95). <sup>68</sup>Ga-PSMA PET was potentially a more effective and appropriate imaging modality to predict LN metastasis prior to surgery, as indicated by the area under the symmetric receiver-operating characteristic (SROC) curve. Another prospective trial reported superior sensitivity of PSMA PET/CT as compared to mpMRI for nodal staging of 36 high-risk PCa patients [329]. Therefore, PSMA PET/CT has higher sensitivity for LN metastases as compared to mpMRI, abdominal contrast-enhanced CT or choline PET/CT; however, small LN metastases, under the spatial resolution of PET (~5 mm), may still be missed.

### 5.3.3 *M-staging*

#### 5.3.3.1 *Bone scan*

<sup>99m</sup>Tc-Bone scan has been the most widely used method for evaluating bone metastases of PCa. A recent meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73-83%) and 82% (95% CI: 78-85%) at patient level and 59% (95% CI: 55-63%) and 75% (95% CI: 71-79%) at lesion level [330]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade and these three factors were the only independent predictors of bone scan positivity in a study of 853 patients [331]. The mean bone scan positivity rate in 23 different series was 2.3% in patients with PSA levels  $<$  10 ng/mL, 5.3% in patients with PSA levels between 10.1 and 19.9 ng/mL and 16.2% in patients with PSA levels of 20.0-49.9 ng/mL. It was 6.4% in men with organ-confined cancer and 49.5% in men with locally advanced cancers. Detection rates were 5.6% and 29.9% for ISUP grade 2 and  $>$  3, respectively [306]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive bone scan [332, 333].

Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP grade or clinical stage [306].

#### 5.3.3.2 *Fluoride PET and PET/CT, choline PET/CT and MRI*

<sup>18</sup>F-sodium fluoride (<sup>18</sup>F-NaF) PET or PET/CT shows similar specificity and superior sensitivity to bone scan [334, 335]. However, unlike choline PET/CT, <sup>18</sup>F-NaF PET does not detect LN metastases, and is less cost-effective compared to bone scan [333]. A recent publication indicated that <sup>18</sup>F-NaF PET offers no added value over bone scintigraphy in patients with newly diagnosed PCa and negative bone scintigraphy results [336]. It remains unclear whether choline PET/CT is more sensitive than bone scan, but it has higher specificity, with fewer indeterminate bone lesions [315, 337, 338].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa [339, 340]. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [341]. A meta-analysis found that 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 [330].

It is of note that choline PET/CT and diffusion-weighted MRI can also detect visceral metastases.

Bone scan and <sup>18</sup>F-NaF PET/CT only assess the presence of bone metastases.

#### 5.3.3.3 *Prostate-specific membrane antigen-based PET/CT*

There is growing evidence on the performance of <sup>68</sup>Ga-PSMA PET/CT in initial staging. A recent systematic review including 12 studies and comprising a total of 322 patients reported high variation in sensitivity (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) [342]. Table 5.3.1 reports the data of the 5 studies including histopathologic correlation.

**Table 5.3.1: PSMA PET/CT results in primary staging alone** [342]

Study	Sensitivity (per lesion)	Specificity (per lesion)	PPV (per lesion)	NPV (per lesion)
Budaus	33%	100%	100%	69%
Herlemann	84%	82%	84%	82%
Van Leeuwen	58%	100%	94%	98%
Maurer	74%	99%	95%	94%
Rahbar	92%	92%	96%	85%

NPV = negative predictive value; PPV = positive predictive value.

One prospective multicentre study evaluated changes in planned management before and after PSMA PET/CT in 108 intermediate- and high-risk patients referred for primary staging. As compared to conventional staging, additional LNs and bone/visceral metastases were detected in 25% and 6% of patients, respectively [343]; management changes occurred in 21% of patients. A recent retrospective review investigated the risk of metastases identified by Ga-PSMA at initial staging in 1,253 patients (high-risk disease in 49.7%) [344]. Metastatic disease was identified by PSMA PET in 12.1% of men, including 8.2% with a PSA level of < 10 ng/mL and 43% with a PSA level of > 20 ng/mL. Lymph node metastases were suspected in 107 men, with 47.7% outside the boundaries of an extended pelvic LN dissection (eLND). Skeletal metastases were identified in 4.7%. In men with intermediate-risk PCa metastases were identified in 5.2%, compared to 19.9% with high-risk disease.

#### 5.3.4 Summary of evidence and practical considerations on initial N/M staging

The field of non-invasive nodal and metastatic staging of PCa is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and MRI provide a more sensitive detection of LN and bone metastases than the classical work-up with bone scan and abdominopelvic CT. It could be tempting to conclude that bone scan and abdominopelvic CT must be replaced by more sensitive tests in all patients undergoing initial PCa staging. Yet, the clinical benefit of detecting metastases at an earlier time-point remains unclear [325]. In addition 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 MRI, should be managed using systemic therapies, or whether they should be subjected to aggressive local and metastases-directed therapies [345].

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 decision can be made to treat patients based on the results of these tests [346].

#### 5.3.5 Guidelines for staging of prostate cancer

Any risk group staging	LE	Strength rating
Use pre-biopsy mpMRI for local staging information.	2a	Weak
<b>Low-risk localised disease</b>		
Do not use additional imaging for staging purposes.	2a	Strong
<b>Intermediate-risk disease</b>		
In ISUP grade $\geq 3$ , include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	2a	Weak
<b>High-risk localised disease/locally advanced disease</b>		
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong

## 5.4 Evaluating life expectancy and health status

### 5.4.1 Introduction

Evaluation of life expectancy and health status is important in clinical decision-making on 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 [347, 348].

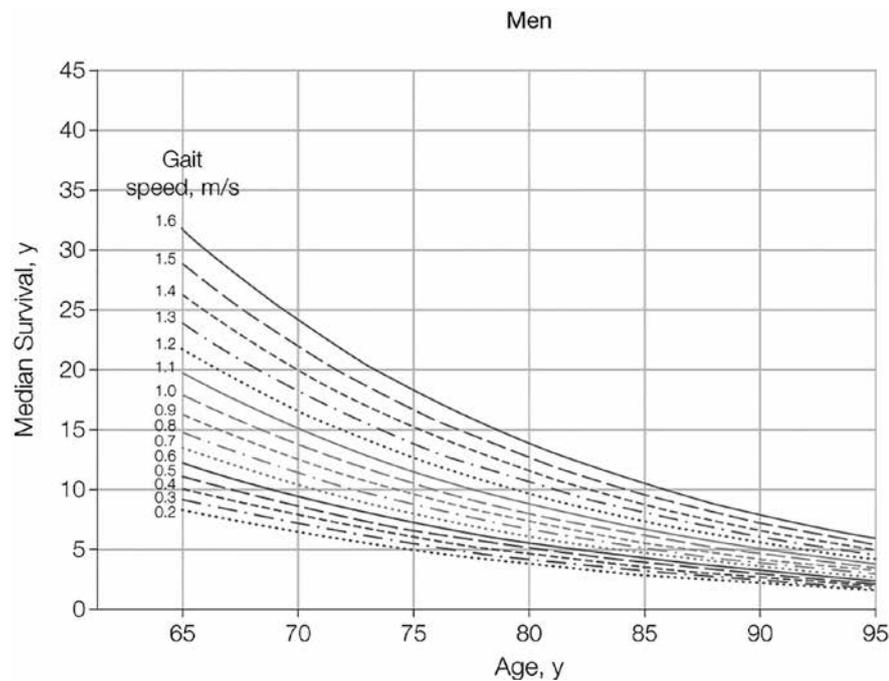
Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over 10 years life expectancy is considered mandatory for any benefit from local treatment and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCa-specific mortality (PCSM) and life expectancy of surgery vs. active surveillance (AS) [349]. 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) [350]. External beam radiotherapy shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [351].

Older men with a high incidence of PCa may be under-treated despite the high overall mortality rates [352, 353]. Of all PCa-related deaths 71% occur in men aged  $\geq 75$  years [354], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [355-357]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease receive curative treatment compared to 88% aged 65-74 [358].

#### 5.4.2 Life expectancy

Life expectancy tables for European men are available at: <https://ec.europa.eu/eurostat/web/products-eurostat-news/-/EDN-20191118-1>. Survival may be very variable and therefore must be individualised. Gait speed is a good single predictive measure (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  $\geq 1.4$  m/s [359].

**Figure 5.4.1: Predicted Median Life Expectancy by Age and Gait Speed for males\*** [359].



\*Figure reproduced with permission of the publisher, from Studenski S, et al. JAMA 2011 305(1)50.

#### 5.4.3 Health status screening

The International SIOG PCa Working Group recommends that treatment for senior adults should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (Table 5.4.1) [360]. 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 (Figure 5.4.1) [360]. Patients with a G8 score  $\leq 14$  should undergo a full geriatric evaluation as this score is associated with 3-year mortality, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [361].

#### 5.4.3.1 Comorbidity

Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [362, 363]. Ten years after not receiving active treatment for PCa, most men with a high comorbidity score had died from competing causes, irrespective of age or tumour aggressiveness [362]. Measures for comorbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [364, 365] (Table 5.4.2) and Charlson Comorbidity Index (CCI) [366].

#### 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) [367].

#### 5.4.3.3 Cognitive function

Cognitive impairment can be measured using mini-COG (<https://mini-cog.com/>), which assesses the patient's ability to make an informed decision which is an increasingly important factor in health status assessment [368-370].

#### 5.4.3.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [371]. 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) [372-374].

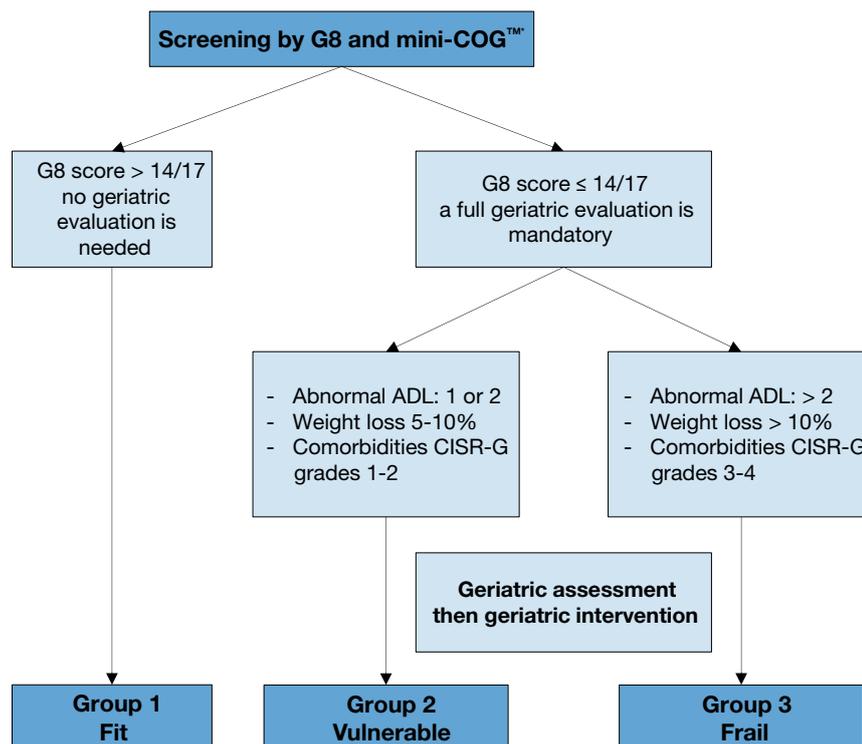
#### 5.4.4 Conclusion

Individual life expectancy, health status, and comorbidity, 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 undertreated. Resolution of impairments in vulnerable men allows a similar urological approach as in fit patients.

**Table 5.4.1: G8 screening tool (adapted from [375])**

	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 <sup>2</sup> )	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
	<b>Total score</b>	<b>0-17</b>

**Figure 5.4.1: Decision tree for health status screening (men > 70 years)\*\* [360]**



Mini-COG™ = Mini-COG™ 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 [360].

**Table 5.4.2: Cumulative Illness Score Rating-Geriatrics (CIRS-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.
<b>Total score 0-52</b>	

Recommendations	Strength rating
Use individual life expectancy, health status, and comorbidity in PCa management.	Strong
Use the Geriatric-8 and mini-COG tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score $\leq$ 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)*

In localised disease a life expectancy of at least 10 years is considered mandatory for any benefit from local treatment. Indeed data is available on patients who did not undergo local treatment with up to 25 years of follow-up, and endpoints of OS and CSS. Several series have shown a consistent CSS rate of 82-87% at 10 years [376-381], and 80-95% for T1/T2 and ISUP grade  $\leq$  2 PCas [382]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [378, 380, 381], and two reported 20-year CSS rates of 57% and 32%, respectively [378, 380]. 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 the pooled analysis [382]. Observation was most effective in men aged 65-75 years with low-risk PCa [383].

Remember that comorbidity is more important than age in predicting life expectancy in men with PCa. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes and for those men with a short life expectancy. In an analysis at 10 years follow up in 19,639 patients aged  $>$  65 years who were not given curative treatment, most men with a CCI score  $\geq$  2 died from competing causes at 10 years whatever their initial age. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score  $\leq$  1 had a low risk of death at 10 years, especially for well- or moderately-differentiated lesions [362]. This highlights the importance of assessing co-morbidity before considering a biopsy.

In screening-detected localised PCa the lead-time bias is likely to be greater. Mortality from untreated screen-detected PCa in patients with ISUP grade 1-2 might be as low as 7% at 15 years follow-up [384]. Consequently, approximately 45% of men with PSA-detected PCa are suitable for close follow-up through a robust surveillance programme. There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and WW (Table 6.1.1).

#### 6.1.1.1 *Definitions*

Active surveillance aims to avoid unnecessary treatment in men with clinically localised PCa who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [385]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up, and curative treatment is prompted by predefined thresholds indicative of potentially life-threatening disease which is still potentially curable, while considering individual life expectancy.

Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment right from the outset, and patients are '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.

**Table 6.1.1: Definitions of active surveillance and watchful waiting [384]**

	<b>Active surveillance</b>	<b>Watchful waiting</b>
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Mainly low-risk patients	Can apply to patients with all stages

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

#### 6.1.1.2 Active surveillance

No formal RCT is available comparing this modality to standard treatment. The Prostate Testing for Cancer and Treatment ( ProtecT) trial is discussed later as it is not a formal AS strategy but rather Active Monitoring (AM), which is a significantly less stringent surveillance strategy in terms of clinical follow-up, imaging and repeat biopsies [386].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review [387]. More recently, the largest prospective series of men with low-risk PCa managed by AS was published [388]. Table 6.1.2 summarises the results of selective AS cohorts. It is clear that the long-term OS and CSS for 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 mpMRI scan, 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 [385]. These will be discussed further in section 6.2.1.

**Table 6.1.2: Active surveillance in screening-detected prostate cancer**

<b>Studies</b>	<b>N</b>	<b>Median FU (mo)</b>	<b>pT3 in RP patients*</b>	<b>10-year OS (%)</b>	<b>10-year CSS (%)</b>
Van As, <i>et al.</i> 2008 [389]	326	22	8/18 (44%)	98	100
Carter, <i>et al.</i> 2007 [390]	407	41	10/49 (20%)	98	100
Adamy, <i>et al.</i> 2011 [391]	533-1,000	48	4/24 (17%)	90	99
Soloway, <i>et al.</i> 2010 [392]	99	45	0/2	100	100
Roemeling, <i>et al.</i> 2007 [393]	278	41	-	89	100
Khatami, <i>et al.</i> 2007 [394]	270	63	-	n.r.	100
Klotz, <i>et al.</i> 2015 [395]	993	77	-	85	98.1
Tosoian, <i>et al.</i> 2015 [388]	1,298	60	-	93	99.9
<b>Total</b>	<b>4,204-4,671</b>	<b>46.5</b>	<b>-</b>	<b>93</b>	<b>100</b>

\* 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.

#### 6.1.1.3 Watchful Waiting

##### 6.1.1.3.1 Outcome of watchful waiting compared with active treatment

The SPCG-4 study randomised patients to either WW or RP (Table 6.1.3) [350] before the PSA era and found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 13.4 years (range 3 weeks-23.2 years). The PIVOT trial made a similar comparison in 731 randomised men (50% with non-palpable disease) [396] but in contrast to SPCG-4, it found no benefit of RP within a median follow-up period of 12.7 years (interquartile range, 7.3 to 15.5 years). Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a RR reduction in mortality of 33% and 31%, respectively. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%). Overall, no adverse effects on HRQoL and psychological well-being was apparent in the first years

[397]. However, one of the criticisms of the PIVOT trial is the relatively high-observed overall mortality rate in the WW group (almost 50% at a median of 10 years), compared with more contemporary series.

**Table 6.1.3: Outcome of SPCG-4 at 15-year follow-up [350]**

	RP (n = 348) (%)	Watchful waiting (n = 348) (%)	Relative risk (95% CI)	p-value
Disease-specific mortality	14.6	20.7	0.62	0.010
Overall mortality	46.1	57.2	0.75 (0.61-0.92)	0.007
Metastatic progression	21.7	33.4	0.59 (0.45-0.79)	< 0.001
Local progression	21.5	49.3	0.34 (0.26-0.45)	n.r.

CI = confidence interval; n.r. = not reported; RP = radical prostatectomy.

#### 6.1.1.4 The ProtecT study

The ProtecT trial randomised 1,643 patients, three-ways, between active treatment (RP or EBRT) and AM [386]. In this AM schedule, patients with a PSA rise of more than 50% in 12 months underwent a repeat biopsy, but none had systematic repeat biopsies. Fifty-six percent of patients had low-risk disease, with 90% having a PSA < 10 ng/mL, 77% ISUP grade 1 (20% ISUP grade 2-3), and 76% T1c, while the other patients were mainly intermediate risk. After 10 years of follow up, the CSS was the same between those actively treated and those on AM (99% and 98.8%, respectively), as was the OS. Only metastatic progression differed (6% in the AM group as compared to 2.6% in the treated group).

The key finding is that AM is as effective as active treatment at 10 years, at a cost of increased progression and double the metastatic risk. Metastases remained quite rare (6%), but more frequent than seen with AS protocols probably driven by differences in intensity of monitoring and patient selection. It is important to note that the AM arm in ProtecT represents 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 mpMRI scan either at recruitment nor during the monitoring period, nor was there any protocol-mandated repeat prostate biopsies at regular intervals. In addition, approximately 40% of randomised patients had intermediate-risk disease.

Nevertheless, in spite of these caveats, 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 for patients with low-grade and low-stage disease. Beyond 10 years, no data is available as yet, although AS is likely to give more reassurance, especially in younger men, based on initial patient selection and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must be evaluated before considering any active treatment in low-risk situations, and for those with up to 10 years individual life expectancy.

#### 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 [398]. The procedure involves removing the entire prostate with its capsule intact and seminal vesicles, followed by undertaking vesico-urethral anastomosis. Since its description in 1904, the technique has evolved markedly. 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 [399]. The main results from multicentre RCTs involving RP are summarised in Table 6.1.4.

**Table 6.1.4: Oncological results of radical prostatectomy in organ-confined disease in RCTs**

Study	Acronym	Population	Year of treatment	Median FU (mo)	Risk category	CSS (%)
Bill-Axelsson, <i>et al.</i> 2018 [400]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and Intermediate risk	80.4 (at 23 yr.)
Wilt, <i>et al.</i> 2017 [396]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk Intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, <i>et al.</i> 2016 [386]	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 [401]. Augmentation of standard verbal and written educational materials, such as use of interactive multimedia tools [402, 403] and pre-operative patient-specific 3D printed prostate models [404] has been shown to improve patient understanding and satisfaction and should be considered to optimise patient-centred care.

#### *Pre-operative pelvic floor exercises*

Although many patients who have undergone RP will experience a return to urinary continence [405], temporary urinary incontinence is common early after surgery, reducing quality of life. 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-op with an OR of 0.64 ( $p = 0.005$ ), but not at 1 month or 6 months [406]. 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.

#### *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). In addition, as the susceptibility of bacterial pathogens and antibiotic availability varies worldwide, any use of prophylactic antibiotics should adhere to local guidelines.

### 6.1.2.3 *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 [399], 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 retroperitoneal (RRP)- or laparoscopic approach. The open retroperitoneal 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 [407]. This led to the demise in popularity of perineal RP, and eventually to the first laparoscopic RP reported in 1997 using retroperitoneal principles, but performed transperitoneally [408]. The initial 9 cases averaged 9.4 hours, indicating significant technical and ergonomic difficulties of the technique. Most recently, RARP was introduced using the da Vinci Surgical System® by Binder in 2002 [409]. This technology combined the minimally-invasive advantages of laparoscopic RP with improved surgeon ergonomics and greater technical ease of suture reconstruction of the vesico-urethral anastomosis, and has now become the preferred minimally-invasive approach, where the equipment is available.

In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss but not early (12 weeks) functional or oncological outcomes, compared to open RP [410]. An updated analysis with follow-up at 24 months did not reveal any significant differences in functional outcomes between the approaches [411]. Increased surgical experience has lowered the complication rates of RP and improved cancer cure [380-383]. 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 [412-414]. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [379, 396, 397, 415]. A first systematic review and meta-analysis of non-RCTs demonstrated that RARP had lower perioperative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy (LRP), although there was considerable methodological uncertainty [416]. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions based on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes. Another systematic review and meta-analysis included two small RCTs comparing RARP vs. LRP [417]. 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 recent Cochrane review comparing either RARP or LRP vs. open RP included two RCTs and found no significant differences between the comparisons for oncological-, urinary function- 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 [418]. Therefore, no surgical approach can be recommended over another.

Outcome after prostatectomy has been shown to be dependent on both surgeon [419] as well as hospital

volume [420]. 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, recently the posterior approach (Retzius-sparing - RS-RARP) has gained favour following two RCTs showing improved early post-operative continence.

Galfano *et al.* first described RS-RARP in 2010 [421]. This approach commences dissection posteriorly at the pouch of Douglas, first dissecting the seminal vesicles 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. Retzius-sparing-RARP thus offers the same potential advantage as the open perineal approach, but without disturbance of the perineal musculature.

Both RCTs were single-surgeon studies comparing post-operative continence in RS-RARP vs. traditional anterior dissection RARP in men with low- to intermediate-risk PCa. Defining continence as 0-1 pad per day in 120 patients, Dalela *et al.* found a continence rate of 71% at 1 week post-catheter removal in the RS-RARP group vs. 48% in the control group ( $p = 0.01$ ) [422]. The positive margin rate was higher in the RS-RARP group (25% vs. 13%), but this was not statistically significant ( $p = 0.1$ ). Asimakopoulos *et al.* studied 102 patients, assessing continence more stringently as 0 pads at catheter removal [423]. Fifty-one percent of patients following RS-RARP were continent at catheter removal vs. 21% in the standard group ( $p = 0.001$ ). Positive margin rates were again higher in the RS-RARP group (28% vs. 10%), however this was attributed to the higher incidence of pT3 disease in the RS-RARP group (44% vs. 23%).

Until these results are replicated in larger numbers in a multi-centre setting, it remains too early to recommend RS-RARP over the traditional anterior dissection. 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 the 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 [424].

#### 6.1.2.3.2 Pelvic lymph node dissection

A recent systematic review demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [425]. However, it is generally accepted that eLND provides important information for staging and prognosis which cannot be matched by any other currently available procedure [425]. The individual risk of finding positive LNs can be estimated using pre-operative tools. Another systematic review and meta-analysis found similar diagnostic accuracy in predicting LN invasion for the Briganti, Partin and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms [426]. However, only a few of these tools are based on eLND templates and have been externally validated. A risk of nodal metastases over 5% (Briganti nomogram [427, 428] or Roach formula [429] which has been shown to be almost as good as the nomogram) is an indication to perform nodal sampling by an extended nodal dissection [430-432]. Extended LND 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 [433].

#### 6.1.2.3.3 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. There is heterogeneity and variation in techniques in relation to SNB (e.g. the optimal tracer), but a multidisciplinary collaborative endeavour attempted to standardise definitions, thresholds and strategies in relation to techniques of SNB using consensus methods [434].

Intraprostatic injections of indocyanine green (ICG) has been used to visualise prostate-related LNs during lymphadenectomy. In a randomised comparison, Harke *et al.* found more cancer containing LNs in men that underwent a LN dissection guided by ICG, but no difference in BCR at 22.9 month follow up [435]. A systematic review showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at eLND [436]. However, there is still insufficient quality evidence supporting oncological effectiveness of SNB for nodal staging. Sentinel node biopsy is therefore still considered as an experimental nodal staging procedure.

#### 6.1.2.3.4 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) [437-443]. 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 cases.

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.

#### 6.1.2.3.5 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 [407]. In the open setting, blood loss and transfusion rates have been found to be significantly reduced when ligating the DVC prior to transection [444]. 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 [445]. In another study, mean blood loss was statistically significantly less with prior DVC ligation (184 vs. 176 mL,  $p = 0.033$ ), however it is debatable whether this was clinically significant [446]. 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 [447].

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.

#### 6.1.2.3.6 Nerve-sparing surgery

During prostatectomy, preservation of the neurovascular bundles with parasympathetic nerve branches of the pelvic plexus may spare erectile function [448, 449].

Although age and pre-operative function may remain the most important predictors for postoperative erectile function, nerve-sparing has also been associated with improved continence outcomes and may therefore still be relevant for men with poor erectile function [450, 451]. The association with continence may be mainly due to the dissection technique used during nerve-sparing surgery, and not due to the preservation of the nerve bundles themselves [450].

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 [452-455]. Furthermore, many different techniques are propagated such as retrograde approach after anterior release (vs. antegrade), and athermal and traction-free handling of bundles [456-458]. Nerve-sparing does not compromise cancer control if patients are carefully selected depending on tumour location, size and grade [459-461].

#### 6.1.2.3.7 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 [462]. As a consequence there is no role for performing frozen section of suspicious LNs.

#### 6.1.2.3.8 Removal of seminal vesicles

The more aggressive forms of PCa may spread directly into the seminal vesicles (SVs). For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen [463]. 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 [464]. However, an RCT comparing nerve-sparing RP with and without SV-sparing found no difference in margin status, PSA recurrence, continence or erectile function outcomes. Another study of 71 consecutive RPs showed no cancer in any of the distal 1 cm of SVs, even in 12 patients with SV invasion [465]. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement.

#### 6.1.2.3.9 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 [466].

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 [467] compared unidirectional barbed suture vs. conventional non-barbed suture for vesico-urethral anastomosis during robotic-assisted laparoscopic prostatectomy (RALP). 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 [468] compared continuous vs. interrupted suturing for vesico-urethral anastomosis during RP. The study included only one RCT [469] which had only 60 patients. Although the review found slight advantages of 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 [470] compared the technique of suturing using a single absorbable running suture vs. a double-needle, single-knot running suture (i.e. Van Velthoven technique) [471] in laparoscopic RP. 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 [466-477].

#### 6.1.2.3.10 Bladder neck management

##### Bladder neck mucosal eversion

Some surgeons perform mucosal eversion of the bladder neck as its own step in open RP in 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 retard 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 [478]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [479].

##### 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 [480]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. An RCT assessing incontinence 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 [481]. These findings were confirmed by a systematic review [482]. 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 [480]. 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. Bladder neck preservation, however, cannot be performed in the presence of a large median lobe, or a previous TURP.

#### 6.1.2.3.11 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. A systematic review and meta-analysis has found that every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post-RP [483]. It is likely therefore 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 this urethral length pre-operatively in order to advise patients on their relative likelihood of early post-operative continence.

#### 6.1.2.3.12 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 standard of care before catheter removal 8-10 days after surgery [484]. 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 [485, 486]. Contrast-enhanced transrectal US is an alternative [487].

#### 6.1.2.3.13 Urinary catheter

A urinary catheter is routinely placed during RP to enable bladder rest and drainage of urine while the vesico-urethral 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 [488-491]. 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 [492]. 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 [493].

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 [494-498], while others did not find any differences [499, 500]. No impact on long-term functional outcomes were seen.

#### 6.1.2.3.14 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 [501, 502]. 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 surgery*

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. Recent systematic reviews have documented complication rates after RALP [416, 503-506], and can be compared with contemporaneous reports after radical retropubic prostatectomy (RRP) [507]. Recently, a prospective, controlled, non-RCT of patients undergoing RP in 14 centres using RALP or RRP was published. At 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted 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 adjusted OR was 0.81 (95% CI: 0.66-0.98) [508]. A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at 2 years [410]. 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 retropubic RP and RALP are listed in Table 6.1.5. 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).

##### 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 intraperitoneal vs. extraperitoneal. 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 [509, 510]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to 1 pad per day (median 18 vs. 30 days,  $p = 0.024$ ) [511]. 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 [512].

Four RCTs including anterior suspension have also shown conflicting results. Anterior suspension alone, through the pubic periosteum, in the setting of extraperitoneal RALRP, showed no advantage [513]. 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%,  $p = 0.609$ ) [514]. 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 [515]. 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%,  $p = 0.313$ ) [516]. 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 [517]. However these recommendations should be adapted based on national recommendations when available.

**Table 6.1.5: Intra- and peri-operative complications of retropubic RP and RALP (Adapted from [416])**

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 I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

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

#### 6.1.2.4.3 Early complications of extended lymph node dissection

Pelvic eLND increases morbidity in the treatment of PCa [425]. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event. Other authors have reported more acceptable complication rates [518]. 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%) [519, 520]. Briganti *et al.* [521] also showed more complications after extended compared to limited LND. Twenty percent of men suffer a complication of some sort after eLND. Thromboembolic events occur in less than 1% of cases.

#### 6.1.2.5 Comparing effectiveness of radical prostatectomy versus other interventions for localised disease

##### 6.1.2.5.1 Radical prostatectomy versus deferred treatment

Currently, three large prospective RCTs have compared RP over deferred treatment (see Section 6.1.2). In summary, there was conflicting evidence regarding the benefit of RP over deferred treatment. The only study to find a benefit of RP over WW (SPCG-4) was conducted in the pre-PSA era [350]. When comparing RP against WW [396] or against AM [386], no statistically significant benefit in OS at 10 years' of follow-up was observed. These findings indicate the good prognosis for the majority of patients with low-risk localised PCa,

and highlight the need to carefully risk stratify patients to ensure that patients are appropriately managed and treated.

#### 6.1.2.5.2 Radical prostatectomy versus radiotherapy

ProtecT compared RP vs. AM vs. EBRT (combined with 6 months of ADT) [386]. At a median follow-up of 10 years, there were no differences between surgery vs. EBRT in all oncological outcomes.

#### 6.1.2.5.3 Neoadjuvant androgen deprivation therapy

Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of them using a 3-month period. The main findings were summarised in a Cochrane review [522]. 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. One recent RCT compared neoadjuvant luteinising hormone-releasing hormone (LHRH) alone vs. LHRH plus abiraterone plus prednisone prior to RP in 65 localised high-risk PCa patients [523]. Patients in the combination arm were found to have both significantly lower tumour volume and significantly lower BCR at > 4 years follow-up ( $p = 0.0014$ ). Further supportive evidence is required before recommending combination neoadjuvant therapy including abiraterone prior to RP.

### 6.1.3 Radiotherapy

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT.

#### 6.1.3.1 External beam radiation therapy

##### 6.1.3.1.1 Technical aspects: intensity-modulated external-beam radiotherapy and volumetric arc external-beam radiotherapy (VMAT)

Intensity-modulated external-beam radiotherapy and VMAT employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes. Both techniques allow for a more complex distribution of the dose to be delivered within the treatment field 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, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of image-guided radiotherapy (IGRT), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [524]. 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.

##### 6.1.3.1.2 Dose escalation

Several RCTs have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year biochemical relapse [525-531]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant hormone therapy (HT) has varied (see Table 6.1.6). The best evidence of an OS benefit for patients with intermediate- or high-risk PCa, but not with low-risk PCa, comes from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database covering a total of 42,481 patients [532]. In everyday practice, a minimum dose of  $\geq 74$  Gy is recommended for EBRT plus HT, with no different recommendations according to the patient's risk group. If IMRT and IGRT are used for

dose escalation, rates of severe late side-effects ( $\geq$  grade 3) for the rectum are 2-3% and for the GU tract 2-5% [528, 531, 533-546].

**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 [526]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs. 78 Gy	9 yr.	DSM vs. other cause of death	High risk/PSA > 10 16% DSM at 70 Gy 4% DSM at 78 Gy ( $p = 0.05$ ) Higher risk 15% DSM at 70 Gy 2% DSM at 78 Gy ( $p = 0.03$ )
PROG 95-09 2010 [527]	393	T1b-T2b PSA 15 ng/mL 75%	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 [547]	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 [531]	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 [530]	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 [525]	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, $p < 0.001$ )

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

#### 6.1.3.1.3 Hypofractionation (HFX)

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 [548]. 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 [549]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at with lower cost.

Moderate HFX is defined as RT with 2.5-4 Gy/fx. Several studies report on moderate HFX applied in various techniques and, in part, also including HT [550-560]. A systematic review concludes that studies on moderate HFX (2.5-4 Gy/fx) delivered with conventional three-dimensional conformal radiotherapy (3D-CRT)/IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking

[559]. Moderate HFX should only be done by experienced teams using high-quality EBRT using IGRT and IMRT in carefully selected patients and adhere to published phase III protocols (see Table 6.1.7 below).

**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, <i>et al.</i> 2016 [554]	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, <i>et al.</i> CHHiP 2012 [550] and 2016 [555]	1077/19 fx 1074/20 fx 1065/37 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)
Aluwini, <i>et al.</i> 2015 [553], 2016 [556, 557]	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	60	5 yr. RFS 80.5% (n.s.) 5 yr. RFS 77.1%
Catton, <i>et al.</i> 2017 [558]	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  $\alpha/\beta$  of 1.5 Gy; DFS = disease-free survival; EBRT = external beam radiotherapy; FU = follow-up; fx = fractions; HR = hazard ratio; mo. = month; n = number of patients; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; n.s. = not significant; yr. = year.

Ultra-HFX has been defined as radiotherapy with > 3.4 Gy per fraction [560]. It requires IGRT and stereotactic body radiotherapy (SBRT). Table 6.1.8 provides an overview of selected studies. Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade GU and rectal toxicity and long-term side-effects may not all be known yet [559, 561, 562]. 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  $\geq 2$  GU toxicity was 23% vs. 28% (p = 0.057), favouring conventional fractionation. There were no significant differences in long-term toxicity [563]. A systematic review by Jackson *et al.* included 38 studies with 6,116 patients who received RT with < 10 fractions and  $\geq 5$  Gy per fraction. Five- and 7-year bRFS rates were 95.3% and 93.7%, respectively and estimated late grade  $\geq 3$  genitourinary- and gastrointestinal toxicity rates were 2.0% and 1.1%, respectively [564]. 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 “conventional” IMRT/VMAT for ultra-HFX. In their review on SBRT, Cushman and co-workers 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 [565]. In the Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B) trial, acute grade  $\geq 2$  GU or GI toxicities did not differ significantly between conventional

fractionation and ultra-HFX [566]. Therefore, it seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

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

Reference	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark <i>et al.</i> 2019 HYPO-RT-PC [563]	1,200	60	89% intermediate 11% high	78 Gy / 39 fx, 8 w 42.7 Gy / 7 fx, 2.5 w No SBRT	FFS at 5 yr. 84% in both arms
Brand <i>et al.</i> 2019 PACE-B [566]	847	variable	8% low 92% intermediate	78 Gy / 39 fx, 8 w 36.25 Gy / 5 fx, 1-2 w 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 = gastrointestinal toxicity, GU: genitourinary toxicity, mo. = months; n = number of patients; TD = total dose; SBRT = stereotactic body radiotherapy; w = 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 [567-571] (Table 6.1.9). The main message is that for intermediate risk a short duration of around 6 months is optimal, while a longer one, around 3 years, is needed for high-risk patients.

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

Trial	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [568]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65-70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade 2-5
RTOG 94-13 2007 [572]	T1c-4 N0-1 M0	1292	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 [569]	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, <i>et al.</i> 2008 [570]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit (HR: 0.55, 95% CI: 0.34-0.90, p = 0.01) that may pertain only to men with no or minimal comorbidity
RTOG 92-02 2008 [573]	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 RT	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 [574]	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 [567]	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 [571]	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 [575]	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

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 with 3 RCTs. All showed a clear benefit of adding EBRT to long-term ADT (see Table 6.1.10).

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

Trial	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [576]	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 2011 [577] and 2015 [578]	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 P, et al. 2019 [579]	T3-4 N0 M0	273 264	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

Zelevsky *et al.* reported a retrospective analysis comprising 571 patients with low-risk PCa, 1,074 with intermediate-risk PCa, and 906 with high-risk PCa. 3D-conformal RT or IMRT were administered [580]. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before RT. The 10-year biochemical disease-free rate was significantly improved by dose escalation: above 75.6 Gy in low risk, and above 81 Gy for the intermediate- and high-risk groups. It was also improved by adding 6 months of ADT in intermediate- and high-risk patients. In the

multivariate analysis, neither the dose > 81 Gy, nor adding ADT influenced OS. 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 radiotherapy dose:

1. The GICOR study which shows a better biochemical DFS for high-risk patients for 3D-CRT radiation dose > 72 Gy when combined with long-term ADT [538].
2. DART01/05 GICOR which shows that 2 years of adjuvant ADT combined with high-dose RT improved biochemical control and OS in high-risk patients [581].
3. EORTC trial 22991 which shows that 6 months ADT improves biochemical and clinical DFS whatever the dose (70, 74, 78 Gy) in intermediate-risk and low-volume high-risk localised PCa [582].

#### 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 per se [527]. Thus, unequivocal information that shows 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 for protons [583, 584]. In terms of longer-term gastrointestinal (GI) toxicity, proton therapy might even be inferior to IMRT [584].

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

#### 6.1.3.3 Brachytherapy

##### 6.1.3.3.1 Low-dose rate (LDR) brachytherapy

Low-dose rate brachytherapy uses radioactive seeds permanently implanted into the prostate. There is a consensus on the following eligibility criteria for LDR monotherapy [585]: Stage cT1b-T2a N0, M0; ISUP grade 1 with ≤ 50% of biopsy cores involved with cancer or ISUP grade 2 with ≤ 33% of biopsy cores involved with cancer; an initial PSA level of ≤ 10 ng/mL; a prostate volume of < 50 cm<sup>3</sup>; an International Prostatic Symptom Score (IPSS) ≤ 12 and maximal flow rate > 15 mL/min on urinary flow tests [586].

The only available RCT comparing RP and brachytherapy as monotherapy was closed due to poor accrual [587]. Outcome data are available from a number of large population cohorts with mature follow-up [588-595]. The biochemical disease-free survival for ISUP grade 1 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [588-595]. A significant correlation has been shown between the implanted dose and biochemical control [596]. 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 benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [588].

Low-dose rate brachytherapy can be combined with EBRT in intermediate-/high-risk patients (see Section 6.2.3.2.3).

##### 6.1.3.3.2 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 published guidelines is strongly recommended [597]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [598]. A single 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 [599]. In 218 patients with organ-confined 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 year (75% and 46% compared to 61% and 39%). However, a very high, uncommon, 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 [599]. A systematic review of non-RCTs has suggested outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective RCT [600].

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 [601, 602]. 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 [601, 602].

**Table 6.1.11: Difference between LDR and HDR brachytherapy**

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	<ul style="list-style-type: none"> <li>• Permanent seeds implanted</li> <li>• Uses Iodine-125 (I-125) (most common), <sup>103</sup>Palladium (Pd-103) or Cesium-131 isotopes</li> <li>• Radiation dose delivered over weeks and months</li> <li>• Acute side-effects resolve over months</li> <li>• Radiation protection issues for patient and carers</li> </ul>
High dose rate (HDR)	<ul style="list-style-type: none"> <li>• Temporary implantation</li> <li>• Iridium-192 (Ir-192) isotope introduced through implanted needles or catheters</li> <li>• Radiation dose delivered in minutes</li> <li>• Acute side-effects resolve over weeks</li> <li>• No radiation protection issues for patient or carers</li> </ul>

#### 6.1.3.4 Acute side-effects of external beam radiotherapy and brachytherapy

Gastrointestinal 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 [537]. 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 [603]. 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 [604]. Similar findings are reported using HFX; in a pooled analysis of 864 patients treated using extreme HFX and stereotactic radiotherapy, declines in urinary and bowel domains were noted at 3 months, which returned to baseline, or better, by 6 months [605].

### 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 either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor. These two methods can be combined to achieve what has been known as complete (or maximal or total) androgen blockade (CAB) using the old-fashioned anti-androgens [606].

##### 6.1.4.1.1.1 Testosterone-lowering therapy (castration)

###### 6.1.4.1.1.1.1 Castration level

The castration level 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 [607]. Therefore, a more appropriate level should be defined as < 20 ng/dL (1 nmol/L). This definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [608-610]. 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 [611].

###### 6.1.4.1.1.2 Oestrogens

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [612]. 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 [613-615].

#### 6.1.4.1.1.3 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 [616]. 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 [617, 618].

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 [619]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [620]. No survival difference with orchiectomy has been reported, despite the lack of high quality trials [621].

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.

#### 6.1.4.1.1.4 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 [619]. An extended follow-up has been published, suggesting a better PSA PFS compared to monthly leuprorelin [622]. A systematic review did not show 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 [623]. Its definitive superiority over the LHRH analogues remains to be proven.

#### 6.1.4.1.1.5 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.

##### 6.1.4.1.1.5.1 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.

###### 6.1.4.1.1.5.1.1 Cyproterone acetate

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 [624]. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in disease-specific and OS at a median follow-up of 8.6 years [625]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

###### 6.1.4.1.1.5.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [626]. Non-androgen-related pharmacological side-effects differ between agents. Bicalutamide shows a more favourable

safety and tolerability profile than flutamide and nilutamide [627]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

#### 6.1.4.1.1.5.2.1 Nilutamide

Nilutamide monotherapy has not been compared to castration and is not licensed for monotherapy. Direct drug-related side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, and of note, severe interstitial pneumonitis (potentially life-threatening). As a consequence it is rarely used.

#### 6.1.4.1.1.5.2.2 Flutamide

Flutamide has been studied as monotherapy. Flutamide is a pro-drug, and the half-life of the active metabolite is 5 to 6 hours, requiring a three times daily dose. The recommended total daily dose is 750 mg. The non-androgen-related pharmacological side-effect of flutamide is diarrhoea.

#### 6.1.4.1.1.5.2.3 Bicalutamide

The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [626, 628].

#### 6.1.4.1.1.6 New compounds

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 [629]. This has led to the development of several new compounds targeting the androgen axis. Abiraterone acetate and enzalutamide are both approved for mCRPC. Abiraterone acetate has also been approved for hormone-sensitive PCa, combined with ADT. Apalutamide, darolutamide and enzalutamide have been approved for M0 CRPC at high risk of further metastases [630, 631].

##### 6.1.4.1.1.6.1 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17 $\alpha$ -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.

##### 6.1.4.1.1.6.2 New non-steroidal anti-androgens

Enzalutamide, apalutamide and darolutamide 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, these drugs also block AR transfer and therefore suppress any possible agonist-like activity.

### 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 [632-635]. In this section, both whole gland and focal treatment will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy, as sufficient data are available to form the basis of some initial judgements. Other options, such as radiofrequency ablation and electroporation, among others, are considered to be in the early phases of evaluation [636]. In addition, a relatively newer development is focal ablative therapy [636, 637], whereby lesion-targeted ablation is undertaken in a precise, organ-sparing manner. All these modalities have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity and improved functional outcomes.

#### 6.1.5.2 Cryotherapy

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 [632-635]. 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 cryosurgery are ED (18%), urinary incontinence (2-20%), urethral sloughing (0-38%), rectal pain and bleeding (3%) and recto-urethral fistula formation (0-6%) [638]. 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 periods [638].

#### 6.1.5.3 High-intensity focused ultrasound

High-intensity focused ultrasound consists of focused US waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation [639]. The goal of HIFU is to heat malignant tissues above 65°C so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anaesthesia, with the patient lying in the lateral or supine position. High-intensity focused US has previously been widely used for whole-gland therapy. The major adverse effects of HIFU include acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), recto-urethral fistula (0-5%) and urinary incontinence 10% [638]. Disadvantages of HIFU include difficulty in achieving complete ablation of the prostate, especially in glands larger than 40 mL, and in targeting cancers in the anterior zone of the prostate. Similar to cryosurgery, the lack of any long-term prospective comparative data on oncological outcomes prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [638].

#### 6.1.5.4 Focal therapy

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 to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [640-642]. Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU, photodynamic therapy, electroporation, and focal RT by brachytherapy or CyberKnife® Robotic Radiosurgery System technology (Accuray Inc., Sunnyvale, CA, USA). The main purpose of focal therapy is to ablate tumours selectively whilst limiting toxicity by sparing the neurovascular bundles, sphincter and urethra [643-645].

A previous systematic review and network meta-analysis [638] on ablative therapy in men with localised PCa performed a sub-group analysis of focal therapy vs. RP and EBRT. Nine case series reporting on focal therapy were identified (5 studies reporting on focal cryosurgical ablation of the prostate [CSAP], three studies on focal HIFU, and one study reported on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at 3 years. For focal HIFU vs. RP or EBRT, there were neither comparable data on oncological-, continence- nor potency outcomes at one year, or more. More recently, Valerio *et al.* [637] performed a systematic review to summarise the evidence regarding the effectiveness of focal therapy in localised PCa. Data from 3,230 patients across 37 studies were included, covering different energy sources including HIFU, CSAP, photodynamic therapy, laser interstitial thermotherapy, focal brachytherapy, irreversible electroporation and radiofrequency ablation. 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, approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review suggests that focal therapy has a favourable toxicity profile in the short to medium-term, its oncological effectiveness remains unproven due to lack of reliable comparative data against standard interventions such as RP and EBRT.

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 in English between January 1<sup>st</sup> 2010 and May 31<sup>st</sup> 2019. Primary outcomes included oncological outcomes, adverse events and functional outcomes. A total of 707 abstracts

were screened; 12 articles were eligible for full text screening, and ultimately only 4 articles (3 studies) were eligible for inclusion [646-649]. Azzouzi *et al.* [646] and Gill *et al.* [647] reported on a RCT comparing focal therapy using padeliporfin-based vascular-targeted photodynamic therapy (PDT) vs. AS in men with very low-risk PCa. The study found, at a median follow-up of 24 months, 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%,  $p < 0.0001$ ). In addition, more men in the PDT arm had a negative prostate biopsy at two years than men in the AS arm (adjusted RR: 3.67, 95% CI: 2.53-5.33). Updated results were published in 2018 [647], showing that these benefits were maintained after four years. Nevertheless, limitations of the study include inappropriately comparing an intervention designed to destroy cancer tissue in men with low-risk PCa against an intervention primarily aimed at avoiding unnecessary treatment in men with low-risk PCa, and an unusually high observed rate of disease progression in the AS arm (58% in two years). Furthermore, more patients in the AS arm chose to undergo radical therapy without a clinical indication, and this may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy nor any mpMRI scanning, which is not representative of contemporary practice. Two further studies identified in the review were non-randomised comparative studies. Albisinni *et al.* was a small retrospective matched-pair study comparing focal HIFU vs. RALRP; Tourinho-Barbosa *et al.* was a retrospective cohort study comparing focal HIFU vs. focal cryotherapy for patients with low- or intermediate-risk localised PCa. The certainty of the evidence relating to both studies was low due to the retrospective and unmatched nature of the data.

Given the lack of robust comparative data on medium to long-term oncological outcomes for focal therapy against curative interventions (i.e. RP or EBRT), significant uncertainties remain in regard to focal therapy as a proven alternative to either AS or radical therapy. Consequently, robust prospective trials reporting standardised outcomes [650] are needed before recommendations in support of focal therapy for routine clinical practice can be made [636, 650, 651]. For now, focal therapy should only be performed within the context of a clinical trial setting or well-designed prospective cohort study.

#### 6.1.6 General guidelines for active treatment

<b>Recommendations</b>	<b>Strength rating</b>
Inform patients that no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and prostate cancer-specific survival for clinically localised disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Inform patients that all active treatments have side effects.	Strong
<b>Surgical treatment</b>	
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, perform an extended LND template for optimal staging.	Strong
Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, multiparametric magnetic resonance imaging).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
<b>Radiotherapeutic treatment</b>	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
<b>Active therapeutic options outside surgery and radiotherapy</b>	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

### 6.1.7 *Discussing treatment options*

Management decisions should be made after all treatments have been discussed in a multidisciplinary team (including urologists, radiation oncologists, medical oncologists pathologists and radiologists), and after the balance of benefits and side-effects of appropriate therapy modalities has been considered together with the patient. The following paragraphs will only address active modalities where the aim is to try to be “curative” in patients where that is appropriate.

## 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) and therefore AS should be considered for all such patients.

##### 6.2.1.1.1 *Active surveillance - inclusion criteria*

Selection criteria for AS are limited by a lack of prospective RCTs. As a consequence, the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline 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) [7]. The criteria most often published include: ISUP grade 1, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc [387, 652]. The latter threshold remains controversial [652, 653]. These criteria were supported by the DETECTIVE consensus. There was no agreement around the maximum number of cores that can be involved with cancer or the maximum percentage core involvement although there was recognition that T2c disease and extensive disease on mpMRI should exclude men from AS.

DETECTIVE did agree that men with favourable ISUP 2 cancer (PSA < 10 ng/mL, clinical stage [ $\leq$  cT2a] and a low number of positive cores) should also be considered for deferred treatment [7]. In this setting, re-biopsy within 6 to 12 months to exclude sampling error is mandatory [652, 654] even if this could be modified in the future [655]. A systematic review and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, which were; PSA density, > 2 positive cores, and African-American race [656].

The DETECTIVE consensus group were clear that those with ISUP 3 disease should not be considered. 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), sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [657] and perineal invasion [658] and this view was supported.

##### 6.2.1.1.2 *Biological markers*

Biological markers, including urine PCA3, transmembrane protease, serine 2-*TMPRSS2-ERG* fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself [659-661]. However, further data will be needed before such markers can be used in standard clinical practice [167].

##### 6.2.1.1.3 *Imaging for treatment selection*

In men eligible for AS based upon systematic biopsy findings alone, mpMRI can detect suspicious lesions inducing reclassification at confirmatory biopsy [662, 663]. However, systematic biopsy retains substantial added value at confirmatory biopsy.

A recent meta-analysis evaluated the proportion of men eligible for AS based on systematic TRUS-guided biopsy in whom the cancer was upgraded by MRI-TBx (17%) and systematic biopsy (20%) at confirmatory biopsy [664]. Ten per cent of patients were upgraded by both biopsy methods, meaning MRI-TBx upgraded an additional 7% (95% CI: 5-10%) of men, whilst systematic biopsy upgraded an additional 10% (95% CI: 8-14%) of men. Even if the analysed series used different definitions for csPCa (and thus for cancer upgrading), MRI-TBx and systematic biopsy appear to be complementary to each other, both missing a significant proportion of cancer upgrading or reclassification. Therefore, combining the two biopsy techniques seems the best way to select patients for AS at confirmatory biopsy.

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, avoiding oversampling in the MRI arm [665]. The initial report showed little benefit from targeted biopsy. However, 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  $\geq 2$  cancer (9.9% vs 23%,  $p = 0.048$ ) [666].

Upgrading at 1-year confirmatory biopsy by saturation biopsy (24 cores) in combination with MRI-

targeted biopsy (2 cores) was investigated in two subgroups of men eligible for AS [662]. Upgrading in men who were eligible for active surveillance, based on initial 12-core systematic biopsy findings, occurred in 59% (93/157), in contrast to 19% (22/116) upgrading in men eligible based on initial 12-core systematic and MRI-targeted biopsy ( $p < 0.001$ ).

At the DETECTIVE consensus meeting it was agreed that men eligible for AS after combined systematic- and MRI-targeted biopsy do not require a confirmatory biopsy [7].

#### 6.2.1.1.4 Monitoring during active surveillance

The follow-up strategy is based on serial DRE (at least once yearly), PSA (at least once, every 6 months) and repeated biopsy [7]. Several authors have reported data on sequential mpMRI evaluation, summarised in a review [667], the overall upgrading from ISUP 1 to ISUP  $\geq 2$  PCa was 30% (81/269), following combined targeted and standard biopsies. Upgrading occurred in 39% of patients with MRI showing progression and in 21% of patients with MRI showing stable findings or regression. However, in a recent study not included in this review, an association between mpMRI progression and pathological upgrade was not observed [668]. Data is more limited on unchanged negative mpMRI. In a small study on 75 men included within PRIAS, with an mpMRI at baseline, 46 (61%) had a negative mpMRI. Twenty-six percent (12/46) were reclassified at 12 months by systematic biopsies; however, this reclassification was based on volume ISUP grade 1 in five, and on upgrading to ISUP grade 2 cancers in 7 men [669]. Two other studies on serial negative MRI showed upgrading to ISUP grade 2 in only 2% (1/56) [663] and 5% (2/41) [668].

Data on the combination of serial mpMRI and PSA as a trigger for re-biopsy are even more limited. Using mpMRI and PSA changes as the sole triggers for re-biopsy would have detected only 14/20 (70%) of progressions and resulted in 15 additional biopsy procedures which failed to show pathological progression [670]. Protocol based re-biopsy, without mpMRI or PSA changes, however, detected pathological progressions in 6 out of 87 (6.9%) men. In another study of serial mpMRI in AS, PSA velocity was significantly associated with subsequent requirement for radical therapy in patients with no visible lesions (negative MRI). PSA doubling time was significant in patients with visible lesions (positive MRI). The AUC of PSA velocity for prediction of progression in MRI-negative patients was 0.85 (95% CI: 0.75-0.94); for PSA doubling time in MRI-positive patients, the AUC was 0.65 (95% CI: 0.52-0.78). In patients with no visible lesions on first MRI, a cut-off of 0.5 ng/mL/year in PSA velocity had a sensitivity of 89% (8/9 progressions identified) and a specificity of 75% for progression to radical therapy.

#### 6.2.1.1.5 Active Surveillance - when to change strategy

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 [671] and was recognised as a valid reason for active treatment [7]. 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 (especially a PSA-DT  $< 3$  years) is a less powerful indicator to change management based on its weak link with grade progression [672, 673]. As a consequence, this should instead trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting that a change in PSA should lead to repeat-mpMRI and biopsy. It was also agreed that changes on follow-up mpMRI needed a confirmatory biopsy before considering active treatment. However, there was no agreement on the histopathology criteria (neither the extent of core involvement nor the number of cores involved) required to trigger a change in management [7].

### 6.2.1.2 Guidelines for the treatment of low-risk disease

Recommendations	Strength rating
<b>Active surveillance (AS)</b>	
Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong
If required perform mpMRI before a confirmatory biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
Perform digital rectal examination (DRE) every 12 months.	Strong
Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
During follow-up, if mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
Counsel patients about the possibility of needing further treatment in the future.	Strong
<b>Active treatment</b>	
Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
<b>Pelvic lymph node dissection (PLND)</b>	
Do not perform a PLND (estimated risk for pN+ ≤ 5%).	Strong
<b>Radiotherapeutic treatment</b>	
Offer low-dose rate brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate, with a good International Prostatic Symptom Score and a prostate volume < 50 mL.	Strong
Use intensity-modulated radiation therapy with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy.	Strong
<b>Other therapeutic options</b>	
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

### 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 [674].

#### 6.2.2.1 Active Surveillance

In the ProtecT trial, up to 22% of the randomised patients in the AM arm had ISUP grade > 1 and 10% a PSA > 10 ng/mL [386]. A Canadian consensus group proposes that low volume ISUP grade 2 (< 10% Gleason pattern 4) may also be considered for AS. These recommendations have been endorsed by the American Society of Clinical Oncology ASCO [675] and the recent DETECTIVE consensus meeting [7] for those with a PSA < 10 ng/mL and low core positivity. However, data is less consistent. It is clear that the presence of any grade 4 pattern is associated with a 3-fold increased risk of metastases although from a low baseline, compared to ISUP grade 1, while a PSA up to 20 ng/mL might be an acceptable threshold [654, 676, 677]. In addition, it is likely that mpMRI and targeted biopsies will detect small focuses of Gleason 4 cancer that might have been missed with systematic biopsy. Therefore, care must be taken when explaining this treatment strategy especially in patients with the longest life expectancy.

#### 6.2.2.2 Surgery

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. The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [678]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [427]. In all other cases eLND can be omitted, which means accepting a low risk of missing positive nodes.

### 6.2.2.3 Radiation therapy

#### 6.2.2.3.1 Recommended external beam radiation therapy for intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months) [679-681]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT or VMAT at an escalated dose (76-80 Gy) or a combination of IMRT or VMAT and brachytherapy (see Section 6.2.3.2.3).

#### 6.2.2.3.2 Brachytherapy monotherapy

Low-dose rate brachytherapy can be offered to highly selected patients (ISUP grade 2 with  $\leq 33\%$  of biopsy cores involved with cancer), provided they fulfil all the other criteria. 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 [601, 682]. There are no direct data to inform on the use of ADT in this setting.

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

A prospective study on focal therapy using HIFU on patients with localised intermediate-risk disease was recently published [651], but the data was derived from an uncontrolled, single-arm case series. 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 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 [636].

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from EORTC 30891 [678], which was a RCT comparing deferred ADT vs. immediate ADT in 985 patients with T0-4 N0-2 M0 disease. 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
<b>Active surveillance (AS)</b>	
Offer AS to highly selected patients (< 10% pattern 4) accepting the potential increased risk of further metastases.	Weak
<b>Radical prostatectomy (RP)</b>	
Offer RP to patients with intermediate-risk disease and a life expectancy of > 10 years.	Strong
Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
<b>Pelvic lymph node dissection (ePLND)</b>	
Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
<b>Radiotherapeutic treatment</b>	
Offer low-dose rate brachytherapy to selected patients (see Section 6.2.3.2.3); patients without a previous transurethral resection of the prostate, with a good International Prostatic Symptom Score and a prostate volume < 50 mL.	Strong
For external-beam radiation therapy (EBRT), use 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 neoadjuvant plus concomitant androgen deprivation therapy (ADT) (4 to 6 months).	Strong
In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
<b>Other therapeutic options</b>	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak

### 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 [683]. 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 [674]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

#### 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 reasonable option in selected patients with a low tumour volume. Extended PLND should be performed in all high-risk PCa cases undergoing RP as the estimated risk for positive LNs is > 5% [427]. Patients should be aware pre-operatively that surgery may be part of multi-modal treatment.

##### 6.2.3.1.1 ISUP grade 4-5

The incidence of organ-confined disease is 26-31% in men with an ISUP grade  $\geq$  4 on systematic biopsy. A high rate of downgrading exists between the biopsy ISUP grade and the ISUP grade of the resected specimen [684]. 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) for patients with a biopsy ISUP grade 5 [350, 410, 685, 686].

##### 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% [350, 410, 417, 687-689].

##### 6.2.3.1.3 Radical prostatectomy in cN0 patients who are found to have pathologically confirmed lymph node invasion (pN1)

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, at 15 years [690-696]. However, this is a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Section 6.2.5.2).

6.2.3.2 *External beam radiation therapy*

6.2.3.2.1 Recommended external beam radiation therapy treatment policy for high-risk localised PCa

For high-risk localised PCa, use a combined modality approach, consisting of dose-escalated IMRT or VMAT, plus long-term ADT. The duration of ADT has to take into account PS, comorbidities 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 [569, 570, 572], and long-term ADT (at least 2 to 3 years) is currently recommended for these patients.

6.2.3.2.2 Lymph node irradiation in cNO

There is no high level evidence for prophylactic whole-pelvic irradiation, since RCTs have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic LNs in high-risk cases [697-699]. In the RTOG 94-13 study [572], there were no PFS differences between patients treated with whole-pelvic or prostate-only RT, but interactions between whole-pelvic RT and the duration of ADT were reported following the subgroup analysis. Furthermore, in most trials dealing with high-risk PCa, a whole pelvis field was considered standard of care. The benefits of pelvic nodal irradiation using IMRT or VMAT merit further investigation in RCTs as conducted by the RTOG or the UK NCRI group. Performing an ePLND in order to decide whether or not pelvic RT is required (in addition to combined prostate EBRT plus long-term ADT) remains purely experimental in the absence of high level evidence.

6.2.3.2.3 Low-dose rate brachytherapy boost

In men with intermediate- or high-risk PCa, LDR brachytherapy boost with supplemental EBRT and hormonal treatment [700] may be considered. Dose-escalated EBRT (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 a randomised trial with 12 months of ADT in both arms [701]. The LDR boost resulted in 5- and 7-year PSA PFS increase (89% and 86%, respectively, compared to 84% and 75%). This improvement came with an increase in late grade 3+ urinary toxicity (18% compared to 8%) [702]. Toxicity was mainly due to urethral strictures and incontinence and great care should be taken during treatment planning.

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

Currently there is a lack of evidence supporting any other treatment option or focal therapy in localised high-risk PCa.

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

Recommendations	Strength rating
<b>Radical Prostatectomy (RP)</b>	
Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong
<b>Extended pelvic lymph node dissection (ePLND)</b>	
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.	Strong
<b>Radiotherapeutic treatment</b>	
In patients with high-risk localised disease, use external-beam radiation therapy (EBRT) with 76-78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
In patients with high-risk localised disease, use EBRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
<b>Therapeutic options outside surgery and radiotherapy</b>	
Do not offer either whole gland or focal therapy to high-risk patients.	Strong
Do not use ADT monotherapy in asymptomatic patients.	Strong

6.2.4 *Treatment of locally advanced PCa*

No standard treatment can be defined in the absence of high level evidence. But a local treatment combined with a systemic one provides the best outcome, provided the patient is ready and fit enough to receive both. The optimal local treatment is still a matter of debate [703]. Randomised controlled trials are only available for EBRT.

6.2.4.1 *Surgery*

Surgery for locally advanced disease as part of a multi-modal therapy has been reported [684, 704, 705].

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 [706]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at 10 years [682, 684, 704, 705, 707-710]. For cT3b-T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [711-713]. The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement (cN0). 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 [462]. Only limited evidence exists supporting RP for cN+ 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 [714]. 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). In clinical or pathological node-positive disease, RT monotherapy is associated with poor outcomes [574], and these patients should receive RT plus long-term ADT. A subgroup analysis from RTOG 85-31 with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic RT with immediate HT had better 5-year (54%) and 9-year (10%) PFS rates vs. 33% and 4%, respectively, for radiation alone ( $p < 0.0001$ ). Multivariate analysis showed that this combination had a statistically significant impact on OS [568]. These findings were also confirmed by the control arm of the STAMPEDE trial (HR: 0.48 [95% CI: 0.29-0.79]) in a non-randomised comparison [715].

#### 6.2.4.3 Treatment of cN1 PCa

The treatment of cN+ PCa was evaluated in a systematic review including 5 studies. Papers addressing LND-proven pelvic nodal metastases after RP for cN0M0 disease and publications including cM+ patients were excluded from the review [716-721].

The findings suggest an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT, as compared to ADT alone, but none of the included studies were RCTs and neither of the two local treatment approaches proved superior in this setting.

#### 6.2.4.4 Options other than surgery and 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 [678]. 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 disease unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50 ng/mL and a PSA-DT < 12 months [678, 722], or those that are symptomatic. The median time to start deferred treatment was 7 years. In the deferred treatment arm, 25.6% died without needing treatment.

##### 6.2.4.4.3 Adjuvant androgen ablation in pN1 disease

###### 6.2.4.4.3.1 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 [723, 724]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and the findings may not apply to men with less extensive nodal metastases.

###### 6.2.4.4.3.2 Adjuvant radiotherapy combined with ADT in pN1 disease

In a retrospective multicentre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated “adjuvantly” (within 6 months after surgery irrespective of PSA) with continuous ADT. 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 were not [725].

These results were confirmed by a US National Cancer Database analysis based on 5,498 patients [726]. Another US National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT + 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 [727].

In a series of 2,596 pN1 patients receiving ADT (n = 1,663) or ADT plus RT (n = 906), combined treatment was associated with improved OS, with a HR of 1.5 for ADT alone [728]. In a SEER retrospective population-based analysis, adding RT to RP showed a non-significant trend to improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [716]. Radiotherapy should be given to the pelvic lymphatics and the prostatic fossa [725, 729-731]. No data is available regarding adjuvant EBRT without ADT.

#### 6.2.4.5 Guidelines for radical treatment of locally-advanced disease

Recommendations	Strength rating
<b>Radical Prostatectomy (RP)</b>	
Offer RP to highly selected patients with cT3b-T4 N0 or any cN1 only as part of multi-modal therapy.	Strong
<b>Extended pelvic lymph node dissection (ePLND)</b>	
Perform an ePLND in high-risk PCa.	Strong
<b>Radiotherapeutic treatments</b>	
In patients with locally advanced cN0 disease, offer radiotherapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer long-term ADT for at least two years.	Weak
<b>Therapeutic options outside surgery and radiotherapy</b>	
Do not offer whole gland treatment or focal treatment to high-risk patients.	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, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
Offer patients with cN1 disease a local treatment (either RP or external beam radiation therapy) plus long-term ADT.	Weak

#### 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. Clearly 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

ISUP score  $\geq 2$  or patients classified as pT3 pN0 after RP due to positive margins (highest impact), capsule rupture and/or invasion of the seminal vesicles are at high risk of relapse which can be as high as 50% after 5 years [732]. Irrespective of the pT stage, the number of removed nodes [733-740], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [741]. A LN density (defined as the percentage of positive LNs in relation to the total number of analysed/removed LNs) over 20% was found to be associated with poor prognosis [742]. Finally the number of involved nodes seems to be a major factor for predicting relapse [735, 736, 743], the threshold being considered to be less than 3 positive nodes from an ePLND [425, 735, 743]. However, prospective data are needed before defining a definitive threshold value.

##### 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]), demonstrating an advantage (endpoint, development of BCR) in high-risk patients (e.g. pT2/pT3 with positive surgical margins and GS 8-10) 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. It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial, representing a major limitation in interpretation, as patients with a detectable PSA would now be considered for salvage therapy rather than adjuvant radiotherapy (ART) [744]. Therefore, for patients at increased risk of local relapse, who present with a PSA level of < 0.1 ng/mL,

two options can be offered in the framework of informed consent.

These are:

- Immediate ART to the surgical bed after recovery of urinary function, during the first 6 months post-surgery [744-746];
- or
- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [747, 748] (see Section 6.3.5.1 on Salvage EBRT).

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

Reference	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [744]	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 [745]	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 [746]	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 [749]	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; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

Preliminary data from RAVES and RADICALS, as well as a meta-analysis combining all findings have been reported, suggesting that SRT and ART offer similar outcomes for event-free survival [750-752]. Full publications are needed before any further conclusions can be drawn. Until then, ART remains a recommended treatment option in highly selected patients with combined high-risk features, such as pT3/R1/GS 8-10.

#### 6.2.5.4 Adjuvant androgen ablation

##### 6.2.5.4.1 Adjuvant androgen ablation in men with 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 [753]. A systematic review showed a possible benefit for PFS, but not OS for adjuvant androgen ablation [522].

##### 6.2.5.5 Adjuvant chemotherapy

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (6 cycles) ended prematurely due to poor accrual. A recent phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [754]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [755].

### 6.2.5.6 Guidelines for adjuvant treatment options after radical prostatectomy

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients.	Strong
Offer adjuvant external-beam radiation therapy to the surgical field to highly selected patients.	Strong
Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional radiotherapy; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

### 6.2.5.7 Guidelines for non-curative or palliative treatments in prostate cancer

Recommendations	LE	Strength rating
<b>Watchful waiting (WW) for localised prostate cancer</b>		
Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	1b	Strong
<b>Watchful waiting for locally advanced prostate cancer</b>		
Offer a deferred treatment policy using androgen deprivation (ADT) monotherapy to M0 asymptomatic patients with a prostate-specific antigen (PSA) doubling time > 12 months, a PSA < 50 ng/mL and well-differentiated tumour, who are unwilling or unable to receive any form of local treatment.	1b	Weak

## 6.2.6 Persistent PSA after radical prostatectomy

### 6.2.6.1 Introduction

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) [756, 757]. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue.

### 6.2.6.2 Natural history of persistently elevated PSA after RP

Several studies (See table 6.2.6.1) have shown that persistent PSA after RP is associated with more advanced disease (such as positive surgical margins (PSM), 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 [758, 759]. 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 [759]. 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 [758]. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively. In line with these data, Ploussard *et al.* reported that approximately 74% of patients with persistent PSA develop BCR [756]. Spratt *et al.* confirmed that a persistently detectable PSA after RP represents one of the worst prognostic factors associated with oncological outcome [760]. 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 recent data from Preisser *et al.* who showed that persistent PSA is prognostic of an increased risk of metastasis and death [761]. 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 that 5-year BCR-free survival for men who had a persistent PSA level > 0.1 but ≤ 0.2 ng/mL at 6-8 weeks after RP and were monitored was 50% [762].

Rogers *et al.* assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [763]. No patient received adjuvant therapy before documented metastasis. In their study, 38% of patients had no evidence of metastases for  $\geq 7$  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.

**Table 6.2.6.1: Studies on the natural history of patients with persistent PSA after RP**

Authors	Study population	n	Definition PSA persistence	Treatment	Outcome	Other details/comments
Ploussard <i>et al.</i> , J Urol 2013 [756]	496 men pN0 with persistent PSA 14 centres 1998 - 2011		PSA $\geq 0.1$ ng/mL at 6 wk.		74.4% with BCR 5% with metastasis	
Moreira <i>et al.</i> , BJUI 2010 [759]	901 men Shared Equal Access Regional Cancer Hospital (SEARCH) database. 2001-2008	230 (8 pN1)	PSA persistence definition of a PSA nadir $\geq 0.03$ ng/mL,	No RT info	Increased risk for BCR after surgery	Relative to men with undetectable PSA levels, those with a PSA nadir of 0.03 (HR: 3.88, $p < 0.001$ ), 0.04 (HR: 4.87, $p < 0.001$ ), 0.05-0.09 (HR: 12.69, $p < 0.001$ ), 0.1-0.19 (HR: 13.17, $p < 0.001$ ), and 0.2 ng/mL (HR: 13.23, $p < 0.001$ ) were at increased risk of BCR while men with a nadir of 0.01 (HR: 1.36, $p = 0.400$ ) and 0.02 (HR: 1.64, $p = 0.180$ ) were not.
Moreira <i>et al.</i> , J Urol 2009 [758]	1,156 men Shared Equal Access Regional Cancer Hospital (SEARCH) database. After 1997	291 (10 pN1)	PSA $> 0.03$ ng/mL within 6 mo.	No RT info	Increased BCR and overall mortality	Median FU 48 mo. In patients with persistent PSA 1 and 5-yr. BFS was 68% and 36%, significantly lower than 95% and 72%, respectively, in men without persistent PSA. 10-year OS in patients with vs. without persistent PSA was 63% vs. 80%. In men with persistent PSA independent predictors of BCR were higher PSA nadir (HR: 2.19, $p < 0.001$ ), positive surgical margins (HR: 1.75, $p = 0.022$ ) and high pathological ISUP grade (4-5 vs. 1, HR: 2.40, $p = 0.026$ ). Independent predictors of OM were a higher PSA nadir (HR: 1.46, $p = 0.013$ ) and seminal vesicle invasion (HR: 3.15, $p = 0.047$ )

Rogers <i>et al.</i> , Cancer 2004 [763]	224 men Single centre (Johns Hopkins) 1989 - 2002	160 men (58 pN1)	PSA $\geq$ 0.1 ng/mL at 3 mo.	No treatment before onset of metastasis	Metastasis-free survival at 3, 5 and 10 yr. was 68%, 49%, and 22%, respectively.	Mean FU 5.3 yr. 75 men (47%) developed distant metastases after RP (median time to metastases 5.0 yr.; range, 0.5-13 yr.).  The slope of PSA changes approximately 3-12 mo. after RP at a cut-off value $\geq$ 0.05 ng/mL was found to be predictive of distant metastasis-free survival (HR: 2.9, $p < 0.01$ ).
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BCR = biochemical recurrence; FU = follow-up; HR = hazard ratio; mo = months; n = number of patients; OM = overall mortality; PSA = prostate-specific antigen; RT = radiotherapy.

#### 6.2.6.3 Imaging in patients with persistently elevated PSA after RP

Standard imaging with bone scan and MRI has a low pick-up rate for men with a PSA below 2 ng/mL. However, PSMA PET/CT has been shown to identify residual cancer with a positivity rate 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  $\geq$  2ng/mL, respectively [325, 764-768] which can guide salvage radiation therapy (SRT) planning [769]. Using this, Schmidt-Hegemann *et al.* studied 129 patients who had either persistent PSA (52%) or BCR (48%) after RP [770]. Interestingly, men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those developing a detectable PSA. At present there is uncertainty regarding the best treatment if PSMA PET/CT shows metastatic disease.

#### 6.2.6.4 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.

Wiegel *et al.* [757] showed that following salvage RT to the prostate bed, patients with a detectable PSA after RP had significantly worse oncological outcomes when compared with those who achieved an undetectable PSA. Ten-year metastasis-free survival was 67% vs. 83% and OS was 68% vs. 84%, respectively. Recent data from Preisser *et al.* [761] also compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with salvage RT 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 ( $p < 0.01$ ), for salvage RT and no RT, 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 salvage RT and no RT, respectively. In multivariable models, after 1:1 propensity score matching, salvage RT was associated with lower risk for death (HR: 0.42,  $p = 0.02$ ) and lower cancer-specific death (HR: 0.29,  $p = 0.03$ ). These survival outcomes for patients with persistent PSA who underwent SRT suggest they benefit although outcomes are worse than for men experiencing BCR.

It is clear from a number of studies [757, 771-775] that poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade  $\geq$  4 in the RP histology and pT3b disease. Fossati *et al.* suggested that only men with a persistent PSA after RP and ISUP grade  $\leq$  3 benefited significantly [776], although this is not supported by Preisser *et al.* [761]. The current data does not allow making any clear treatment decisions.

Addition of ADT may improve PFS [771]. Choo *et al.* studied the addition of 2-year ADT to immediate RT to the prostate bed for patients with pathologic T3 disease (pT3) and/or positive surgical margins after RP [771]. Twenty-nine of 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 [744, 745]. Patients with persistently detectable post-operative PSA comprised approximately 50% and 12% of the study cohorts in the EORTC and the SWOG studies, respectively.

In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only with 66 Gy per protocol (arm C). The 10-year clinical relapse-free survival was 63% [757]. 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 end-points are yet to be published [777].

#### 6.2.6.5 Conclusion

The available data, suggests that patients with PSA persistence after RP may benefit from early aggressive multi-modality treatment, however, the lack of prospective RCTs makes firm recommendations difficult.

#### 6.2.6.6 Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen positron emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease.	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

The follow-up policy is described in Chapter 7 and will not be discussed here.

#### 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.

#### 6.3.2 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 end-points when comparing treatments.

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [778-780]. 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 [781].

After HIFU or cryotherapy no end-points 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 [782].

#### 6.3.3 Natural history of biochemical recurrence

Once a PSA relapse has been diagnosed, it is important to determine, whether the recurrence has developed at local or distant sites. A recent systematic review and meta-analysis investigated the impact of BCR on hard end-points and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, PCa-specific and overall mortality [782]. 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) [783, 784]. After primary RT, OS rates are approximately 20% lower at 8 to 10 years follow-up, even in men with minimal comorbidity [785, 786]. 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 this systematic review [782].

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 biochemical recurrence 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 the meta-analysis, proposal is to stratify patients into EAU Low-Risk BCR (PSA-DT > 1 year AND pathological ISUP grade < 4 for RP; interval to biochemical failure > 18 months AND biopsy ISUP grade < 4 for RT) or EAU High-Risk BCR (PSA-DT < 1 year OR pathological ISUP grade 4-5 for RP, interval to biochemical failure < 18 months OR biopsy ISUP grade 4-5 for RT), since not all patients with BCR will have similar outcomes. The stratification into “EAU Low-Risk” or “EAU High-Risk” BCR has recently been validated in a European cohort [787].

#### 6.3.4 *The role of imaging in PSA-only recurrence*

Imaging is only of value if it leads to a treatment change and therefore to a better outcome. In practice, limited data are available regarding the outcome based on imaging at relapse.

##### 6.3.4.1 *Assessment of metastases*

###### 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 [737, 788], the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [789]. In men with PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [790, 791].

Only 11-14% of patients with BCR after RP have a positive CT [790]. 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 [792].

###### 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 [793, 794].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [795] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [796]. The specificity of choline PET/CT is also higher than bone scan with fewer false-positive and indeterminate findings [330]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.2). Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [337, 797, 798]. 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 [799-801].

Choline PET/CT should only be recommended in patients fit enough for curative loco-regional salvage treatment. The sensitivity of choline PET is well known to be strongly influenced by PSA level and kinetics and drops to sub-optimal values in patients with a low PSA [798]; after RP a possible PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL [798].

###### 6.3.4.1.3 *Fluoride PET and PET/CT*

<sup>18</sup>F-NaF PET/CT has a higher sensitivity than bone scan in detecting bone metastases [802]. However, <sup>18</sup>F-NaF PET is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [803].

###### 6.3.4.1.4 *Fluciclovine PET/CT*

<sup>18</sup>F-Fluciclovine PET/CT has a slightly higher sensitivity than choline PET/CT in detecting the site of relapse in BCR [804]. In a recent multicentre trial evaluating 596 patients with BCR in a mixed population (33.3% after RP, 59.5% after RT ± RP, 7.1% other), fluciclovine PET/CT showed an overall detection rate of 67.7%, with a sensitivity of 62.7% (95% CI: 56-69%); lesions could be visualised either at local level (38.7%) or in LNs and

bones (9%) [805]. 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.

It is noteworthy that <sup>18</sup>F-fluciclovine has been approved in the US and Europe, and therefore it is currently the only PCa-specific radiotracer widely commercially available.

#### 6.3.4.1.5 Prostate-specific membrane antigen PET/CT

Prostate-specific membrane antigen PET/CT has shown good potential in patients with BCR, although most studies are limited by their retrospective design. Reported predictors of <sup>68</sup>Ga-PSMA PET in the recurrence setting were recently updated in a high-volume series [325]. Scan positivity of <sup>68</sup>Ga-PSMA PET scans increased with higher PSA levels, reaching 33% (95% CI: 16-51), 45% (95% CI: 39-52), 59% (95% CI: 50-68), 75% (95% CI: 66-84), and 95% (95% CI: 92-97), for PSA categories 0-0.19, 0.2-0.49, 0.5-0.99, 1-1.99, and ≥ 2 ng/mL, respectively. Gleason sum was not a strong predictor of a positive <sup>68</sup>Ga-PSMA PET scan. Positivity rates in the prostate bed were significantly different in patients after RP (22%) and RT (52%). High sensitivity (75%) and specificity (99%) were observed on per-lesion analysis.

PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL [806, 807]. PSMA PET/CT identified the site of recurrence in 59 of 88 patients (67%) in a recent prospective trial [808]. A higher PSA velocity seems associated with higher PSMA PET/CT-positivity rates [325, 765].

In a prospective multicentre 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%) [343]. A recent 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 [764]; 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 <sup>68</sup>Ga-PSMA-ligand PET/CT may tailor further therapy decisions (e.g., local vs. systemic treatment) at low PSA values (0.2 to 1 ng/mL) [766].

A single-centre study retrospectively assessed 164 men from a prospectively-acquired database 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 salvage RT, 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 salvage RT [809]. 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 salvage RT.

It is worth noting that the term “PSMA PET” refers to several different radiopharmaceuticals; the majority of published studies used <sup>68</sup>Ga-PSMA-11 [325, 764-766, 809, 810] but other authors are reporting data with <sup>18</sup>F-labelled PSMA [767, 768]. At present there are no conclusive data about comparison of such tracers [811].

#### 6.3.4.1.6 Whole-body and axial MRI

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT [812]. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

#### 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 [789], salvage RT 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 salvage RT without local imaging.

Multiparametric MRI can detect local recurrences in the prostatic bed, but its sensitivity in patients with a PSA level < 0.5 ng/mL remains controversial [813, 814]. Choline PET/CT is less sensitive than mpMRI when the PSA level is < 1 ng/mL [815]. PSMA PET/CT is positive in 15-58% of patients with BCR and PSA levels < 0.5 ng/mL, but published series are difficult to interpret since they usually mix patients with a history of RP and RT [768, 806, 816]. Recent data support the potential role of PSMA PET/CT especially for the identification of distant metastases; even at PSA levels < 0.5 ng/mL [764]. A recent systematic review and meta-analysis on <sup>68</sup>Ga-PSMA PET in advanced PCa revealed a scan positivity-rate in up to 46% in patients with BCR after prostatectomy and PSA levels < 0.5 ng/mL [325].

Precise detection and location of local recurrences after RP will be needed but not until it has been proven that stereotaxic boost to the recurrence site during salvage RT improves the patient outcome which, so far, remains investigational.

#### 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 treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [789].

Transrectal US is not reliable in identifying local recurrence after RT. In contrast, mpMRI has yielded excellent results and can be used for biopsy targeting and guiding local salvage treatment [789, 817-819] even if it slightly underestimates the volume of the local recurrence [820]. Detection of recurrent cancer is also feasible with choline PET/CT [821], but choline PET/CT has not been compared to mpMRI yet. Prostate-specific membrane antigen PET/CT can play a role in the detection of local recurrences after RT [325], but data are still limited by a lack of robust results from well-designed trials.

#### 6.3.4.3 Summary of evidence on imaging in case of biochemical recurrence

In patients with BCR, imaging has the potential to play a role in detecting both distant metastases and local recurrence. Early detection of metastases in a BCR setting is clinically highly relevant, either after RT or after RP in order to optimise salvage treatment. Many recent studies suggest that PSMA PET/CT is substantially more sensitive than abdominopelvic CT, bone scan and choline PET/CT in the detection of distant metastases in patients with BCR. Although most studies are retrospective and/or monocentric, they all come to the same conclusion as confirmed by a recent systematic review [822]. After RP, compared to choline PET/CT, PSMA PET/CT showed high positivity rates, even for PSA levels < 1 ng/mL. Following RT, mpMRI is the best technique to evaluate local recurrence, to guide targeted biopsies and to plan salvage treatment strategies [823].

#### 6.3.4.4 Guidelines for imaging in patients with biochemical recurrence

<b>Prostate-specific antigen (PSA) recurrence after radical prostatectomy</b>	<b>LE</b>	<b>Strength rating</b>
Perform prostate-specific membrane antigen (PSMA) positron emission tomography (PET) computed tomography (CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	2b	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
<b>PSA recurrence after radiotherapy</b>		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	3	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	2b	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 Salvage radiotherapy for PSA-only recurrence after radical prostatectomy

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 [824]. 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% [750, 751].

The PSA level at BCR was shown to be prognostic [824]. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [825-828], corresponding to a ~80% chance of being progression-free 5 years later [748]. 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 salvage RT alone (n = 160) within 2 years of BCR showed that salvage RT 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 [829]. According to an EAU review which also proposed a scoring system [782], men with a PSA-DT > 1 year and a pathological GS (pGS) < 8 have a significantly lower risk of clinical progression and can be classified as ‘EAU low risk’; men with a PSA-DT ≤ 1 year or a pGS 8-10 are at increased risk of clinical progression and should be classified as ‘EAU high risk’. These definitions have been externally validated and may be helpful for individualised treatment decisions [787]. Despite the indication for salvage RT, a “wait and see” strategy remains an option in patients with a PSA-DT of more than 12 months and other favourable factors such a time to BCR > 3 years, ≤ pT3a,

ISUP grade  $\leq 2/3$  [782, 830]. For an overview see Table 6.3.1.

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence; metastatic disease, disease specific- and OS are more meaningful end-points 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 PCa-specific mortality. 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 [782]. A recent, international multi-institutional, analysis of pooled data from RCTs has suggested that metastasis-free survival is the most valid surrogate end-point with respect to impact on OS [831, 832]. Table 6.3.2 summarises results of recent studies on clinical end-points after SRT.

**Table 6.3.1: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy (SRT) PSA level\***

Reference	Year	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, <i>et al.</i> [833]	2017	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. $\geq 0.2$ ng/mL p < 0.0001
Soto, <i>et al.</i> [834]	2012	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16
Stish, <i>et al.</i> [825]	2016	1,106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA $\leq 0.5$ vs. > 0.5 ng/mL p < 0.001
Tendulkar, <i>et al.</i> [835]	2016	2,460	60	0.5	66 Gy 16% ADT	56% (5)	SRT; PSA < 0.2 ng/mL 71% 0.21-0.5 ng/mL 63% 0.51-1.0 ng/mL 54% 1.01-2.0 ng/mL 43% > 2 ng/mL 37% 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 6.3.2: Recent studies reporting clinical end-points after SRT (the majority of included patients did not receive ADT)**

Reference	Year	n	Median FU (mo)	Regimen	Outcome
Bartkowiak, <i>et al.</i> [833]	2017	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 $\geq 0.1$ ng/mL 92% p = 0.005

Jackson, <i>et al.</i> [836]	2014	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, <i>et al.</i> [825]	2016	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, <i>et al.</i> [835]	2016	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10 yr. DM SRT: PSA 0.01-0.2 ng/mL 9% SRT: PSA 0.21-0.50 ng/mL 15% SRT: PSA 0.51-1.0 ng/mL 19% SRT: PSA 1.01-2.0 ng/mL 20% SRT: PSA > 2 ng/mL 37%, 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.

#### 6.3.5.2 Salvage radiotherapy combined with androgen deprivation therapy

Data from RTOG 9601 [837] suggest both CSS and OS benefit when adding 2 years of bicalutamide (150 mg daily) to SRT. 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 (MFS). However, SRT combined with either goserelin or placebo, showed similar DSS and OS rates [838]. Table 6.3.3 provides an overview of these two 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 risk classification may offer guidance in this respect [782, 787].

One of these RCTs reports improved OS and the other one improved MFS but due to methodological discrepancies, 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.

A recent 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 [839]. In a retrospective multicentre-study including 525 patients, only in patients with more aggressive disease characteristics (pT3b/4 and ISUP grade > 4 or pT3b/4 and PSA at early SRT > 0.4 ng/mL) the administration of concomitant ADT was associated with a reduction in distant metastasis [840]. Similarly, in a retrospective analysis of 1,125 patients, stage ≥ pT3b, GS ≥ 8 and a PSA level at SRT > 5 ng/mL were identified as risk factors for clinical recurrence. A significant effect of long-term ADT was observed in patients with ≥ 2 adverse features. For patients with a single risk factor, short-term HT was

sufficient whilst patients without risk factors showed no significant benefit from concomitant ADT [841].

**Table 6.3.3: RCTs comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone**

Reference	Year	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 Carrie, <i>et al.</i> [838]	2019	369 RT + ADT 374 RT	ISUP grade ≤ 2/3 89%,  ISUP grade ≥ 4 11% cN0	112	66 Gy + GnRH analogue 6 mo. 66 Gy	10 yr. PFS 64% p < 0.0001 10 yr. PFS 49% 10 yr. MFS 75% p = 0.034 10 yr. MFS 69%
RTOG 9601 Shipley, <i>et al.</i> [837]	2017	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy + bicalutamide 24 mo. 64.8 Gy + placebo	12 yr. DM 14% p = 0.005 12 yr. DM 23% 12 yr. OS 76% p = 0.04 12 yr. OS 71% 12 yr. DSM 5.8% p < 0.001 12 yr. DSM 13.4%

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; PFS = progression free survival; FU = follow-up; GnRH = gonadotropin-releasing hormone; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = radiotherapy; yr = year.

#### 6.3.5.2.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for “clinical target volumes” of PCa [842-845] and for organs at risk of normal tissue complications [846]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS but not MFS has been reported in patients receiving whole pelvis SRT (± ADT) but the advantages must be weighed against possible side effects [847].

The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the base of the seminal vesicles, depending on the pathological stage after RP) [826, 848]. In a SR, 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 a treatment dose above 70 Gy should be administered at the lowest possible PSA level [849]. 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 [850-852]. 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 [853]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [835].

Salvage RT is also 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. 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 [833].

In a RCT on dose escalation for SRT involving 350 patients, 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. Gastrointestinal tract toxicity of grades 2 and 3 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 [854, 855].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side-effects, especially genitourinary symptoms, clearly increases, even with newer planning and treatment techniques [856, 857]. 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 had no differential effect on the relatively high level of GU toxicity (5-year, 3D-CRT

15.8% vs. IMRT 16.8%) [856]. After a median salvage IMRT dose of 76 Gy, the 5-year risk of grade 2-3 toxicity rose to 22% for genitourinary and 8% for gastrointestinal symptoms, respectively [857]. Doses of at least 66 Gy, and up to 72 Gy can be recommended [833, 854].

#### 6.3.5.2.2 Comparison of adjuvant radiotherapy and salvage radiotherapy

The largest retrospective risk-matched study evaluating ART vs. early SRT comprised 510 pT3N0 R0/R1 patients (ADT was excluded). With a median follow-up of 94 months, MFS did not differ significantly when comparing 243 patients who had ART and 267 patients who had SRT at a PSA < 0.5 ng/mL (92% vs. 91%,  $p = 0.9$ ) or OS (89% vs. 92%,  $p = 0.9$ ). Conclusion was that early salvage RT does not impair PCa control but clearly helps reducing over-treatment, which is a major issue in both ART and in SRT [851]. Similarly, Buscarillo *et al.* reported no difference in MFS or OS among two groups of 149 propensity-matched PCa patients with adverse pathologic features [858]. However, these retrospective studies are underpowered for high-risk cases such as pT3b/R1/ ISUP grade 4-5. 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 end-points, biochemically no evidence of disease, MFS, and OS [859].

Both approaches (ART and SRT) together with the efficacy of adjuvant ADT are currently being compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG 17). Preliminary data from RAVES and RADICALS, as well as a meta-analysis combining all three RCTs have been presented, suggesting that SRT and ART offer similar outcomes for event-free survival [750-752]. Full publications are needed before any further conclusions can be drawn. Until then, ART remains a recommended treatment option in highly selected patients with combined high-risk features, such as pT3/R1/ GS 8-10.

#### 6.3.5.2.3 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or local procedures such as salvage RP (SRP), cryotherapy, interstitial brachytherapy and HIFU [860-869]. As the available evidence for these treatment options is of low quality, strong recommendations regarding the choice of any of these techniques cannot be made as. The following is an overview of the most important findings for each of these techniques with a proposal for their indications.

#### 6.3.5.3 Salvage radical prostatectomy

Salvage RP after RT has the best likelihood of achieving local control relative to other salvage treatments. However, this must be weighed against the possible adverse events, which are increased compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation.

#### 6.3.5.3.1 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 [870].

In most contemporary series, organ-confined disease, negative surgical margins, and the absence of seminal vesicle and/or LN metastases were favourable prognostic indicators associated with a better DFS of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [869].

**Table 6.3.4: Oncological results of selected salvage radical prostatectomy case series, including at least 30 patients**

Reference	n	Median FU (mo)	Pathologic Organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability (yr.)
Sanderson, <i>et al.</i> 2006 [871]	51	-	25	36	28	47	-	5
Leonardo, <i>et al.</i> 2009 [872]	32	35	53	34	0	75	-	3
Heidenreich, <i>et al.</i> 2010 [868]	55	23 (2-56)	73	11	20	87	-	2
Chade, <i>et al.</i> 2011 [873]	404	55	55	25	16	37	83	10
Mandel, <i>et al.</i> 2016 [874]	55	36	50	27	22	49	89	5

BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin.

#### 6.3.5.3.2 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%) [875]. In more recent series, these complications appear to be less common [867, 870]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [870].

**Table 6.3.5: Peri-operative morbidity in selected salvage radical prostatectomy case series, including at least 30 patients**

Reference	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5 (%)	Blood loss, mL, mean, range
Stephenson, <i>et al.</i> 2004 [867]	100	15 vs. 2*	30	33 vs. 13*	-
Ward, <i>et al.</i> 2005 [876]	138	5	22	-	-
Sanderson, <i>et al.</i> 2006 [871]	51	2	41	6	-
Gotto, <i>et al.</i> 2010 [875]	98	9	41	25	-
Heidenreich, <i>et al.</i> 2010 [868]	55	2	11	3.6	360 (150-1450)

\* SRP performed before vs. after 1993.

n = number of patients.

#### 6.3.5.3.3 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, a pre-SRP PSA < 10 ng/mL and 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 [870]. A meta-regression analysis suggested that SRP may be associated with worse continence outcomes than non-surgical approaches [877].

#### 6.3.5.4 Salvage cryoablation of the prostate

##### 6.3.5.4.1 Oncological outcomes

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year biochemical DFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [878]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year BCR-free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [879].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The 5-year OS was significantly higher in the SRP group (95% vs. 85%) [880].

**Table 6.3.6: Oncological results of selected salvage cryoablation of the prostate case series, including at least 50 patients**

Reference	n	Median FU (mo)	BCR-free probability (%)	Time probability (yr.)	Definition of failure
Pisters, <i>et al.</i> 1997 [880]	150	17	44	-	Nadir + 0.2
Bahn, <i>et al.</i> 2003 [881]	59	82	59	7	PSA > 0.5
Ismail, <i>et al.</i> 2007 [878]	100	33	73 (low risk)	5	ASTRO
Pisters, <i>et al.</i> 2008 [879]	279	22	58	5	ASTRO and Phoenix
Williams, <i>et al.</i> 2011 [882]	187	7.46 yr.	39	10	Nadir +2
Spiess, <i>et al.</i> 2010 [883]	450	40.8	34	-	PSA > 0.5

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.

#### 6.3.5.4.2 Morbidity

According to Cespedes, *et al.*, the risks of urinary incontinence and ED at at least 12 months after SCAP were as high as 28% and 90%, respectively [884]. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In an on-line registry by Pisters, *et al.*, urinary incontinence rates were 4.4%. The rectal fistulae rate was 1.2% and 3.2% of patients requiring a TURP for removal of sloughed tissue [879]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.3.5) [885].

**Table 6.3.7: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage cryoablation of the prostate case series, including at least 50 patients**

Reference	n	Incontinence (%)	Obstruction/Retention (%)	Rectourethral fistula (%)	ED (%)
Pisters, <i>et al.</i> 1997 [886]	150	73	67	1	72
Bahn, <i>et al.</i> 2003 [881]	59	8	-	3.4	-
Ismail, <i>et al.</i> 2007 [878]	100	13	4	1	-
Pisters, <i>et al.</i> 2008 [879]	279	4.4	3.2	1.2	-
Ahmad, <i>et al.</i> 2013 [887]	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

#### 6.3.5.4.3 Summary of salvage cryoablation of the prostate

In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, an initial organ-confined PCa cT1c to cT2, initial ISUP grade ≤ 2/3, a pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL.

#### 6.3.5.5 Salvage brachytherapy for radiotherapy failure

Although there is no role for salvage EBRT following local recurrence after previous definitive RT, in carefully selected patients with a good PS, primary localised PCa and histologically proven local recurrence (based on Phoenix criteria [885]), HDR- or LDR brachytherapy remain effective treatment options with an acceptable toxicity profile [888-890]. However, the published series are relatively small and consequently this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR brachytherapy over a period of 9 years [888]. With a median follow-up of 60 months the 5-year biochemical control was 51% and only 2% grade 3 genitourinary toxicities were reported (Phoenix criteria). Comparable with these data, 42 patients were treated in a phase II trial at MSKCC in New York [891]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after 5 years was 69% (median follow-up 36 months). Grade 2 late side-effects were seen in 15% and one patient developed grade 3 incontinence. However, older data with higher rates of side-effects have been reported [892].

Using LDR brachytherapy with <sup>103</sup>palladium, long-term outcome was reported in 37 patients with a median follow-up of 86 months [889]. The biochemical control rate after 10 years was 54%. However, the crude rate of ≥ grade 2 toxicity was 46% and ≥ grade 3 toxicity was 11%. These side-effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side-effects seem to be lower with HDR brachytherapy [893]. In conclusion, freedom from BCR

after salvage HDR- and LDR brachytherapy is promising and the rate of severe side-effects in experienced centres seem to be acceptable. Salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

### 6.3.5.6 Salvage high-intensity focused ultrasound

#### 6.3.5.6.1 Oncological outcomes

Salvage HIFU has more recently emerged as an alternative thermal ablation option for radiation-recurrent PCa. Most of the data were generated by one high-volume centre. Median follow-up was very short, and outcome measures were non-standardised.

**Table 6.3.8: Oncological results of selected salvage high-intensity focused ultrasound case series, including at least 20 patients**

Reference	n	Median FU (mo)	BCR-free probability (%) ASTRO and Phoenix criteria	Negative biopsy rate
Colombel, <i>et al.</i> 2006 [894]	224	15-18	-	80
Uchida, <i>et al.</i> 2011 [895]	22	24	59 (Phoenix) (24 mo)	92 (only 12 biopsied)
Berge, <i>et al.</i> 2011 [896]	46	9	60.9 (9 mo)	-
Crouzet, <i>et al.</i> 2017 [897]	418	42	49% (5 yr.); 82% CSS (7 yr.)	-

BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; yr. = year.

#### 6.3.5.6.2 Morbidity

Most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

#### 6.3.5.6.3 Summary of salvage high-intensity focused ultrasound

There is a lack of quality data which prohibits any recommendation regarding the indications for salvage HIFU.

### 6.3.6 Salvage lymph node dissection

Novel imaging modalities improve the early detection of nodal metastases [898]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [898-900]. The majority of treated patients showed BCR but clinical recurrence-free and CSS 10-year survival over 70% has been reported [899, 901]. Neither the template nor the real value of nodal salvage dissection is available. It must, however, be remembered that the imaging modalities under-evaluate the real nodal involvement. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [902]. Addition of RT to the lymphatic template after salvage LND may improve the BCR rate [903]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival [904].

### 6.3.7 Hormonal therapy

The Guidelines Panel conducted a systematic review including studies published from 2000 onwards [905]. 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) [906]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [907]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic work-up 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 comorbidities. In some studies, such as the Boorjian, *et al.* study [830], 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 in 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 [829]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [908]. 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. 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 comorbidities, the side-effects of HT may even decrease life expectancy; in particular, cardiovascular risk factors need to be considered [909, 910]. Early HT should be reserved for those at 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.

#### 6.3.8 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 [737]. 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.

#### 6.3.9 Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
<b>Recommendations for biochemical recurrence after radical prostatectomy</b>	
Offer prostate-specific antigen (PSA) monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
Offer salvage radiotherapy (SRT) to patients with a PSA rise from the undetectable range. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak
<b>Recommendations for biochemical recurrence after radiotherapy</b>	
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	Weak
Salvage RP should only be performed in experienced centres.	Weak
Only offer salvage high intensity focused ultrasound, salvage cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence within a clinical trial setting or well-designed prospective cohort study.	Strong
<b>Recommendations for systemic salvage treatment</b>	
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling-time > 12 months.	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 and bone scan. The influence on treatment and outcome of newer, more sensitive imaging has not been assessed yet.

### 6.4.2 Prognostic factors

Median survival of patients with newly diagnosed metastases is approximately 42 months [911], however, the M1 population is heterogeneous. 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 alkaline phosphatase, but only few have been validated [912-915].

“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) [915-917] and has been shown to be predictive in a powered subgroup analysis for benefit of addition of prostate radiotherapy ADT [918].

Based on a large SWOG 9346 cohort, the PSA level after 7 months of ADT was used to create 3 prognostic groups (see Table 6.4.1) [919]. A PSA  $\leq$  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 [920].

**Table 6.4.1 Definition of high- and low-volume and risk in CHARTED [915-917] and LATITUDE [921]**

	High	Low
<b>CHARTED (volume)</b>	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or spine <b>OR</b> Visceral metastasis	Not high
<b>LATITUDE (risk)</b>	≥ 2 high-risk features of: <ul style="list-style-type: none"> <li>• ≥ 3 Bone metastasis</li> <li>• Visceral metastasis</li> <li>• ≥ ISUP grade 4</li> </ul>	Not high

**Table 6.4.2: Prognostic factors based on the SWOG 9346 study [919]**

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

#### 6.4.3 First-line hormonal treatment

Primary ADT has been the standard of care for over 50 years [606]. There is no high level evidence in favour of a specific type of ADT, neither for orchiectomy or for an LHRH analogue or antagonist, with the exception of patients with impending spinal cord compression for whom either a bilateral orchidectomy or LHRH antagonists are the preferred options.

##### 6.4.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events [922]. The evidence quality of the studies included in this review was rated as moderate.

##### 6.4.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [923-925] and two meta-analyses [926, 927], 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. The 5 remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [928]. Out of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that, at best, only 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.

Other trials did not show any survival difference with an overall HR for OS of 1.02 (0.94-1.11) [923]. These reviews and the meta-analyses came to the conclusion that a difference in OS or CSS between IAD and continuous ADT is unlikely. A recent review of the available phase III trials highlighted the limitations of most trials and suggested a cautious interpretation of the non-inferiority results [929]. None of the trials that addressed IAD vs. continuous ADT in M1 patients showed a survival benefit, but there was a constant trend towards improved OS and PFS with continuous ADT. However, most of these trials were non-inferiority trials. In some cohorts the negative impact on sexual function was less pronounced with IAD. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side-effects, such as hot flushes [930, 931].

##### 6.4.3.3 Immediate versus deferred androgen deprivation therapy

In symptomatic patients immediate treatment is mandatory, however, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies. A first Cochrane review extracted four RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [920, 922]. These studies were conducted in the pre-PSA era and included patients with advanced metastatic or non-metastatic PCa who received immediate vs. deferred ADT [932]. No improvement in PCa CSS was observed, although immediate ADT

significantly reduced disease progression. The Cochrane analysis was updated in 2019 and concluded that early ADT probably extends time to death of any cause and time to death from PCa [933]. Since the analysis included only a very limited number of M1 patients who were not evaluated separately, the benefit of immediate ADT in this setting remains unclear.

#### 6.4.4 Combination therapies

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

##### 6.4.4.1 Complete androgen blockade

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [934]. However, results with other anti-androgens or castration modalities have differed and systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [935, 936] beyond 5 years of survival [937] but this minimal advantage in a small subset of patients must be balanced against the increased side-effects associated with long-term use of NSAAs.

##### 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 [679, 915, 938]. All trials compared ADT alone as the standard of care 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 OS. The key findings are summarised in Table 6.4.3.

**Table 6.4.3: Key findings - Hormonal treatment combined with chemotherapy**

	STAMPEDE James [679]		GETUG Gravis [938]		CHAARTED Sweeney [915]	
	ADT	ADT + Docetaxel + P	ADT	ADT + Docetaxel	ADT	ADT + Docetaxel
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		50		29	
HR (95% CI)	0.78 (0.66-0.93)		1.01 (0.75-1.36)		0.61 (0.47-0.80)	
M1 only						
n	1,086		-		-	
HR (95% CI)	0.76 (0.62-0.92)		-		-	

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; HR = hazard ratio; ISUP = 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 newly diagnosed M1 PCa, either *de novo* or after a primary treatment [938]. They were stratified based on previous treatment, and Glass risk factors [912]. In the CHARTED trial, the same inclusion criteria applied and patients were stratified according to disease volume; high volume being

defined as either presence of visceral metastases or four, or more, bone metastases, with at least one outside the spine and pelvis [915].

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  $\geq 40$  ng/mL or ISUP grade 4-5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA  $\geq 4$  ng/mL with a PSA-DT  $< 6$  months or a PSA  $\geq 20$  ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [679].

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 [939, 940].

Based on these data, upfront docetaxel 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 [940]. Docetaxel is used at the standard dose of 75 mg/sqm combined with steroids as pre-medication. Continuous oral corticosteroid therapy is not mandatory.

In subgroup analyses from GETUG-AFU 15 and CHARTED the beneficial effect of the addition of docetaxel to ADT is most evident in men with *de novo* metastatic high-volume disease [916, 917], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [941]. The effects were less apparent in men who had prior local treatment although the numbers were small and the event rates lower.

A recent systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to standard of care improved survival [940]. The HR of 0.77 (95% CI: 0.68-0.87;  $p < 0.0001$ ) translates to an absolute improvement in 4-year survival of 9% (95% CI: 5-14). Docetaxel in addition to standard of care also improves failure-free survival, with a HR of 0.64 (0.58-0.70;  $p < 0.0001$ ) translating into a reduction in absolute 4-year failure rates of 16% (95% CI: 12-19).

#### 6.4.4.2.2 Combination with the new hormonal treatments (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 hormone-sensitive PCa (mHSPC) was studied [35, 921, 942]. The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit, but in LATITUDE in high-risk metastatic patients only with a HR of 0.62 (0.51-0.76) [921]. 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 [35]. The inclusion criteria in the two trials differed, but both trials were positive for OS. 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 [943].

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. The key findings are summarised in Table 6.4.4. No difference in treatment-related deaths was observed with the combination of ADT plus abiraterone acetate and prednisone 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%). Based on these data, upfront abiraterone acetate plus prednisone 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 (see Table 6.4.4) [942].

In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with hormone-sensitive PCa (mHSPC) was tested [944-946]. In ARCHES the primary endpoint was radiographic progression-free survival (rPFS). Radiographic PFS 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 ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT improved OS with a HR of 0.67 (0.52-0.86). Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [946]. In the TITAN trial, apalutamide was used as AR antagonist with rPFS and OS as co-primary endpoints. Radiographic PFS 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 this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [944].

In summary, the addition of AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. Again the majority of patients treated had *de novo*

metastatic disease and the evidence is most compelling in this situation. It may still be considered for men progressing after local therapy but this men make up a smaller fraction of the included patients. Lastly, whether the addition of an AR antagonist plus docetaxel adds further benefit is currently not clear as longer follow-up is needed. At the moment, since toxicity clearly increases, AR antagonists plus docetaxel should not be given outside of clinical trials.

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

	<b>STAMPEDE [James] [35]</b>		<b>LATITUDE [Fizazi] [921]</b>	
	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 $\geq$ 4, PSA $\geq$ 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 $\geq$ 4, $\geq$ 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)	
<b>M1 only</b>				
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	Failure-free survival (biological, radiological, clinical or death): 0.29 (0.25-0.34)		Radiographic PFS: 0.49 (0.39-0.53)	

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval;  
 ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mo = month; n = number of patients;  
 NA = not available; OS = overall survival; P = prednisone; PFS = progression-free survival; PSA = prostate-specific antigen; yr. = year.

**Table 6.4.5 Results from the ENZAMET and TITAN studies**

	ENZAMET [945]		TITAN [944]	
	ADT+ older antagonist +/-docetaxel (SOC)	ADT + enzalutamide +/-docetaxel	ADT + placebo	ADT + apalutamide
n	562	563	527	525
Newly diagnosed M+	61.7%	59.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS Radiographic PFS	
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; NA = not available; OS = overall survival; SOC = standard of care; PFS = progression-free survival; yr = year.

#### 6.4.5 Treatment selection and patient selection

There are no head-to-head data comparing 6 cycles of docetaxel and the long-term use of abiraterone acetate plus prednisone in newly diagnosed mHSPC. However, for a period, patients in STAMPEDE were randomised to either the addition of abiraterone or docetaxel to standard of care. Data from the two experimental arms has been extracted although this was not pre-specified in the protocol and therefore the data were not powered for this comparison. The survival advantage for both drugs appeared similar [947]. A recent meta-analysis also found no significant OS benefit for either drug [948]. In the STOPCAP systematic review and meta-analysis, abiraterone acetate plus prednisone was found to have the highest probability of being the most effective treatment [949]. Both modalities have different and agent-specific side-effects and require strict monitoring of side-effects during treatment. Therefore, the choice will most likely be driven by patient preference, the specific side-effects, availability and cost.

#### 6.4.6 Deferred treatment for metastatic PCa (stage M1)

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. However, since the median survival is only 42 months, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even dying from PCa, without receiving any benefit from hormone treatment has been highlighted [674, 683]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

#### 6.4.7 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. 432 patients were randomised to ADT alone or ADT plus EBRT 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]) [950]. The STAMPEDE trial evaluated 2,061 men with mCSPC who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed radiotherapy to the primary tumour did not improve OS in unselected patients [918]. However, following the results from CHARTED, 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. Therefore RT of the prostate 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 abiraterone acetate plus prednisone 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, results of ongoing trials are awaited.

In a recent 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; heterogeneity chi-square = 0.08, degree of freedom = 1, p = 0.78) [951]. 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.

#### 6.4.8 Metastasis-directed therapy

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There is one randomised phase II trial testing metastasis-directed therapy (MDT) vs. surveillance in men with oligo-recurrent PCa. Oligo-recurrence was defined as  $\leq 3$  lesions on pet-choline only. The sample size was small with 62 patients and only about half of them had nodal disease. Androgen deprivation therapy-free survival was the primary end-point which was longer with MDT than with surveillance [952]. Currently there is no data to suggest an improvement in OS. A systematic review highlighted that at this time this approach must, as yet, be considered as experimental [902].

#### 6.4.9 Guidelines for the first-line treatment of 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
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment also to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
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 antagonists monotherapy to patients with M1 disease.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong

### 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:

- 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
- 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) [953]. 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 mCRPC;
- quality of response and pace of progression on previous treatment;
- known cross resistance between androgen receptor targeted agents (ARTA);
- co-medication and known drug interactions (see approved summary of product characteristics);
- known genetic alterations;
- known histological variants and DNA repair deficiency (consider platinum or targeted therapy like poly-ADP ribose polymerase (PARP) inhibitors [still unapproved, but first phase III data available]);
- local approval status of drugs and reimbursement situation;
- available clinical trials.

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel and radium-223. In general, sequencing of ARTA like abiraterone/prednisolone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARTA was short ( $\leq 12$  months) and high-risk features of rapid progression are present [954, 955]. In case the ARTA sequence is the only option, first prospective cross-over data suggest that abiraterone followed by enzalutamide is the preferred choice [956].

The earlier use of chemotherapy with cabazitaxel in the treatment sequence is recommended and supported by high level evidence [954].

Clinical parameters of aggressive disease like a short response to mHSPC therapy, high tumour burden, rapid pace of progression, visceral metastases, poor genomics (p53, RB, myc) should rather prompt the use of chemotherapy or clinical trials than e.g. ARTA [957]. Clinical trials should be the preferred treatment option whenever available.

Genetic sequencing of the primary tumour, liquid biopsy (ctDNA), or the use of fresh tissue biopsies of metastatic spread should be considered early on and in particular as soon as the patient becomes castration resistant. Open questions for genetic testing include the quality of tissue, which panels to use, availability of a molecular tumour board and interpretation of results. Level 1 evidence for the use of PARP (poly-ADP ribose polymerase)-inhibitors has been reported [958]. Microsatellite instability (MSI)-high is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA [959, 960] and could be a valuable additional treatment option.

### 6.5.3 *Non-metastatic CRPC*

Frequent PSA testing for men on treatment with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases detectable on bone scan within two years [961].

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 and OS [961, 962]. 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 [963] 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 for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are expected to be diagnosed with early mCRPC.

Three large randomised controlled phase III trials, PROSPER [630], SPARTAN [964] and ARAMIS [631], evaluated MFS as the primary end-point in patients with non-metastatic CRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide vs. placebo (ARAMIS), respectively. 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  $\leq 10$  months were included. Patient characteristics in both trials revealed that about two-thirds of participants had a PSA-DT of  $< 6$  months. All trials showed a significant MFS benefit (PROSPER: median MFS was 36.6 months in the enzalutamide group vs. 14.7 months in the placebo group [HR for metastasis or death, 0.29; 95% CI: 0.24-0.35,  $p < 0.001$ ]; SPARTAN: median MFS was 40.5 months in the apalutamide group vs. 16.2 months in the placebo group [HR for metastasis or death, 0.28, 95% CI: 0.23-0.35,  $p < 0.001$ ]; ARAMIS: median MFS was 40.4 months in the darolutamide group vs. 18.4 months in the placebo group (HR: 0.41, 95% CI: 0.34-0.50; 2-sided  $p < 0.0001$ ). None of the trials showed a survival benefit, after a median follow-up of approximately 20 months. In view of the long-term treatment with these AR targeted agents in asymptomatic patients, potential adverse events need to be taken into consideration and the patient informed accordingly.

### 6.5.4 *Metastatic CRPC*

The remainder of this section focuses on the management of men with proven metastatic CRPC (mCRPC).

#### 6.5.4.1 *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 [965, 966]. However, in the absence of prospective data, the modest potential benefits of a 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.

**Table 6.5.1: Randomised phase III controlled trials - first-line treatment of mCRPC**

Author	Intervention	Comparison	Selection criteria	Main outcomes
<b>DOCETAXEL</b>				
SWOG 99-16 Petrylak, DP, <i>et al.</i> 2004 [967]	docetaxel/EMP, every 3 weeks, 60 mg/m <sup>2</sup> , EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m <sup>2</sup> 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 2008 [968, 969]	docetaxel, every 3 weeks, 75 mg/m <sup>2</sup> prednisone 5 mg BID or docetaxel, weekly, 30 mg/m <sup>2</sup> prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m <sup>2</sup> , 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)
<b>ABIRATERONE</b>				
COU-AA-302 Ryan CJ, <i>et al.</i> 2013 [970-972]	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)
<b>ENZALUTAMIDE</b>				
PREVAIL Beer TM, <i>et al.</i> 2014 [973]	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)
<b>SIPULEUCEL-T</b>				
SIPULEUCEL-T Kantoff PW, <i>et al.</i> 2010 [974]	sipuleucel-T [975]	placebo [975]	- 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)
Small EJ, <i>et al.</i> 2006 [976]	sipuleucel-T [976]	placebo [976]	- ECOG 0-1. - No visceral metastases. - No prior immunotherapy - No corticosteroids.	OS: 25.9 vs. 21.4 mo. (p = 0.1). FU: 36 mo. PFS: 11.7 vs. 10.0 wk.

*BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mo = month; PFS = progression-free survival; (r)PFS = (radiographic) progression-free survival; OS = overall survival.*

### 6.5.5 First-line treatment of metastatic CRPC

#### 6.5.5.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients in the phase III trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [970]. 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 radiographic PFS (rPFS) were the co-primary end-points. 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 end-point was significantly positive (34.7 vs. 30.3 months, HR: 0.81,

95% CI: 0.70-0.93,  $p = 0.0033$ ) [972]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1-2. Sub-set analysis of this trial showed the drug to be equally effective in an elderly population ( $> 75$  years) [977].

#### 6.5.5.2 Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [973]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naïve mCRPC population of 1,717 men and showed a significant improvement in both co-primary end-points, 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  $\geq 50\%$  decrease in PSA was seen in 78% of patients. The most common clinically relevant adverse events were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men  $> 75$  years [978] as well as in those with or without visceral metastases [979]. However, for men with liver metastases, there seems to be no discernible benefit [979, 980].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double blind phase II study (TERRAIN) [981] showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44,  $p < 0.0001$ ) in favour of enzalutamide. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [982].

#### 6.5.5.3 Docetaxel

A significant improvement in median survival of 2-2.9 months has been shown with docetaxel-based chemotherapy compared to mitoxantrone plus prednisone therapy [969, 983]. The standard first-line chemotherapy is docetaxel 75 mg/m<sup>2</sup>, 3-weekly doses combined with prednisone 5 mg twice a day (BID), up to 10 cycles. Prednisone can be omitted if there are contraindications 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 [984].

Age by itself is not a contraindication to docetaxel [985] but attention must be paid to careful monitoring and comorbidities as discussed in Section 5.4 [986]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m<sup>2</sup> every two weeks seems to be well tolerated with less grade 3-4 adverse events and a prolonged time to treatment failure [987].

#### 6.5.5.4 Sipuleucel-T

In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [962]. 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 adverse events grade 1-2 in the sipuleucel-T group, but the same grade 3-4 adverse events in both arms. Sipuleucel-T is not available in Europe (and has had its licence withdrawn).

**Table 6.5.2: Randomised controlled phase III - second-line / third-line trials in mCRPC**

Author	Intervention	Comparison	Selection criteria	Main outcomes
<b>ABIRATERONE</b>				
Fizazi, <i>et al.</i> 2012 [988]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	<b>OS: 15.8 vs. 11.2 mo.</b> HR: 0.74, 95% CI: 0.64-0.86; $p < 0.0001$ ). FU: 20.2 mo. <b>rPFS: no change</b>
de Bono, <i>et al.</i> 2011 [989]				<b>OS: 14.8 vs. 10.9 mo.</b> ( $p < 0.001$ HR: 0.65; 95% CI: 0.54-0.77). FU: 12.8 mo. <b>rPFS: 5.6 vs. 3.6 mo.</b>

<b>Radium-223</b>				
Parker, <i>et al.</i> 2013 [990]	radium-223	placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	<b>OS: 14.9 vs. 11.3 mo.</b> ( $p = 0.002$ , HR: 0.61; 95% CI: 0.46-0.81). All secondary end-points show a benefit over best standard of care.
<b>CABAZITAXEL</b>				
Bahl, <i>et al.</i> 2013 [991]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	<b>OS: 318/378 vs. 346/377 events</b> (OR: 2.11; 95% CI: 1.33-3.33). FU: 25.5 months OS $\geq 2$ yr 27% vs. 16% PFS: not reported.
deBono, <i>et al.</i> 2010 [992]				<b>OS: 15.1 vs. 12.7 mo.</b> ( $p < 0.0001$ , 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)
De Wit, <i>et al.</i> 2019 [954]	Cabazitaxel (25 mg/m <sup>2</sup> Q3W) + prednisone + G-CSF	Abiraterone+ prednisone OR Enzalutamide (ARTA)	Previous docetaxel. Progression $\leq 12$ mo. on prior alternative ARTA (either before or after docetaxel)	<b>Med OS 13.6 vs. 11.0 mo.</b> ( $p = 0.008$ , HR: 0.64, 95% CI: 0.46-0.89). <b>rPFS 8.0 vs. 3.7 mo.</b> ( $p < 0.001$ , HR: 0.54 95% CI: 0.40-0.73). FU: 9.2 mo.
<b>ENZALUTAMIDE</b>				
Scher, <i>et al.</i> 2012 [993]	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. <b>rPFS: 8.3 vs. 2.9 mo.</b> (HR: 0.40; 95% CI: 0.35-0.47 $p < 0.0001$ ).
<b>PARP inhibitor</b>				
Hussain, <i>et al.</i> 2019 [958]	Olaparib	Abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARTA, alterations in Cohort A: <i>BRCA1</i> , <i>BRCA2</i> or <i>ATM</i>	<b>rPFS: 7.39 vs. 3.55 mo.</b> ( $p < 0.0001$ ; HR: 0.34; 95% CI: 0.25-0.47). ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18-379.18).

\*Only studies reporting survival outcomes as primary end-points have been included.

ARTA = androgen receptor targeting agents; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; HR = hazard ratio; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; yr = year.

### 6.5.6 Second-line treatment for mCRPC and sequencing

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.2. High level evidence exists for second-line treatments after first-line treatment with docetaxel and for third-line therapy.

#### 6.5.6.1 Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [992]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m<sup>2</sup>) or mitoxantrone (12 mg/m<sup>2</sup>) plus prednisone (10 mg/day). Overall survival was the primary end-point, 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 adverse events 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 [994]. 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<sup>2</sup> cabazitaxel was not inferior to 25 mg/m<sup>2</sup>, but less toxic. Therefore, the lower dose should be preferred [995, 996]. 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 [997].

#### 6.5.6.2 *Abiraterone acetate after prior docetaxel*

Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [989] and confirmed by the final analysis [988]. A total of 1,195 patients with mCRPC were randomised 2:1 to abiraterone acetate plus prednisone 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 end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone 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 abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3-4 adverse events did not differ significantly between arms, but mineralocorticoid-related side-effects were more frequent in the abiraterone group, mainly grade 1-2 (fluid retention, oedema and hypokalaemia).

#### 6.5.6.3 *Enzalutamide after docetaxel*

The planned interim analysis of the AFFIRM study was published in 2012 [993]. 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 end-point 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 [982]. 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 adverse events in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

#### 6.5.6.4 *Radium-223*

The only bone-specific drug that is associated with a survival benefit is the  $\alpha$ -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 standard of care. The primary end-point 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 [990]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, it did not differ significantly from that in the placebo arm [990]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [998]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent [999]. In particular, the use of radium-223 in combination with abiraterone acetate plus prednisolone showed significant safety risks related to fractures and more deaths. This was particularly striking in patients without the concurrent use of anti-resorptive agents [1000].

#### 6.5.7 *Treatment after docetaxel and one line of hormonal treatment for mCRPC*

For men progressing quickly on AR targeted therapy (< 12 months) it is now clear that cabazitaxel is the treatment with the best supporting data. The CARD, an open label randomised phase III trial evaluated cabazitaxel after docetaxel and one line of ARTA (either abiraterone plus prednisolone or enzalutamide) [954]. It included patients progressing in less than 12 months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARTA and reduced the risk of death by 36% vs. ARTA. The rPFS with cabazitaxel remained superior regardless of the ARTA sequence and if docetaxel was given before, or after, the first ARTA.

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open for patients who have a > 12 months response to first-line abiraterone or enzalutamide for mCRPC [1001]. 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 [1002, 1003] and there is evidence of cross-resistance between enzalutamide and abiraterone [1004, 1005]. 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 novel hormonal agent and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate [1006].

In a randomised phase II trial which assigned 142 patients to receive olaparib and abiraterone (n = 71) or placebo and abiraterone (n = 71) patients demonstrated clinical benefit regardless of HRD status. Combination treatment is toxic with serious side effects reported in 34% of the olaparib/abiraterone group vs. 18% in the placebo/abiraterone group [1007]. Nevertheless, although not yet available, PARP inhibitors offer an exciting new opportunity to tailor therapy based on the mutation profile contained within a tumour [960].

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARTA in mCRPC with alterations in  $\geq 1$  of any qualifying gene with a role in HRR and progression on an ARTA. Most patients were heavily pre-treated with 1-2 chemotherapies and up to 2 ARTAs [958]. Radiographic PFS by blinded independent central review in the overall cohort favoured olaparib (HR: 0.49, 95% CI: 0.38-0.63). The interim results for OS demonstrated improved non-significant survival among men with *BRCA1/2* or *ATM* mutations (Cohort A) (HR: 0.64, 95% CI: 0.43-0.97), as well as for Cohort A and in men with any HRR alteration (Cohort B) (HR: 0.67, 95% CI: 0.49-0.93). Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 80.6% in Cohort A and 84.6% in Cohort B, crossed over to receive olaparib. When looking specifically at the Cohort B patients, there was no advantage to olaparib in the rPFS by blinded independent central review (HR: 0.88, 95% CI: 0.58-1.36) or in OS (HR: 0.73, 95% CI: 0.45-1.23), however there was a benefit to olaparib for rPFS by investigator assessment (HR: 0.60, 95% CI: > 0.39-0.93).

The most common adverse events 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 adverse event, 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 for mCRPC.

For patients with mismatch repair deficiency, the PD-1 inhibitor pembrolizumab was approved by the FDA irrespective of the tumour origin, which also includes PCa.

## 6.5.8 Prostate-specific membrane antigen (PSMA) therapy

### 6.5.8.1 Background

During the 90s several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 [1008] were developed for the treatment of bone pain secondary to metastasis from PCa. They were effective at palliation; relieving pain and improving QoL, especially in the setting of diffuse bone metastasis. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223 (see Section 6.5.5.4.)

### 6.5.8.2 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) [1009]. Therefore, after identification of the target, usually with diagnostic <sup>68</sup>Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with beta (lutetium-177 or yttrium-90) or  $\alpha$  (actinium-225) emitting isotopes could be used to treat metastatic PCa. At present, all of these agents should be regarded as investigational.

### 6.5.8.3 Lutetium (Lu)-PSMA

The PSMA therapeutic radiopharmaceutical supported with the most robust data is Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [1010]. Nonetheless, most of the literature is based on single-centre experience and RCTs are lacking [1011]. Recently, data from uncontrolled prospective phase II trials have been published [1012, 1013], reporting high response rates, with low toxic effects. More robust data are expected from ongoing trials.

### 6.5.9 *Monitoring of treatment*

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, FBC, renal function, LFTs, ALP), bone scan and CT of chest, abdomen and pelvis [1014]. 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-naïve disease. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARTA have been described [1015]. Prostate-specific antigen alone is not reliable enough [1016] for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA [1017]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [983]. 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 [1014]. 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 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 [1018]. 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. Although, the number of effective treatments is increasing, head-to-head comparisons are still lacking, as are data assessing the sequencing of available agents. Therefore it is not clear how to choose the appropriate “second-line” treatment. In the absence of other data, the inclusion criteria from licensing trials have been used to prioritise treatment sequencing [954].

The ECOG performance status (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  $\geq 2$  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 treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in a summery paper published following the St. Gallen Advanced Prostate Cancer Consensus Conference 2017 [1014, 1019].

### 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 [1019, 1020]. 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 radiotherapy is highly effective, even as a single fraction [1021, 1022]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [1023]. 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 [1024]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1025, 1026]. 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 [1027]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

### 6.5.12 *Preventing skeletal-related events*

#### 6.5.12.1 *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, was available. Six hundred and forty three patients who had CRPC [1028] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg

every three weeks for 15 consecutive months, or placebo. 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.

#### 6.5.12.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor kappa-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,  $p = 0.028$ ) [1021]. 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 [1029].

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 recent *post-hoc* re-evaluation of end-points, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1030].

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) [1030-1032]. 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 [1033]. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in the pivotal trial [1034] (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1029]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab as well as zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy [1035].

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 [1032]. 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 ( $\geq 500$  mg) and vitamin D ( $\geq 400$  IU equivalent) are recommended in all patients, unless in case of hypercalcaemia [1032, 1036, 1037].

#### 6.5.13 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 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. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong

#### 6.5.14 Guidelines for cytotoxic treatment of castrate-resistant disease

Recommendations	Strength rating
Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with $75$ mg/m <sup>2</sup> every 3 weeks.	Strong

Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
Base further treatment decisions of mCRPC on pre-treatment performance status, response to previous treatment, symptoms, comorbidities, extent of disease and patient preference.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	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 external beam radiotherapy, 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

#### 6.5.16 Guidelines 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.	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+
<b>Localised</b>			<b>Locally advanced</b>

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

#### 6.6.1 General guidelines recommendations for active treatment

Recommendations	Strength rating
Inform patients that no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and prostate cancer-specific survival for clinically localised disease.	Strong
Offer a watchful waiting (WW) policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Inform patients that all active treatments have side effects.	Strong
<b>Surgical treatment</b>	
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, perform an extended LND template for optimal staging.	Strong

Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, multiparametric magnetic resonance imaging).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
<b>Radiotherapeutic treatment</b>	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
<b>Active therapeutic options outside surgery and radiotherapy</b>	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

### 6.6.2 Guidelines recommendations for the various disease stages

Recommendations		Strength rating
<b>Low-risk disease</b>		
<b>Active surveillance (AS)</b>	Offer AS to patients with life expectancy > 10 years and low-risk disease.	Strong
	If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
	Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong
	If required, perform mpMRI before a confirmatory biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS $\geq$ 3 lesion) and systematic biopsy if confirmatory biopsy performed.	Strong
	Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
	Perform digital rectal examination (DRE) every 12 months.	Strong
	Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
	During follow-up, if mpMRI is negative (i.e., PI-RADS $\leq$ 2), and clinical suspicion of PCa progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
Counsel patients about the possibility of needing further treatment in the future.	Strong	
<b>Active treatment</b>	Offer surgery and radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
<b>Pelvic lymph node dissection (PLND)</b>	Do not perform a PLND (estimated risk for pN+ $\leq$ 5%).	Strong
<b>Radiotherapeutic treatment</b>	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP), with a good International Prostatic Symptom Score (IPSS) and a prostate volume < 50 mL.	Strong
	Use intensity-modulated radiation therapy (IMRT) with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks, or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
<b>Other options</b>	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

<b>Intermediate-risk disease</b>		
<b>Active surveillance</b>	Offer AS to highly selected patients (< 10% Gleason pattern 4) accepting the potential increased risk of further metastases.	Weak
<b>Radical Prostatectomy (RP)</b>	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
<b>Extended pelvic lymph node dissection (ePLND)</b>	Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
<b>Radiotherapeutic treatment</b>	Offer LDR brachytherapy to selected patients; patients without a previous TURP, with a good IPSS and a prostate volume < 50 mL.	Strong
	For external-beam radiation therapy (EBRT), use 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 neoadjuvant plus concomitant ADT (4 to 6 months).	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
<b>Other therapeutic options</b>	Only offer whole-gland ablative therapy (such as cryotherapy, HIFU, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak
<b>High-risk localised disease</b>		
<b>Radical prostatectomy</b>	Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong
<b>Extended pelvic lymph node dissection</b>	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.	Strong
<b>Radiotherapeutic treatments</b>	In patients with high-risk localised disease, use ERBT with 76-78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
<b>Therapeutic options outside surgery and radiotherapy</b>	Do not offer either whole gland or focal therapy to high-risk patients.	Strong
	Do not use ADT monotherapy in asymptomatic patients.	Strong
<b>Locally-advanced disease</b>		
<b>Radical prostatectomy</b>	Offer RP to highly selected patients with cT3b-T4 N0 or any cN1 only as part of multi-modal therapy.	Strong
<b>Extended pelvic lymph node dissection</b>	Perform an ePLND in high-risk PCa.	Strong
<b>Radiotherapeutic treatments</b>	In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT.	Strong
	Offer long-term ADT for at least two years.	Weak
<b>Therapeutic options outside surgery and radiotherapy</b>	Do not offer whole gland treatment or focal treatment to high-risk patients.	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, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
	Offer patients with cN1 disease a local treatment (either RP or EBRT) plus long-term ADT.	Weak

<b>Adjuvant treatment after radical prostatectomy</b>		
	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Offer adjuvant EBRT to the surgical field to highly-selected patients.	Strong
	Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional RT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak
<b>Non-curative or palliative treatments in a first-line setting</b>		
<b>Localised disease</b>		
<b>Watchful waiting</b>	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
<b>Locally-advanced disease</b>		
<b>Watchful waiting</b>	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA-DT > 12 months, a PSA < 50 ng/mL and well-differentiated tumour who are unwilling or unable to receive any form of local treatment.	Weak
<b>Persistent PSA after radical prostatectomy</b>		
	Offer a prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease.	Weak
	Treat men with no evidence of metastatic disease with salvage RT and additional hormonal therapy.	Weak

### 6.6.3 Guidelines for metastatic disease, second-line and palliative treatments

<b>Recommendations</b>	<b>Strength rating</b>	
<b>Metastatic disease in a first-line setting</b>		
<b>M1 patients</b>	Offer immediate systemic treatment with 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
	Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
	Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
	Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
	Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored.	Weak
	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 antagonists monotherapy to patients with M1 disease.	Strong
	Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
	Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit for the regimen.	Strong
	Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
	Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high-volume M1 disease (CHAARTED criteria) outside of clinical trials (except for symptom control).	Strong

<b>Biochemical recurrence after treatment with curative intent</b>		
<b>Biochemical recurrence after radical prostatectomy (RP)</b>	Offer PSA monitoring to patients with biochemical recurrence with low-risk features at relapse who may not benefit from intervention.	Weak
	Offer SRT to patients with a PSA rise from the undetectable range. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with biochemical recurrence.	Weak
<b>Biochemical recurrence after RT</b>	Treat highly selected patients with localised PCa and a histologically proven local recurrence with SRP.	Weak
	Salvage RP should only be performed in experienced centres.	Weak
	Only offer salvage high intensity focused ultrasound, salvage cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence within a clinical trial setting or well-designed prospective cohort study.	Strong
<b>Systemic salvage treatment</b>	Do not offer ADT to M0 patients with a PSA-DT > 12 months.	Strong
<b>Life-prolonging treatments of castration-resistant disease</b>		
	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. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong
<b>Cytotoxic treatments of castration-resistant disease</b>		
	Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m <sup>2</sup> every 3 weeks.	Strong
	Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
	Base further treatment decisions of mCRPC on pre-treatment performance status, response to previous treatment, symptoms, comorbidities, extent of disease and patient preference.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
<b>Supportive care of castration-resistant disease</b>		
	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 EBRT, 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
<b>Non-metastatic castrate-resistant disease</b>		
	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.	Strong

## 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.

### 7.1 Follow-up: After local treatment

#### 7.1.1 Definition

Local treatment is defined as RP or RT, either by EBRT or LDR- or HDR-brachytherapy, or any combination of these. 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 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 [1038, 1039]. Tumour or patient characteristics may prompt changing the follow-up schedule.

#### 7.1.3 How to follow-up?

The procedures indicated at follow-up visits vary according to the clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. Prostate specific antigen level and DRE are the only tests that should be performed routinely. 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 must be individualised, which is beyond the scope of these Guidelines. 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 a cornerstone in follow-up after local treatment. Normal PSA values differ after RP and RT, but PSA recurrence almost always precedes clinical recurrence [780, 1040]. No recent consensus exists regarding the best definition of PSA relapse after local treatment. Main aim is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value (see Section 6.3) [782].

##### 7.1.3.2 Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP [1041]. Persistently measurable PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual disease in the prostatic fossa (see chapter on persistent PSA). Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with an ultrasensitive PSA nadir < 0.01 ng/mL have a 4% likelihood of biochemical relapse within 2 years [1042]. Detectable post-operative ultrasensitive PSA does not predict BCR in all cases, although it adds prognostic value. In men with ultrasensitive PSA > 0.05 ng/mL, 67% remained free of biochemical disease at 5 years [1043]. If survival is improved by early additional treatment after RP (before the PSA level reaches > 0.2 ng/mL), lower PSA nadir levels, as well as a lower PSA-DT calculated based on the first detectable PSA level up to 0.2 ng/mL, may help identify suitable candidates [1044]. Post-prostatectomy ultrasensitive 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 [1045].

##### 7.1.3.3 Prostate-specific antigen monitoring after radiotherapy

Following RT, PSA drops more slowly as compared to RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT, although the optimal cut-off value remains controversial [1046]. 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, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [781]. This definition also applies to patients who received HT [781]. After RT, PSA-DT correlates with the site of recurrence; patients with local recurrence have a PSA-DT of 13 months compared to 3 months for those with distant failure [1047].

#### 7.1.3.4 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [1048]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Prostate-specific antigen measurement 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 [1049]. 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 [1050, 1051].

#### 7.1.3.5 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).

##### 7.1.3.5.1 TRUS/MRI-guided biopsy

Biopsy of the prostate bed and urethrovesical anastomosis of the remaining prostate after radiotherapy are only indicated if detection of a local recurrence affects treatment decisions (See Section 6.2.6.3 on imaging).

#### 7.1.4 How long to follow-up?

Most patients who fail treatment for PCa do so within 7 years after local therapy [396]. Patients should be followed up more closely during the initial post-treatment period when risk of failure is highest. Prostate-specific antigen measurement, disease-specific history and DRE (if considered) are recommended at 3, 6 and 12 months post-operatively, every 6 months thereafter until 3 years, and then annually. Whether follow-up should be stopped in case PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question.

#### 7.1.5 Summary of evidence and guidelines for follow-up after treatment with curative intent

Summary of evidence	LE
After radical prostatectomy rising serum PSA level is considered a BCR.	3
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is considered as clinically meaningful BCR.	3
Palpable nodules and increasing serum PSA are signs of local recurrence.	2a

Recommendations	Strength rating
Routinely follow up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	Strong
At recurrence, only perform imaging to detect local recurrence if the outcome will affect treatment planning.	Strong
Only offer bone scans and other imaging modalities to men with biochemical recurrence or symptoms suggestive of progression without signs of biochemical relapse.	Strong

## 7.2 Follow-up: During first line hormonal treatment (androgen sensitive period)

### 7.2.1 Introduction

Follow-up must be individualised as a rising PSA might be associated with rapid symptomatic progression or evolve without progression on imaging or symptoms over time. Follow-up for mCRPC is addressed in treatment Section 6.5.8, as management of mCRPC and follow-up are closely linked.

### 7.2.2 Purpose of follow-up

The main objectives of follow-up in these patients are to ensure treatment compliance, to monitor treatment response and side-effects, and to guide treatment at the time of CRPC.

Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs.

### 7.2.3 Methods of follow-up

#### 7.2.3.1 Clinical follow-up

Clinical follow-up is mandatory on a regular basis, and it cannot be replaced, neither by laboratory tests or by

imaging modalities. Of utmost importance in metastatic situations is to advise patients about early signs of spinal cord compression, check for occult cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk.

#### 7.2.3.1.1 Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive PCa. Treatment response may be assessed using the change in serum PSA level as a surrogate end-point for survival in patients with newly diagnosed metastatic PCa receiving ADT [919], or ADT combined with docetaxel [920]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. Clinical progression has been reported without a rising PSA in up to 25% of patients [1052]. However, due to a lack of follow-up data a recommendation cannot be provided.

Other serum markers may be considered for prognostication [1053-1055] but the effects of their use on patient outcome are, as yet, unknown.

#### 7.2.3.1.2 Creatinine, haemoglobin and liver function monitoring

Estimated glomerular filtration rate monitoring is good clinical practice as an increase may be linked to bilateral ureteral obstruction or bladder retention. Liver function tests may suggest treatment toxicity (especially NSAA), but rarely disease progression. A decline in Hb after 3 months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue [1056]. 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 HT [1057].

#### 7.2.3.1.3 Imaging

Asymptomatic patients with a stable PSA level should not undergo imaging [1058]. New symptomatic bone lesions require a bone scan, as well as a PSA progression suggesting CRPC status if a treatment modification is considered. The PCWG has clarified the definition of bone scan progression as the appearance of at least two new lesions, which was later confirmed [983].

Suspicion of disease progression indicates the need for additional imaging modalities, most often initially a CT-scan but further imaging will be guided by symptoms or possible subsequent treatments. In CRPC imaging must be individualised with the aim of maintaining the patient's QoL.

#### 7.2.3.1.4 Testosterone monitoring

Testosterone monitoring should be considered part of clinical practice in men on LHRH therapy. 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 this goal and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [1041], known as the 'acute on-chronic effect' or 'breakthrough response'.

The timing of measurements is not clearly defined. A 3 to 6-month testosterone level assessment has been suggested to ensure castration is achieved and maintained. If not, switching to another agonist or antagonist or to an orchiectomy, should be considered. In patients with a rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state. Ideally, suboptimal testosterone castrate levels should be confirmed with mass spectrometry or an immunoassay [1059, 1060].

#### 7.2.3.1.5 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 men older than 65 years. Men on enzalutamide or abiraterone acetate are at increased risk of cardiovascular problems and hypertension and regular checks are required [1061]. Monitoring serum levels of vitamin D and calcium is important. It is suggested that routine bone monitoring should be performed every two years during castration [1062], or yearly if there are other risk factors [1063, 1064]. However, there is no evidence that this favourably impacts on bone complications due to ADT. The FRAX score can help identify men at risk of osteoporotic complications but validation of the score in the ADT settings is required [1065, 1066].

Men on ADT should have their transaminase levels checked at least twice a year in view of potential liver toxicity.

Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc.) and should be treated for existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [1056, 1057]. Androgen deprivation therapy may affect mental health and men with ADT are three times more likely to report depression [1067]. Attention for mental health should therefore be part of the follow-up scheme. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

#### 7.2.4 *When to follow-up*

After the initiation of ADT, it is recommended that patients are followed at 3 to 6 month intervals. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

##### 7.2.4.1 *Stage M0 - M1 patients*

In case there is a favourable treatment response, i.e. PSA response (< 4 ng/mL), symptomatic improvement, good psychological coping and good treatment compliance, follow-up visits may be scheduled every 3 to 6 months.

#### 7.2.5 *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 [1068, 1069].

Quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1070]. 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. As a result, the PCWG suggested that all patients with at least two new lesions on the first follow-up bone scan require a confirmatory bone scan at least 6 weeks later while the treatment is continued [983]. This means that a management change for primary therapy resistance cannot occur until after at least 14 weeks of treatment. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. The ability of PET/CT to assess response has been evaluated in a few studies but, until further data are available, PET/CT has no role in this setting. 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 [1071].

In practice, imaging to assess progression leading to treatment change must be limited to a clear progression: RECIST criteria for non-bone lesions; for bone lesions, only bone scan progression (occurrence of two new hot spots, later confirmed) should be considered. The practical impact of mpMRI in assessing bone progression remains unclear.

#### 7.2.6 *Disease progression during androgen deprivation therapy*

The PCWG3 recommendations, which were developed for clinical trial design, may serve as a guide to plan follow-up in men with progression during ADT [983].

Progression of disease whilst undergoing ADT is defined by the development of cancer-related symptoms or a PSA rise. The most recently proposed PCWG3 definitions do not suggest that a treatment change is needed in case of documented progression, however, in order to monitor PSA doubling time as a useful predictor of outcome, it is recommended to follow up men on ADT with a rising PSA at least every 3 months [983].

In case of radiographical progression, a more frequent follow-up scheme can be recommended depending on location, size and complaints of metastases [983].

##### 7.2.6.1 *CRPC patients*

Follow-up care of CRPC patients will be guided by the type of treatment provided. Generally, PSA assessment is included in the follow-up of men treated for non-metastatic CRPC even though clinical progression may occur without PSA progression and regular imaging is advised (bone scan and CT imaging every 6 months, at PSA progression or development of symptoms). In non-metastatic CRPC a PSADT < 3 months was associated with an approximately 9-fold increased risk of metastases (HR: 8.63, 95% CI: 5.07-14.7) [1072, 1073].

Prostate-specific membrane antigen/PET imaging has not been prospectively evaluated in CRPC patients and can therefore not be recommended in a CRPC setting.

Recommendations	Strength rating
Evaluate patients at 3 to 6 months after the initiation of treatment.	Strong
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 patients with stage M1 disease, schedule follow-up every 3 to 6 months. As a minimum requirement, include an initial FRAX-score assessment, disease-specific history, digital-rectal examination (DRE), serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year. Pay attention to symptoms associated with metabolic syndrome as a side effect of androgen deprivation therapy. Phospholipid profiles and glucose levels should be checked and treated if abnormal.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, adapt/individualise follow-up.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration resistant PCa requires a testosterone level < 50 ng/dL (< 1 mL/L).	Strong
Do not offer routine imaging to otherwise stable asymptomatic patients.	Weak

## 8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (8.2) will summarise long-term consequences ( $\geq 12$  months) of therapies for PCa. Based on two systematic reviews, the second (8.3) will make 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 his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of QoL [1074]. 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. Attention to the psychosocial concerns of men with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1075]. 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. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed.

### 8.2 Adverse effects of PCa therapies

#### 8.2.1 Surgery

The absence of standardisation in reporting surgical complications for RP 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 [1076-1079]. The most common post-operative issue 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) [1080]. The second most commonly occurring complication is long-term incontinence [1076-1079] but voiding difficulties may also occur associated with bladder neck contracture (e.g. 1.1% after RALP) [1081].

For those men undergoing minimally invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar [1082] and can occur more rarely with 8 mm and 5 mm trocars [1082]. A key consideration for men is whether long-term consequences of surgery are reduced by using

newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [416, 503-506], and can be compared with contemporaneous reports after RRP [507]. 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 demonstrates 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) [508, 1083]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1083, 1084]. A single centre randomised phase III study comparing RALP and RRP (n = 326) also demonstrates similar functional outcomes with both techniques at 24 months [411].

## 8.2.2 Radiotherapy

### 8.2.2.1 Side-effects of external beam radiotherapy

Analysis of the toxicity outcomes of the Prostate Testing for Cancer and Treatment ( ProtecT) trial [1085] shows that men 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). 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 [1086].

A systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to radiotherapy 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 men in particular [1087].

### 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%) [1088]. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for BPH increases the risk of post-implantation incontinence and urinary morbidity. Prevention of morbidity depends on careful patient selection, and expert assessment of 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 Ramsay *et al.*'s 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 [638]. 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 was 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) [638].

## 8.2.4 Hormonal therapy

A summary of impacts on psychological factors due to the use of ADT such as sexual function, mood, depression, cognitive function and impact on men's partners can be found in two clinical reviews [1089, 1090]. A small RCT evaluated the QoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. ADT patients reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue and irritability during treatment [1091]. 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 [1092]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [1093]. 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 orchiectomised patients. The stage at diagnosis had no effect on health outcomes [1094].

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 [1095]. 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 [1096], preserved libido and erectile function [1097]. Intermittent androgen deprivation has been discussed elsewhere (see Section 6.4.3.2).

#### 8.2.4.1 Sexual function

Cessation of sexual activity is very common in men undergoing ADT, affecting up to 93% of men [1098]. ADT reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1099].

#### 8.2.4.2 Hot flushes

Hot flushes are a common side-effect of ADT (prevalence estimated between 44-80% of men on ADT) [1098]. They appear 3 months after starting ADT, usually persist long-term and have a significant impact on QoL. Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications [1100].

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 [1101]. 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% (IQR -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 [1102], the efficacy of clonidine, veralipride, gabapentine [1103] and acupuncture [1104] need to be compared in prospective RCTs.

#### 8.2.4.3 Non-metastatic bone fractures

Due to increased bone turnover and decreased bone mineral density (BMD) in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% RR with long-term ADT) [1105]. Hip fractures in men are associated with a significant risk of death [1106]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before 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. The WHO FRAX tool (<http://www.shef.ac.uk/FRAX>) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) 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 [1107]. These changes increase the fracture risk [1108].

##### 8.2.4.3.1 Hormonal treatment modalities

Bicalutamide monotherapy may have less impact on BMD [1109, 1110], but is limited by its suboptimal efficacy (see Section 6.1.4.1.1.5.2.3). The intermittent LHRH-agonist modality might be associated with less bone impact [1111].

#### 8.2.4.4 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [1107]. ADT 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 [1112], 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 [1113]:

- 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 [1114].

Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [1115]. 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  $\geq 70$  years of age [1116].

#### 8.2.4.5 Cardiovascular morbidity

Cardiovascular mortality is a common cause of death in PCa patients [910, 1117, 1118]. Several studies showed that ADT, after only 6 months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1119]. The RTOG 92-02 [1120] and 94-08 [1121] 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 a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 [1122]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [1123, 1124]. Meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease in men treated for PCa e.g. the associations between GnRH 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 [1125]. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1126] or presenting with a metabolic syndrome [1127]. It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [1128]. However, the methodology used in these studies does not provide convincing evidence to show a clear superiority of these compounds.

These concerns resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [909]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, improved nutrition and smoking cessation [1129].

#### 8.2.4.6 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure. Anaemia may be a cause of fatigue [1098, 1130]. Anaemia requires an aetiological diagnosis (medullar invasion, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusions are required if severe anaemia is present. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [1131].

#### 8.2.4.7 Neurological side-effects

Castration seems also to be associated with an increased risk of stroke [1132], and is suspect to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1133].

### 8.3 Overall quality of life in men with PCa

Living longer with PCa, does not necessarily equate to living well [1074, 1075]. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa [1134]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety and stress in caregivers [1135]. 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 [1089, 1136]. Direct symptoms from advanced or metastatic cancer, e.g. pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1137, 1138]. Men's QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1139, 1140].

The concept of 'quality of life' is subjective and can mean different things to different men, but there are some generally common features across virtually all patients. Drawing from these common features, specific tools or 'patient-reported outcome measures' (PROMs) have been developed and validated for men with PCa. These questionnaires assess common issues that affect men 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 men with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

**Table 8.3.1: PROMs assessing cancer specific quality of life**

Questionnaire	Domains / items
Functional Assessment of Cancer Therapy-General (FACT-G) [1141]	Physical well-being, Social/family well-being, Emotional well-being, and Functional well-being
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1142]	12 cancer site specific items to assess for prostate related symptoms. Can be combined with FACT-G or reported separately.
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [1143]	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) [1144]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Expanded prostate cancer index composite (EPIC) [1145]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [1146]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1147]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [1148]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [1149]	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 Prostate Testing for Cancer and Treatment ( 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 [1085]. 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 [1079, 1150]. The Prostate Cancer Outcomes Study (PCOS) [1079] studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT. 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. More recently, investigators 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 [1086]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side-effects in contemporary treatments may be slightly less. This is supported by a contemporary 5-year prospective, population-based cohort study where PROs were compared in men with favourable- and unfavourable-risk localised disease [1150]. 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.

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 comparing to pre-treatment values [1151]. 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 [1152]. 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 [1153].

### 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.	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.	Strong
Advise patients treated with brachytherapy 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

#### 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) [1154].

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 [1155]. Surgical interventions including sling and artificial urinary sphincter 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% [1156].

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 [1157]. However, a multicentre 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 [547]. 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 [1158]. A detailed discussion can be found in the EAU Sexual and reproductive health Guidelines [1159].

#### 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 [1160].

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 [1161]. 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 [1162, 1163]. 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) [1130].

In case 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 [1164].

Bisphosphonates increase BMD in the hip and spine by up to 7% in one year. The optimal regimen for zoledronic acid remains unclear: quarterly [1165] or yearly [1166] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1167]. A quarterly regimen could be considered for a BMD  $\leq 2.5$  as a yearly injection is unlikely to provide sufficient protection [1168].

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 [1169]. 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 [1030] without any impact on OS, but with an increase in side-effects. Therefore, this later regimen cannot be recommended.

### 8.3.2.1 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 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
Use the WHO FRAX tool to guide monitoring and treatment of bone mineral density in men on long-term ADT.	Strong

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## 10. CONFLICT OF INTEREST

All members of the EAU-EANM-ESTRO-ESUR-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/>.

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## 11. CITATION INFORMATION

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