

# EAU - EANM - ESTRO - ESUR - ISUP - 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, a geriatrician and a patient representative.

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

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

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

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

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

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

## 1.3 Available publications

A quick reference document (Pocket guidelines) is available, 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 2022 document presents a limited update of the 2021 EAU-EANM-ESTRO-ESUR-ISUP-SIOG 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.

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

- **4.3 Clinically significant prostate cancer**
- 4.5.1.2.4. Risk assessment to determine the need for biopsy
- 4.5.2.1.2 Repeat PSA testing - Table 5.5: Risk data table of clinically significant prostate cancer (csPCa), related to PI-RADS score and PSA-D categories in biopsy-naive men, clinically suspected of having significant disease
- Section 5.2.7.1.4 Towards 'extended' MRI-directed biopsy?

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

Recommendation	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination, repeat the PSA test prior to further investigations.	Weak

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

Summary of evidence	LE
Literature review including multiple biopsy schemes suggests that a 10 to 12-core scheme is optimal in the majority of initial and repeat biopsy patients, dependent on prostate size. These biopsy schemes should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [3].	3
A systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%).	2
Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique (cognitive guidance, US/MR fusion software or direct in-bore guidance) over the other.	2

Recommendations	Strength rating
At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc and 10 to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive.	Strong
Transperineal biopsies are preferred over transrectal biopsies.	Strong
Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak

#### 5.2.8.2.1 Recommended terminology for reporting prostate biopsies

Recommendation	Strength rating
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern.	Strong

#### 5.3.5 Summary of evidence and guidelines for staging of prostate cancer

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

Recommendation	Strength rating
<b>High-risk localised disease/locally advanced disease</b>	
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

- 6.1.4.1.1.3.4. Radiopharmaceutical therapy

#### 6.1.6 General guidelines for the treatment of prostate cancer

Recommendations	Strength rating
<b>Surgical treatment</b>	
Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined into a nomogram).	Weak

<b>Radiotherapeutic treatment</b>	
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or intermediate-risk disease with ISUP grade 2 and ≤ 33% of biopsy cores involved.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10-20 ng/mL.	Weak
Offer LDR or HDR brachytherapy boost combined with IMRT /VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak

- 6.2.1.2.1 ADT monotherapy

### 6.2.1.3 Summary of evidence and guidelines for the treatment of low-risk disease

<b>Summary of evidence</b>	<b>LE</b>
Systematic biopsies have been scheduled in AS protocols, the number and frequency of biopsies varied, there is no approved standard.	NR

<b>Recommendations</b>	<b>Strength rating</b>
<b>Active surveillance (AS)</b>	
<i>Selection of patients</i>	
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed	Weak
<i>Follow-up of patients</i>	
Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
In case of PSA progression or change in DRE or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
<b>Active treatment</b>	
<i>Radiotherapeutic treatment</i>	
Offer low-dose rate brachytherapy to patients with low-risk PCa and good urinary function.	Strong

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

<b>Recommendations</b>	<b>Strength rating</b>
<b>Active surveillance (AS)</b>	
Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA <10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP grade group 3 disease must be excluded from AS protocols.	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
<b>Radiotherapeutic treatment</b>	
Offer low-dose rate brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
Offer low-dose rate brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Weak
Offer high-dose rate brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	Weak

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

Recommendation	Strength rating
<b>Radiotherapeutic treatment</b>	
In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak

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

Recommendation	Strength rating
<b>Radiotherapeutic treatment</b>	
Offer patients with locally advanced disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or $\geq 2$ high-risk factors (cT3–4, Gleason $\geq 8$ or PSA $\geq 40$ ng/mL).	Strong

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

Summary of evidence	LE
After RP there is no specific PSA threshold defining recurrence.	NR

#### 6.4.9 Guidelines for the first-line treatment of metastatic disease

Recommendations	Strength rating
Offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong

#### 6.5.15 Guidelines for systematic treatments of castrate-resistant disease

Recommendation	Strength rating
<b>Novel agents</b>	
Offer $^{177}\text{Lu}$ -PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

## 2. METHODS

### 2.1 Data identification

For the 2022 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the PCa Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between May 1<sup>st</sup> 2020 and April 14<sup>th</sup> 2021. A total of 2,536 unique records were identified, retrieved and screened for relevance resulting in 193 new publications having been included in the 2022 print. A detailed search strategy is available online: <https://uroweb.org/guideline/prostate-cancer/?type=appendices-publications>.

Changes in recommendations were only considered on the basis of high-level evidence (i.e. systematic reviews with meta-analysis, randomised controlled trials [RCTs], and prospective comparative studies) published in the English language. A total of 193 new references were added to the 2022 PCa Guidelines. Additional information can be found in the general Methodology section of this print and online at the EAU website: <https://uroweb.org/guidelines/policies-and-methodological-documents/>.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [4, 5]. 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 [6];
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' [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

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

## **2.2 Review**

All RT sections from the 2021 print were peer-reviewed prior to publication, as were Sections 5.4 (Evaluating life expectancy and health status) and Chapter 8 (Quality of life). Publications ensuing from systematic reviews have all been peer-reviewed.

## **2.3 Future goals**

Results of ongoing and new systematic reviews will be included in the 2022 update of the PCa Guidelines:

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

# **3. EPIDEMIOLOGY AND AETIOLOGY**

## **3.1 Epidemiology**

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020 [8, 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), but rising [12]. Rates in Eastern and Southern Europe were low but have also shown a steady increase [9, 10]. Incidence and disease stage distribution patterns



follow biological-, genetic-, and/or lifestyle factors, but are also influenced by (inter)national organisations' recommendations on screening and diagnosis (see Section 5.1) [13].

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/hereditary prostate cancer

Family history and ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [14, 15]. Only a small subpopulation of men with PCa have true hereditary disease. Hereditary PCa (HPCa) is associated with a six to seven year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways [14, 16].

In a large USA population database, HPCa (in 2.18% of participants) showed a relative risk (RR) of 2.30 for diagnosis of any PCa, 3.93 for early-onset PCa, 2.21 for lethal PCa, and 2.32 for clinically significant PCa (csPCa) [17]. These increased risks of HPCa were higher than for familial PCa ( $\geq 2$  first- or second-degree relatives with PCa on the same side of the pedigree), or familial syndromes such as hereditary breast and ovarian cancer and Lynch syndrome. The probability of high-risk PCa at age 65 was 11.4% (vs. a population risk of 1.4%) in a Swedish population-based study [18].

#### 3.2.1.1 Germline mutations and prostate cancer

Genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for PCa [19-21]. Clinical cohort studies have reported rates of 15% to 17% of germline mutations independent of stage [22, 23]. Giri *et al.*, studied clinical genetic data from men with PCa unselected for metastatic disease undergoing multigene testing across the US [22]. The authors found that 15.6% of men with PCa have pathogenic variants identified in genes tested ([Breast Cancer genes] *BRCA1*, *BRCA2*, *HOXB13*, *MLH1*, *MSH2*, *PMS2*, *MSH6*, *EPCAM*, *ATM*, *CHEK2*, *NBN*, and *TP53*), and 10.9% of men have germline pathogenic variants in DNA repair genes (see Table 5.2). Pathogenic variants were most commonly identified in *BRCA2* (4.5%), *CHEK2* (2.2%), *ATM* (1.8%), and *BRCA1* (1.1%) [22].

Castro *et al.*, found a carrier rate of 16.2% in unselected patients at diagnosis of metastatic castrate-resistant PCa (mCRPC) who were screened for DNA damage repair (DDR) mutations in 107 genes [24].

Nicolosi *et al.*, reported frequency and distribution of positive germline variants in 3,607 unselected PCa patients and found that 620 (17.2%) had a pathogenic germline variant [23]. Among unselected men with metastatic PCa, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes [25].

Targeted genomic analysis of genes associated with an increased risk of PCa could offer options to identify families at high risk [26, 27].

Nyberg *et al.*, presented results of a prospective cohort study of male *BRCA1* and *BRCA2* carriers and their PCa risk confirming *BRCA2* association with aggressive PCa [28]. Castro *et al.*, analysed the outcomes of 2,019 patients with PCa (18 *BRCA1* carriers, 61 *BRCA2* carriers, and 1,940 non-carriers). Prostate cancers with germline *BRCA1/2* mutations were more frequently associated with ISUP  $\geq 4$ , T3/T4 stage, nodal involvement, and metastases at diagnosis than PCa in non-carriers [29]. *BRCA*-susceptibility gene mutation carriers were reported to have worse outcome when compared to non-carriers after local therapy [30].

In a retrospective study of 313 patients who died of PCa and 486 patients with low-risk localised PCa, the combined *BRCA1/2* and *ATM* mutation carrier rate was significantly higher in lethal PCa patients (6.07%) than in localised PCa patients (1.44%) [31].

The Identification of Men With a Genetic Predisposition to Prostate Cancer (IMPACT) study, which evaluated 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 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 [32]. The influence of *BRCA1* mutations on PCa remained unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* non-carriers. Limitations of the IMPACT study include the lack of magnetic resonance imaging (MRI) data and targeted biopsies as it was initiated before that era.

Similarly, Mano *et al.*, reported on an Israeli cohort in which men with *BRCA1* and *BRCA2* mutations had a significantly higher incidence of malignant disease. In contrast to findings of the IMPACT study, the rate of PCa among *BRCA1* carriers was more than twice as high (8.6% vs. 3.8%) compared to the general population [33].



### 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 [34]. 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 [35]. However, currently there are no known effective preventative dietary or pharmacological interventions.

#### 3.2.2.1 Metabolic syndrome

The single components of metabolic syndrome (MetS), hypertension ( $p = 0.035$ ) and waist circumference  $> 102$  cm ( $p = 0.007$ ), have been associated with a significantly greater risk of PCa, but in contrast, having  $\geq 3$  components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60–0.82) [36, 37].

##### 3.2.2.1.1 Diabetes/metformin

The association between metformin use and PCa is controversial. At population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never-users (adjusted OR: 0.84, 95% CI: 0.74–0.96) [38]. 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,  $p = 0.50$ ) [39]. The ongoing Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial assesses metformin use in advanced PCa (Arm K) [40].

##### 3.2.2.1.2 Cholesterol/statins

A meta-analysis of 14 large prospective studies did not show any association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of 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 [37].

##### 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,  $p = 0.042$ ) [41]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [42].

#### 3.2.2.2 Dietary factors

The association between a wide variety of dietary factors and PCa have been studied, but there is still a paucity of quality evidence (Table 3.1).

**Table 3.1: Main 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 [43]. A meta-analysis shows a dose-response relationship with PCa [44].
<b>Coffee</b>	Coffee consumption may be associated with a reduced risk of PCa; with a pooled RR of 0.91 for the highest category of coffee consumption [45].
<b>Dairy</b>	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [46].
<b>Fat</b>	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [47]. A relation between intake of fried foods and risk of PCa may exist [48].
<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 [49, 50]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [51].
<b>Meat</b>	A meta-analysis did not show an association between red meat or processed meat consumption and PCa [52].
<b>Soy (phytoestrogens [isoflavones/ coumestans])</b>	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [53]. Total soy food intake has been associated with reduced risk of PCa, but also with increased risk of advanced disease [54, 55].

<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 [55, 56].
<b>Vitamin E/Selenium</b>	An inverse association of low blood levels of selenium and vitamin E, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [57, 58]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [59].

### 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 PCas, although these do not seem to impact PCa mortality [60-63]. 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 [64]. 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 [65].

#### 3.2.2.4 *Other potential risk factors*

A significantly higher rate of ISUP  $\geq 2$  PCa (hazard ratio [HR]: 4.04) was found in men with inflammatory bowel disease when compared with the general population [66]. Balding was associated with a higher risk of PCa death [67]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31, 95% CI: 1.14–1.52) [68]. 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 [69]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24, 95% CI: 1.18–1.31) and with aggressive tumour features and worse prognosis, even after cessation [70, 71]. 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 [72]. Men positive for human papillomavirus-16 may be at increased risk [73]. Plasma concentration of the estrogenic insecticide chlordecone is associated with an increase in the risk of PCa (OR: 1.77 for highest tertile of values above the limit of detection) [74].

A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [75] and self-reported acne [76]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa and mortality [77, 78].

Ultraviolet radiation exposure decreased the risk of PCa (HR: 0.91, 95% CI: 0.88–0.95) [79]. A review found a small but protective association of circumcision status with PCa [80]. Higher ejaculation frequency ( $\geq 21$  times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [81].

To date the current body of evidence will not support a causal relationship between specific (dietary and otherwise) factors and the development of PCa. Consequently, no effective preventative strategies can be suggested.

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

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

## 4. CLASSIFICATION AND STAGING SYSTEMS

### 4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for 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) [82] and the EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, are used (Table 4.2) [83]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT). Magnetic resonance imaging and targeted biopsy may cause a stage shift in risk classification systems [84].

**Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [82]**

<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 digital rectal examination (DRE) findings; local 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 T1 and the T2 substages. Pathological stages pT1a/b/c do not exist and histopathologically confirmed organ-confined PCas after RP are pathological stage pT2. The current Union for International Cancer Control (UICC) no longer recognises pT2 substages [82].

Of note: the EANM recently proposed a 'miTNM' (molecular imaging TNM) classification, taking into account prostate-specific membrane antigen positron emission tomography-computed tomography (PSMA PET/CT) findings [85]. The prognosis of the miT, miN and miM substages is likely to be better to their T, N and M counterparts due to the 'Will Rogers phenomenon'; the extent of this prognosis shift remains to be assessed as well as its practical interest and impact [86].

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

In the original Gleason grading system, 5 Gleason grades (ranging from 1–5) based on histological tumour architecture were distinguished, but in the 2005 and subsequent 2014 International Society of Urological Pathology (ISUP) Gleason score (GS) modifications Gleason grades 1 and 2 were eliminated [87, 88]. The 2005 ISUP modified 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. The grade of intraductal carcinoma should also be incorporated in the GS [89]. 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 limits the number of PCa grades, ranging them from 1 to 5 (see Table 4.2) [88, 90].

Further sub-stratification of the intermediate-risk group can be made and specifically the National Cancer Center Network (NCCN) Guidelines subdivide intermediate-risk disease into favourable intermediate-risk and unfavourable intermediate-risk, with unfavourable features including ISUP grade 3, and/or  $\geq 50\%$  positive biopsy cores and/or at least two intermediate-risk factors [91].

**Table 4.2: 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.

**Table 4.3: International Society of Urological Pathology 2014 grade (group) system**

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

## 4.3 Clinically significant prostate cancer

The descriptor ‘clinically significant’ is widely used to differentiate PCa that may cause morbidity or death from types of PCa that do not. This distinction is particularly important as insignificant PCa that does not cause harm is so common [11]. Unless this distinction is made, such cancers are at high risk of being overtreated, with the treatment itself risking harmful side effects to patients. The over-treatment of insignificant PCas has been criticised as a major drawback of PSA testing [92].

However, defining what is clinically significant and what is insignificant PCa is difficult. In large studies of RP specimens which showed only ISUP grade 1 disease, extraprostatic extension (EPE) was extremely rare (0.28% of 2,502 cases) and seminal vesicle (SV) invasion or lymph node (LN) metastasis did not occur at all [93, 94]. International Society for Urological Pathology grade 1 disease itself can therefore be considered clinically insignificant. Whilst ISUP grade 1 bears the hallmarks of cancer histologically, ISUP grade 1 itself does not behave in a clinically malignant fashion.

However, ISUP grade 1 is first diagnosed at biopsy and guides management decisions, not after the prostate has been removed. The current standard practice of MRI-targeted and template biopsies has reduced diagnostic inaccuracy [95], however sampling error may still occur such that higher grade cancer could be missed. This should be especially considered if the prior MRI showed a suspicious lesion, but only ISUP grade 1 was found at biopsy.

Another complexity in defining insignificant cancer is that ISUP grade 1 may progress to higher grades over time, becoming clinically significant at a later biopsy [96].

Therefore, although ISUP grade 1 itself can be described as clinically insignificant, it is important to take into account other factors, including imaging prior to biopsy and adequate sampling core number. When combined with low-risk clinical factors (see Table 4.2), ISUP grade 1 represents low-risk PCa, with its recommendation of preferred management being active surveillance (AS) or watchful waiting (WW) (see Sections 6.1.1.2 & 6.1.1.3). It should be noted, therefore, that defining ISUP grade 1 as insignificant cancer does not mean it should be ignored, but safely observed.

Epidemiological and autopsy data also suggest that a proportion of ISUP grade 2 PCas would remain undetectable during a man's life [97] and therefore may be overtreated. In current guidelines deferred treatment may be offered to select patients with intermediate-risk PCa [91], but evidence is lacking for appropriate selection criteria [98].

Recent papers have defined clinically significant cancer differently, commonly using ISUP grade 2 and above and even ISUP grade 3 and above, demonstrating the lack of consensus and evolution of its definition [99-102]. Some papers even provide more than one definition within a single study [103, 104]. Although there is insufficient evidence to define clearly what clinically significant (cs)PCa is, it is imperative that authors define and state it in their own studies, including exactly how the disease was diagnosed.

#### 4.4 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 [105, 106]. However, as yet, the best stratification and optimal treatment remain controversial.

#### 4.5 Guidelines for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
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 to identify individuals '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 [107]. 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 [108].

Initial widespread aggressive screening in USA was associated with a decrease in mortality [109]. In 2012 the US Preventive Services Task Force (USPSTF) released a recommendation against PSA-based screening [92], which was adopted in the 2013 AUA Guidelines [110] and resulted in a reduction in the use of PSA for early detection [111]. This 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) [13, 112-115]. While PCa mortality had decreased for two decades since the introduction of PSA testing [116], the incidence of advanced disease and, possibly, cancer-related mortality slowly increased from 2008 and accelerated in 2012 [117]. Moreover, additional evidence suggests a long-term benefit of PSA population screening in terms of reduction of cancer-specific mortality [118, 119]. However, the temporal relationship between PSA testing and decreased mortality, as well as a rising mortality following immediately after the USPSTF and AUA Guidelines recommendation against PSA testing questions the direct causative link between both points.

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 [120], from a previous grade ‘D’ [120-122]. They highlighted the fact that the decision to be screened should be an individual one. 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 early diagnosis to selected men 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 [123].

A Cochrane review published in 2013 [124], which has since been updated [125], 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 included studies applied a range of different screening measures and testing intervals in patients who had undergone prior PSA testing, to various degrees. None included the use of risk calculators, MRI prior to biopsy (vs. a single PSA threshold) or AS (as an alternative to RP) which no longer reflects current standard practice.

The diagnostic tool (i.e. biopsy procedure) was not associated with increased mortality within 120 days after biopsy in screened men as compared to controls in the two largest population-based screening populations (ERSPC and PLCO), in contrast to a 120-day mortality rate of 1.3% in screened vs. 0.3% in controls, respectively, in a Canadian population-based screening study [126]. 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. Population level screening has never been shown to be detrimental [127-129]. 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 [130].

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) [131]. 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 [131, 132]. Long-term follow-up of the PLCO (Prostate, Lung, Colon, Ovarian cancer screening trial) showed no survival benefit for screening at a median follow-up of 16.7 years but a significant 17% increase in Gleason score 2–6 cancers and 11% decrease in Gleason score 8–10 cancers [133].

**Table 5.1: Follow-up data from the ERSPC study [131]**

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

Most screening trials include PSA and prostate biopsies to screen for PCa. Data on screening trials incorporating MRI are emerging. The role of MRI in PSA screening was studied in two RCTs. The STHLM3 trial randomised men with a PSA > 3 ng/mL between standard biopsies (10–12 cores) or MRI and standard plus targeted biopsies in the presence of a suspicious MRI. The percentage of men that underwent prostate



biopsies in the standard group was double that of the MRI group. In this non-inferiority trial, the intention-to-treat (ITT) analysis found 18% and 21% clinically significant (ISUP > 1) disease and 12% and 4% insignificant disease in the standard and the MRI group, respectively [134]. The second trial, the IP1-PROSTAGRAPH study (PSA > 3 ng/mL; MRI Prostate Imaging – Reporting and Data System (PI-RADS) > 2), showed highest detection of csPCa for MRI compared to transrectal ultrasound-guided prostate (TRUS) biopsy [135].

The integration of MRI in the biopsy protocol may reduce the number of men that undergo biopsies while detecting more clinically significant and less clinically insignificant PCa [134, 135].

Currently there is insufficient evidence to support systematic screening; but there is an increased interest in early individualised detection.

### 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 [15, 136].

#### 5.1.2.1 *Risk factors*

Men at elevated risk of having PCa are those > 50 years [137] or at age > 45 years with a family history of PCa (either paternal or maternal) [138] or of African descent [139, 140]. Men of African descent are more likely to be diagnosed with more advanced disease [141] and upgrade was more frequent after prostatectomy as compared to Caucasian men (49% vs. 26%) [142].

Germline mutations are associated with an increased risk of the development of aggressive PCa, i.e., *BRCA2* [143, 144]. Prostate-specific antigen screening in male *BRCA1* and 2 carriers detected more significant cancers at a younger age compared to non-mutation carriers [32, 33].

Men with a baseline PSA < 1 ng/mL at 40 years and < 2 ng/mL at 60 years are at decreased risk of PCa metastasis or death from PCa several decades later [145, 146].

#### 5.1.2.2 *Initial risk assessment by PSA and DRE*

Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [147]. 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 [148].

Prostate-specific antigen measurement and DRE need to be repeated [130], but the optimal intervals for PSA testing and DRE follow-up are unknown as they varied between several prospective trials. 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 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 [149]. 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 ng/mL were found to have a concentration above the biopsy threshold of 3 ng/mL at 4-year follow-up; the cancer detection rate by 8 years was close to 1% [150]. The long-term survival and QoL benefits of extended PSA re-testing (every 8 years) remain to be proven at a population level.

#### 5.1.2.3 *Risk assessment, co-morbidity and life-expectancy*

Data from the Goteborg arm of the ERSPC trial suggest that the age at which early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a 15-year life expectancy are unlikely to benefit, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy; co-morbidity is at least as important as age. A detailed review can be found in Section 5.4 'Estimating life expectancy and health status' and in the SIOG Guidelines [151].

#### 5.1.2.4 *Risk assessment to determine the need for biopsy*

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

Risk calculators, combining clinical data (age, DRE findings, PSA level, etc.) may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available including (among others):

- 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 [152];
- the PCPT cohort: PCPTRC 2.0 <http://myprostatecancerrisk.com/>;
- a local Canadian cohort: <https://sunnybrook.ca/content/?page=asure-calc> (among others).

Prostate MRI stratifies suspected PCa in lower- and higher risk, based on a 1- to 5- risk scale of having csPCa [PI-RADS v2.1 guidelines 2019]. A recent meta-analysis of this risk assessment tool showed (on a patient level) a significant cancer detection rate of 9% (5–13%) for PI-RADS 2 scores, 16% (7–27%) for PI-RADS 3 scores, 59% (39–78%) for PI-RADS 4 scores, and 85% (73–94%) for PI-RADS 5 scores [153]. Men with PI-RADS assessment scores of 3 to 5 are recommended to undergo biopsy [154]. Prostate MRI and related MRI-directed biopsies have shown to be at least as diagnostically effective as systematic biopsies alone in diagnosing significant cancers [155]. However, if the MRI-directed biopsy decision strategy (without performing systematic biopsies) can reduce the number of unnecessary biopsy procedures, this will be at the expense of missing a small percentage of csPCas [156] (see Section 5.2.4.2.4).

PSA-density (PSA-D) is the strongest predictor in risk calculators. Combinations of PSA-D and MRI have been explored [157-162], showing guidance in biopsy-decisions whilst safely avoiding redundant biopsy testing (see Section 5.2.4.2.6.3).

Urine and serum biomarkers as well as tissue-based biomarkers have been proposed for improving detection and risk stratification of PCa patients, potentially avoiding unnecessary biopsies. However, further studies are necessary to validate their efficacy [163]. At present there is too limited data to implement these markers into routine screening programmes (see Section 5.2.3).

### 5.1.3 Genetic testing for inherited prostate cancer

Increasing evidence supports the implementation of genetic counselling and germline testing in early detection and PCa management [164]. Several commercial screening panels are now available to assess main PCa risk genes [165]. However, it remains unclear when germline testing should be considered and how this may impact localised and metastatic disease management. Germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population [166]. It is important to understand the difference between somatic testing, which is performed on the tumour, and germline testing, which is performed on blood or saliva and identifies inherited mutations. Genetic counselling is required prior to and after undergoing germline testing.

Germline mutations can drive the development of aggressive PCa. Therefore, the following men with a personal or family history of PCa or other cancer types arising from DNA repair gene mutations should be considered for germline testing:

- Men with metastatic PCa;
- Men with high-risk PCa and a family member diagnosed with PCa at age < 60 years;
- Men with multiple family members diagnosed with csPCa at age < 60 years or a family member who died from PCa cancer;
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

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

**Table 5.2: Germline mutations in DNA repair genes associated with increased risk of prostate cancer**

Gene	Location	Prostate Cancer risk	Findings
<i>BRCA2</i>	13q12.3	- 2.5 to 4.6 [167, 168] - PCa at 55 years or under: RR: 8–23 [167, 169]	<ul style="list-style-type: none"> <li>• up to 12 % of men with metastatic PCa harbour germline mutations in 16 genes (including <i>BRCA2</i> [5.3%]) [25]</li> <li>• 2% of men with early-onset PCa harbour germline mutations in the <i>BRCA2</i> gene [167]</li> <li>• <i>BRCA2</i> germline alteration is an independent predictor of metastases and worse PCa-specific survival [29, 170]</li> </ul>



<i>ATM</i>	11q22.3	RR: 6.3 for metastatic prostate [25]	<ul style="list-style-type: none"> <li>higher rates of lethal PCa among mutation carriers [31]</li> <li>up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including <i>ATM</i> [1.6%]) [25]</li> </ul>
<i>CHEK2</i>	22q12.1	OR 3.3 [171, 172]	<ul style="list-style-type: none"> <li>up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including <i>CHEK2</i> [1.9%]) [25]</li> </ul>
<i>BRCA1</i>	17q21	RR: 1.8–3.8 at 65 years or under [173, 173]	<ul style="list-style-type: none"> <li>higher rates of lethal PCa among mutation carriers [31]</li> <li>up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including <i>BRCA1</i> [0.9%]) [25]</li> </ul>
<i>HOXB13</i>	17q21.2	OR 3.4–7.9 [26, 175]	<ul style="list-style-type: none"> <li>significantly higher PSA at diagnosis, higher Gleason score and higher incidence of positive surgical margins in the RP specimen than non-carriers [176]</li> </ul>
<i>MMR genes</i> <i>MLH1</i> <i>MSH2</i> <i>MSH6</i> <i>PMS2</i>	3p21.3 2p21 2p16 7p22.2	RR: 3.7 [177]	<ul style="list-style-type: none"> <li>mutations in <i>MMR</i> genes are responsible for Lynch syndrome [146]</li> <li><i>MSH2</i> mutation carriers are more likely to develop PCa than other <i>MMR</i> gene mutation carriers [178]</li> </ul>

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

#### 5.1.4 Guidelines for germline testing\*

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

\*Genetic counseling is required prior to germline testing.

#### 5.1.5 Guidelines for screening and early detection

Recommendations	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: <ul style="list-style-type: none"> <li>men from 50 years of age;</li> <li>men from 45 years of age and a family history of PCa;</li> <li>men of African descent from 45 years of age;</li> <li>men carrying <i>BRCA2</i> mutations from 40 years of age.</li> </ul>	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.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

## 5.2 Clinical diagnosis

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

### 5.2.1 Digital rectal examination

In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [179]. A suspect DRE in patients with a PSA level  $\leq 2$  ng/mL has a positive predictive value (PPV) of 5–30% [180]. In the ERSPC trial, an abnormal DRE in conjunction with an elevated PSA more than doubled the risk of a positive biopsy (48.6% vs. 22.4%) [181]. An abnormal DRE is associated with an increased risk of a higher ISUP grade, predicts csPCa in men under AS [182] and is an indication for MRI and biopsy [181, 183]. cT staging is dependent on DRE and a strong predictor of advanced PCa (OR: 11.12 for cT3 and OR: 5.28 for cT4) [184].

### 5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [185]. Prostate-specific antigen is organ- but not cancer specific; therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than either DRE or TRUS [186].

There are no agreed standards defined for measuring PSA [187]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [188]. Table 5.3 demonstrates the occurrence of ISUP  $\geq$  grade 2 PCa in systematic biopsies at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but csPCa. The use of nomograms and biomarkers may help in predicting indolent PCa [134, 189, 190]. In case of an elevated PSA (up to 10 ng/mL), a repeated test should be considered to confirm the increase before going to the next step.

#### 5.2.2.1 Repeat PSA testing

A repeat PSA test before prostate biopsies in men with an initial PSA 3–10 ng/mL reduced the indication for biopsies in 16.8% of men while missing 5.4% ISUP grade  $> 1$  in the STHLM3 trial [191]. Similarly, in the Prostate Testing for Cancer and Treatment ( ProtecT) trial men with a more than 20% lower repeat-PSA analysis within 7 weeks had a lower risk of PCa (OR: 0.43, 95% CI: 0.35–0.52) as well as a lower risk of ISUP grade  $\geq 2$  (OR: 0.29, 95% CI: 0.19–0.44) [192]. A study with a PSA interval of 4 weeks showed similar findings of a reduced risk of PCa and ISUP grade  $> 1$  [193]. These observations indicate that an early repeat-PSA prior to the decision of prostate biopsies has prognostic information.

**Table 5.3: Risk of PCa identified by systemic PCa biopsy in relation to low PSA values [160]**

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

#### 5.2.2.2 PSA density

Prostate-specific antigen density is the level of serum PSA divided by the prostate volume. The higher the PSA-D, the more likely it is that the PCa is clinically significant; in particular in smaller prostates when a PSA-D cut-off of 0.15 ng/mL/cc was applied [194] (see Section 5.2.4.2.6.3). Several studies found a PSA-D over 0.1–0.15 ng/mL/cc predictive of cancer [195, 196]. Patients with a PSA-D below 0.09 ng/mL/cc were found unlikely (4%) to be diagnosed with csPCa [197]. A systematic review showed heterogeneity among studies using PSA-D to select men with PI-RADS 3 category on MRI reading for biopsies but suggest a cut-off of 0.15 ng/mL/cc [195]. Others found its added value to biparametric (bp) MRI-guided biopsies unclear with an area under the curve (AUC) of 0.87–0.95 for the direction of csPCa based on bpMRI and 0.91–0.95 for the combined test of bpMRI and PSA-D [198].

#### 5.2.2.3 PSA velocity and doubling time

Various PSA kinetics definitions have been proposed with different methods of calculation (log transformed or not) and eligible PSAs:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [199];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [200].

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

Prostate-specific antigen-DT is calculated assuming an exponential rise in serum PSA. The formula takes into account the natural logarithm of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA over time [201]. However, many different PSA-DT calculations have been assessed according to the mathematical formula used and to the included PSA values (number, time period, intervals) [202]. For example, the 'MSKCC' method calculates a regression slope integrating all PSA values. Other methods transform PSA before calculating the slope and do not include all PSA values (different time frames and minimal intervals) [203]. Thus, O'Brien and colleagues identified more than 20 different definitions of PSAV and PSA-DT and demonstrated that obtained values could vary widely between definitions [203].

However, some rules can be considered for PSA-DT calculation:

- At least 3 PSA measurements are required [201];
- A minimum time period between measurements (4 weeks) is preferable due to potential statistical 'noise' when PSA values are obtained too close together (this statement can be reconsidered in case of very active disease);
- All PSA values should be  $\geq 0.20$  ng/mL and follow a global rising trend;
- All included PSA values should be obtained within the past 12 months at most, to reflect the current disease activity;
- PSA-DT is often mentioned in months, or in weeks in very active disease.

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 [201]. These measurements do not provide additional information compared with PSA alone [203-206]. Prostate-specific antigen-DT has been linked with metastasis-free- and OS in non-metastatic CRPC (nmCRPC) and identifies patients with high-risk nmCRPC who could benefit from intensified therapy (PSA-DT threshold  $< 10$  months) [207].

#### 5.2.2.4 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) [208]. 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 [209]. A systematic review including 14 studies found a pooled sensitivity of 70% in men with a PSA of 4–10 ng/mL [210]. Free/total PSA is of no clinical use if the total serum PSA is  $> 10$  ng/mL or during follow-up of known PCa. The clinical value of f/t PSA is limited in light of the new diagnostic pathways incorporating MRI (see Section 5.2.4.2).

### 5.2.3 Biomarkers

#### 5.2.3.1 Blood based biomarkers: PHI/4K score/IsoPSA

Several assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the U.S. Food and Drug Administration (FDA) approved Prostate Health Index (PHI) test (combining free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2] in addition to age, DRE and prior biopsy status). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multi-centre studies demonstrated that both the PHI and 4K score test out-performed f/t PSA PCa detection, with an improved prediction of csPCa in men with a PSA between 2–10 ng/mL [211-214]. In a head-to-head comparison both tests performed equally [215].

In contrast to the 4K score and PHI, which focus on the concentration of PSA isoforms, IsoPSA utilises a novel technology which focuses on the structure of PSA [216]. Using an aqueous two-phase solution, it partitions the isoforms of PSA and assesses for structural changes in PSA. In a multi-centre prospective validation in 271 men the assay AUC was 0.784 for high-grade vs. low-grade cancer/benign histology, which was superior to the AUCs of total PSA and percent free PSA [217]. In men with a negative mpMRI, PSA-D, 4K score and family history predicted the risk of csPCa on biopsy and using a nomogram reduced the number of negative biopsies and indolent cancers by 47% and 15%, respectively, while missing 10% of csPCas [218].

The Stockholm3 test is a prediction model that is based on several clinical variables (age, first-degree family history of PCa, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free PSA to total PSA, human kallikrein 2, macrophage inhibitory cytokine-1, and *microseminoprotein- $\beta$*  [MSMB]), and a polygenic risk score for predicting the risk of PCa with ISUP  $\geq 2$ , and was shown to reduce the percent of clinically insignificant cancers when used on combination of MRI in a PSA screening population [134].

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

Prostate cancer gene 3 (*PCA3*) is an overexpressed long non-coding RNA (lncRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. 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 [219-222]. *PCA3* score increases with PCa volume, but there are conflicting data about whether it independently predicts the ISUP grade [223]. 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 [224]. 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 [225].

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 [226]. A multi-centre trial evaluated SelectMDX in men with a MRI PI-RADS score < 4 or PI-RADS score < 3, and the percentage of missed csPCas was 6.5% and 3.2%, respectively, whereas 45.8% and 40% of biopsies were avoided [227]. Hendriks *et al.*, found more biopsies were avoided and more high-grade PCas detected in a MRI-based biopsy strategy compared to a SelectMDX strategy. When both tests were combined, more GG > 1 lesions were found, but the number of negative or low-grade cancer biopsies more than doubled [190]. Combining SelectMDX and MRI in men with a PSA between 3–10 ng/mL had a negative predictive value (NPV) of 93% [228]

*TMPRSS2-ERG* fusion, a fusion of the trans-membrane protease serine 2 (*TMPRSS2*) and the *ERG* gene can be detected in 50% of PCas [229]. When detection of *TMPRSS2-ERG* in urine was added to *PCA3* expression and serum PSA (Mi(chigan)Prostate Score [MiPS]), cancer prediction improved [230]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [231, 232]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care (SOC). However, currently, both the MiPS-score and ExoDx assay are considered investigational.

In 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 [233]. 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 with an AUC of 0.82 and 0.81, respectively [234]. 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 [235]. 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 [236]. However, upfront MRI is also likely to affect the utility of above-mentioned biomarkers (see Section 5.2.4).

### 5.2.3.3 Biomarkers to select men for a repeat biopsy

In men with an elevated risk of PCa with a prior negative biopsy, 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 [224]. The ConfirmMDX test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. In case PCa is missed at biopsy, demonstration of epigenetic changes in the benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes (Methylated *APC*, *RASSF1* and *GSTP1*) in benign prostatic tissue. A multi-centre 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 [237]. Given the limited available data and the fact that the role of MRI in tumour detection was not accounted for, no recommendation can be made regarding the routine application of ConfirmMDX, in particular in the light of current use of MRI before biopsy.

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

Recommendations	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak

In asymptomatic men with a PSA level between 2–10 ng/mL and a normal DRE, use one of the following tools for biopsy indication:	Strong
<ul style="list-style-type: none"> <li>• risk-calculator;</li> <li>• Magnetic resonance imaging of the prostate</li> </ul>	
<ul style="list-style-type: none"> <li>• an additional serum, urine or tissue-based biomarker test.</li> </ul>	Weak

## 5.2.4 **Imaging**

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

Standard TRUS is not reliable at detecting PCa [238] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [100]. Prostate HistoScanning™ provided inconsistent results across studies [239]. New sonographic modalities such as micro-Doppler, sonoelastography contrast-enhanced US or high-resolution micro-US provided promising preliminary findings, either alone, or combined into the so-called ‘multiparametric US’. However, these techniques still have limited clinical applicability due to lack of standardisation, lack of large-scale evaluation of inter-reader variability and unclear results in transition zones [240–242].

### 5.2.4.2 *Magnetic resonance imaging*

#### 5.2.4.2.1 Magnetic resonance imaging performance in detecting PCa

Correlation with RP specimens shows that MRI has good sensitivity for the detection and localisation of ISUP grade  $\geq 2$  cancers, especially when their diameter is larger than 10 mm [243–245]. This good sensitivity was further confirmed in patients who underwent template biopsies. In a Cochrane meta-analysis which compared MRI to template biopsies ( $\geq 20$  cores) in biopsy-naive and repeat-biopsy settings, MRI had a pooled sensitivity of 0.91 (95% CI: 0.83–0.95) and a pooled specificity of 0.37 (95% CI: 0.29–0.46) for ISUP grade  $\geq 2$  cancers [155]. For ISUP grade  $\geq 3$  cancers, MRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87–0.99) and 0.35 (95% CI: 0.26–0.46), respectively. Magnetic resonance imaging 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 [243]. In series using template biopsy findings as the reference standard, MRI 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 [155].

The probability of detecting malignancy by MRI-identified lesions was standardised first by the use of a 5-grade Likert score [246], and then by the PI-RADS score which has been updated several times since its introduction [247, 248]. In a meta-analysis of 17 studies involving men with suspected or biopsy-proven PCa, the average PPVs for ISUP grade  $\geq 2$  cancers of lesions with a PI-RADSV2.1 score of 3, 4 and 5 were 16% (7–27%), 59% (39–78%), and 85% (73–94%), respectively, but with significant heterogeneity among studies [249].

5.2.4.2.2 Targeted biopsy improves the detection of ISUP grade  $\geq 2$  cancer 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 (median number of cores: 2–7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02–1.23) for ISUP grade  $\geq 2$  cancers and 1.20 (95% CI: 1.06–1.36) for ISUP grade  $\geq 3$  cancers, and therefore in favour of MRI-targeted biopsy.

Another meta-analysis of RCTs limited to biopsy-naive patients with a positive MRI found that MRI-targeted biopsy detected significantly more ISUP grade  $\geq 2$  cancers than systematic biopsy (risk difference, -0.11 [95% CI: -0.2 to 0.0];  $p = 0.05$ ), in prospective cohort studies (risk difference, -0.18 [95% CI: -0.24 to -0.11];  $p < 0.00001$ ), and in retrospective cohort studies (risk difference, -0.07 [95% CI: -0.12 to -0.02];  $p = 0.004$ ).

Three prospective multi-centre trials evaluated MRI-targeted biopsy in biopsy-naive patients. In the Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION) trial, 500 biopsy-naive patients were randomised to either MRI-targeted biopsy only or TRUS-guided systematic biopsy only. The detection rate of ISUP grade  $\geq 2$  cancers was significantly higher in men assigned to MRI-targeted biopsy (38%) than in those assigned to systemic biopsy (26%,  $p = 0.005$ , detection ratio 1.46) [99]. In the Assessment of Prostate MRI Before Prostate Biopsies (MRI-FIRST) trial, 251 biopsy-naive patients underwent TRUS-guided systematic biopsy by an operator who was blinded to MRI findings, and MRI-targeted biopsy by another operator. Magnetic resonance Imaging-targeted biopsy 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) [100]. However, MRI-targeted biopsy 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-targeted biopsy was observed in the Cochrane analysis; however, it was not statistically significant (detection ratio 1.11 [0.88–1.40]) [155]. The Met Prostaat MRI Meer Mans (4M) study included 626 biopsy-naive patients; all patients underwent systematic biopsy, and those with a positive MRI (PI-RADSV2 score of 3–5, 51%) underwent additional in-bore MRI-targeted biopsy. 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-targeted biopsy vs. 23% for systematic biopsy) [101]. However, in this study, MRI-targeted biopsy and systematic biopsy detected an equal number of ISUP grade  $\geq 3$  cancers (11% vs. 12%; detection ratio: 0.92).

The Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies (FUTURE) randomised trial compared three techniques of MRI-targeted biopsy in the repeat-biopsy setting [250]. In the subgroup of 152 patients who underwent both MRI-targeted biopsy and systematic biopsy, MRI-targeted biopsy detected significantly more ISUP grade  $\geq 2$  cancers than systematic biopsy (34% vs. 16%;  $p < 0.001$ , detection ratio of 2.1), which is a finding consistent with the Cochrane agreement analysis (detection ratio: 1.44). An ISUP grade  $\geq 2$  cancer would have been missed in only 1.3% (2/152) of patients, had systematic biopsy been omitted [251]. These findings support that MRI-targeted biopsy significantly out-performs systematic biopsy for the detection of ISUP grade  $\geq 2$  in the repeat-biopsy setting. In biopsy-naive patients, the difference appears to be less marked but remains in favour of MRI-targeted biopsy.

#### 5.2.4.2.3 MRI-targeted biopsy without systematic biopsy reduces the detection of ISUP grade 1 PCa as compared to systematic biopsy

In pooled data of 25 head-to-head comparisons between systematic biopsy and MRI-targeted biopsy, the detection ratio for ISUP grade 1 cancers was 0.62 (95% CI: 0.44–0.88) in patients with prior negative biopsy and 0.63 (95% CI: 0.54–0.74) in biopsy-naive patients [155]. In the PRECISION and 4M trials, the detection rate of ISUP grade 1 patients was significantly lower in the MRI-targeted biopsy group as compared to systematic biopsy (9% vs. 22%,  $p < 0.001$ , detection ratio of 0.41 for PRECISION; 14% vs. 25%,  $p < 0.001$ , detection ratio of 0.56 for 4M) [99, 101]. In the MRI-FIRST trial, MRI-targeted biopsy detected significantly fewer patients with clinically insignificant PCa (defined as ISUP grade 1 and maximum cancer core length  $< 6$  mm) than systematic biopsy (5.6% vs. 19.5%,  $p < 0.0001$ , detection ratio of 0.29) [100]. Consequently, MRI-targeted biopsy without systematic biopsy significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy.

#### 5.2.4.2.4 Added value combining systematic biopsy 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 MRI undergo combined systematic and targeted biopsy, and patients with a negative MRI undergo systematic biopsy; 2) the ‘MRI pathway’, in which patients with a positive MRI undergo only MRI-targeted biopsy, and patients with a negative MRI who are not biopsied at all.

Data from the Cochrane meta-analysis and from the MRI-FIRST and 4M trials suggest that the absolute added value of systemic biopsy for detecting ISUP grade  $\geq 2$  cancers is lower than that of MRI-targeted biopsy (see Table 5.4).

**Table 5.4: 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* [155]	MRI-FIRST trial* [100]	4M trial [101]	Cochrane meta-analysis* [155]	MRI-FIRST trial* [100]	4M trial [101]
Biopsy-naïve	Added value of MRI-TBx	6.3% (4.8–8.2)	7.6% (4.6–11.6)	7.0% (ND)	4.7% (3.5–6.3)	6.0% (3.4–9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6–6.9)	5.2% (2.8–8.7)	5.0% (ND)	2.8% (1.7–4.8)	1.2% (0.2–3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7–32.6)	37.5% (31.4–43.8)	30% (ND)	15.5% (12.6–19.5)	21.1% (16.2–26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7–11.8)	-	-	6.3% (5.2–7.7)	-	-
	Added value of systematic biopsy	2.3% (1.2–4.5)	-	-	1.1% (0.5–2.6)	-	-
	Overall prevalence	22.8% (20.0–26.2)	-	-	12.6% (10.5–15.6)	-	-

\*Intervals in parenthesis are 95% CI.

The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.

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

In Table 5.4, the absolute added values refer to the percentage of patients in the entire cohort; if the cancer prevalence is taken into account, the 'relative' percentage of additional detected PCa can be computed. Adding MRI-targeted biopsy to systematic biopsy in biopsy-naive patients increases the number of ISUP grade  $\geq 2$  and grade  $\geq 3$  PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-targeted biopsy increases detection of ISUP grade  $\geq 2$  and grade  $\geq 3$  PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naive patients would miss approximately 16% of all detected ISUP grade  $\geq 2$  PCa and 18% of all 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.

#### 5.2.4.2.5 Avoiding biopsies in the 'MR pathway'

The diagnostic yield and number of biopsy procedures potentially avoided by the 'MR pathway' depends on the Likert/PI-RADS threshold used to define a positive MRI. In pooled studies on biopsy-naive patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of  $\geq 3$  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) [155]. 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 [155]. Of note, the percentages of negative MRI (Likert/PI-RADS score  $\leq 2$ ) in the MRI-FIRST, PRECISION and 4M trials were 21.1%, 28.9% and 49%, respectively [99–101].

#### 5.2.4.2.6 Practical considerations

##### 5.2.4.2.6.1 Prostate magnetic resonance imaging reproducibility

Despite the use of the PI-RADSv2 scoring system [247], MRI inter-reader reproducibility remains moderate at best which currently limits its broad use by non-dedicated radiologists [252]. However, significant improvement in the accuracy of MRI and MRI-targeted biopsy can be observed over time, both in academic and community hospitals, especially after implementation of PI-RADSv2 scoring and multidisciplinary meetings using pathological correlation and feedback [253–256]. An updated version of the PI-RADS score (PI-RADSv2.1) has been recently published to improve reader reproducibility, showing improved diagnostic performance [153] but it has not yet been fully evaluated [248]. It is still too early to predict whether quantitative approaches and computer-aided diagnostic systems will improve the characterisation of lesions seen at MRI [257]. Standardisation of MRI interpretation and quality check of acquisition and of MRI-targeted biopsy technique is required to optimise the 'MRI pathway' in large-volume and small-volume (non-expert) centres [258–260].

##### 5.2.4.2.6.2 Targeted biopsy accuracy and reproducibility

Clinically significant PCa not detected by the 'MRI pathway' can be missed because of MRI failure (invisible cancer or reader's misinterpretation) or because of targeting failure (target missed or under sampled by MRI-targeted biopsy). In two retrospective studies of 211 and 116 patients with a unilateral MRI lesion, targeted biopsy alone detected 73.5–85.5% of all csPCa (ISUP grade  $\geq 2$ ); combining MRI-targeted biopsy 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 [261, 262]. The difference may reflect targeting errors leading to undersampling of the tumour. The accuracy of MRI-targeted biopsy is substantially impacted by the experience of the biopsy operator [252]. Increasing the number of cores taken per target may partially compensate for guiding imprecision. In a retrospective study of 479 patients who underwent MRI-targeted biopsy with 4 cores per target that were sequentially labelled, the first 3 cores detected 95.1% of csPCa [263]. In two other retrospective studies of 330 and 744 patients who underwent MRI-targeted biopsy with up to 5 cores per target, the one-core and 3-core sampling strategies detected 63–75% and 90–93%, respectively, of the ISUP grade  $\geq 2$  PCas detected by the 5-core strategy [264, 265]. 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.

##### 5.2.4.2.6.3 Risk-stratification

###### *Using risk-stratification to avoid biopsy procedures*

Prostate-specific antigen density may help refine the risk of csPCa in patients undergoing MRI as PSA-D and the PI-RADS score are significant independent predictors of csPCa at biopsy [266, 267]. In a meta-analysis of 8 studies, pooled MRI NPV for ISUP grade  $\geq 2$  cancer was 84.4% (95% CI: 81.3–87.2) in the whole cohort, 82.7% (95% CI: 80.5–84.7) in biopsy-naive men and 88.2% (95% CI: 85–91.1) in men with prior negative biopsies. In the subgroup of patients with PSA-D  $< 0.15$  ng/mL, NPV increased to respectively 90.4% (95% CI: 86.8–93.4), 88.7% (95% CI: 83.1–93.3) and 94.1% (95% CI: 90.9–96.6) [268]. In contrast, the risk of csPCa is as high as 27–40% in patients with negative MRI and PSA-D  $> 0.15$ – $0.20$  ng/mL/cc [101, 159, 267, 269–271].

Based on a meta-analysis of > 3,000 biopsy-naïve men, a risk-adapted data table of csPCa was developed, linking PI-RADS score (1-2, 3, and 4-5) to PSA-D categories (< 0.10, 0.10–0.15, 0.15–0.20 and > 0.20 ng/mL) (Table 5.5) [157]. For example, the risk of having ISUP grade  $\geq 2$  cancer in biopsy-naïve men with a PI-RADS 1–2 assessment score and PSA-D below 0.10 is 3–4%, in a below-average-risk population of < 5% [157]. This risk-adapted matrix table based on PSA-D and on MRI risk assessments may guide the decision to perform a biopsy.

These data are applicable for a mean ISUP grade  $\geq 2$  cancer prevalence of 35% (range 28–46%) in biopsy-naïve men, and would need to be adjusted to other populations' prevalence. Awaiting validation of MRI-based multivariate risk-prediction tools, corroboration linking MRI findings to PSA-D values for biopsy decisions is beginning to emerge which may promote their routine use in clinical practice [16, 272]. It must be emphasised, however, that the use of PSA-D remains currently limited due to the lack of standardisation of prostate volume measurement (assessed by DRE or by imaging [TRUS or MRI using various techniques such as ellipsoid formula or planimetry]). The impact of this lack of standardisation on the volume estimation remains under-evaluated.

**Table 5.5: Risk data table of clinically significant prostate cancer, related to PI-RADS score and PSA-D categories in biopsy-naïve men, clinically suspected of having significant disease [157]\***

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

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

# Thompson IM *et al.* N Engl J Med. 2004 May 27;350(22):2239-46. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng/ml.

## 2019 EAU guidelines: csPCa 9% (95%CI: 6–14%).

Table adapted from: Schoots, IG and Padhani AR. *BJU Int* 2021 127(2):175. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation, with permission from Wiley.



Combining MRI findings with the *PCA3* score may also improve risk stratification [273]. Several groups have developed comprehensive risk calculators which combine MRI findings with simple clinical data as a tool to predict subsequent biopsy results [274]. At external validation, they tended to outperform risk calculators not incorporating MRI findings (ERSPC and Prostate Cancer Prevention Trial) with good discriminative power (as measured by the AUC). However, they also tended to be miscalibrated with under- or over-prediction of the risk of ISUP grade  $\geq 2$  cancer [275, 276]. In one study that externally assessed four risk calculators combining MRI findings and clinical data, only two demonstrated a distinct net benefit when a risk of false-negative prediction of 15% was accepted. The others were harmful for this risk level, as compared to the ‘biopsy all’ strategy [275]. This illustrates the prevalence-dependence of risk models. Recalibrations taking into account the local prevalence are possible, but this approach is difficult in routine clinical practice as the local prevalence is difficult to estimate and may change over time.

#### *Using risk-stratification to avoid MRI and biopsy procedures*

A retrospective analysis including 200 men from a prospective database of patients who underwent MRI and combined systematic and targeted biopsy showed that upfront use of the Rotterdam Prostate Cancer Risk Calculator would have avoided MRI and biopsy in 73 men (37%). Of these 73 men, 10 had ISUP grade 1 cancer and 4 had ISUP grade  $\geq 2$  cancer [277]. A prospective multi-centre study evaluated several diagnostic pathways in 545 biopsy-naive men who underwent MRI and systematic and targeted biopsy. Using a PHI threshold of  $\geq 30$  to perform MRI and biopsy would have avoided MRI and biopsy in 25% of men at the cost of missing 8% of the ISUP grade  $\geq 2$  cancers [278]. Another prospective multi-centre trial including 532 men (with or without history of prostate biopsy) showed that using a threshold of  $\geq 10\%$  for the Stockholm3 test to perform MRI and biopsy would have avoided MRI and biopsy in 38% of men at the cost of missing 8% of ISUP grade  $\geq 2$  cancers [279].

#### 5.2.4.2.6.4 Potential cancer grade shift, induced by improved diagnosis by MRI and MRI-targeted biopsy

Magnetic resonance imaging findings are significant predictors of adverse pathology features on prostatectomy specimens, and of survival-free BCR after RP or RT [84, 280-282]. In addition, tumours visible on MRI are enriched in molecular hallmarks of aggressivity, as compared to invisible lesions [283]. Thus, MRI does identify aggressive tumours.

Nonetheless, as MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer, ISUP grade  $\geq 2$  cancers detected by MRI-targeted biopsy are, on average, of better prognosis than those detected by the classical diagnostic pathway (Will Rogers phenomenon [86]). This is illustrated in a retrospective series of 1,345 patients treated by RP which showed that, in all risk groups, patients diagnosed by MRI-targeted biopsy had better BCR-free survival than those diagnosed by systematic biopsy only [84]. To mitigate this grade shift, in case of targeted biopsies, the 2019 ISUP consensus conference recommended using an aggregated ISUP grade summarizing the results of all biopsy cores from the same MR lesion, rather than using the result from the core with the highest ISUP grade [89]. When long-term follow-up of patients who underwent MRI-targeted biopsy is available, a revision of the risk-groups definition will become necessary. In the meantime, results of MRI-targeted biopsy must be interpreted in the context of this potential grade shift [284].

#### 5.2.4.2.7 MRI and MRI-targeted biopsy results depend on the *a priori* risk of csPCa

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, MRI findings must be interpreted in the light of the *a priori* risk of csPCa. Risk stratification combining clinical data, MRI findings and (maybe) other biomarkers will help, in the future, defining those patients that can safely avoid biopsy. Second, the inter-reader reproducibility of MRI is moderate at best. Current biopsy-targeting methods remain imprecise and their accuracy is substantially impacted by the operator’s experience. As a result, 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. Other ‘extended’ MRI-targeted and perilesional biopsy templates are being investigated (see Section 5.2.7.1.4). Third, the use of pre-biopsy MRI may induce grade shift, even with the use of an aggregated ISUP grade for each MR lesion targeted at biopsy (see Section 5.2.4.2.6). Clinicians must interpret MRI-targeted biopsy results in the context of this potential grade shift. A revision of the definitions of the risk groups will be needed in the future to take into account wider use of MRI and MRI-targeted biopsy.

Finally, it must be emphasized that the ‘MR pathway’ has only been evaluated in patients in whom the risk of csPCa was judged high enough to deserve biopsy based on standard clinical assessment including PSA. Magnetic resonance imaging in individuals without any suspicion of PCa is likely to result in an increase in false-positive findings and subsequent unnecessary biopsies.

### 5.2.4.3 Guidelines for MRI imaging in biopsy decision

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

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

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

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

### 5.2.5 Baseline biopsy decision

The need for prostate biopsy is based on PSA level, other biomarkers and/or suspicious DRE and/or imaging (see Section 5.2.4). Age, potential co-morbidity and therapeutic consequences should also be considered and discussed beforehand [253]. Risk stratification is a potential tool for reducing unnecessary biopsies [285].

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]) [286, 287]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [288].

Ultrasound (US)-guided and/or MRI-targeted biopsy is now the SOC. 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 [257], however, some evidence suggests reduced infection risk with the transperineal route (see Section 5.2.8.1.1) [289, 290]. Transurethral resection of the prostate (TURP) should not be used as a tool for cancer detection [291].

### 5.2.6 Repeat biopsy decision

#### 5.2.6.1 Repeat biopsy after previously negative biopsy

Men with a previous negative systematic biopsy should be offered a prostate MRI and in case of PIRADS > 3 findings, a repeat (targeted) biopsy has to be done. Other indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.3 for risk estimates);
- suspicious DRE, 5–30% PCa risk [179, 180];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade PCa [292];

In a contemporary series of biopsies the likelihood of finding a csPCa after follow-up biopsy after a diagnosis of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia (PIN) was only 6–8%, not significantly different from follow-up biopsies after a negative biopsy [293, 294].

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

#### 5.2.6.2 Saturation biopsy

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30–43% and depends on the number of cores sampled during earlier biopsies [295]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention varies substantially from 1.2% to 10% [296–299].

### 5.2.7 Prostate biopsy procedure

#### 5.2.7.1 Sampling sites and number of cores

##### 5.2.7.1.1 Ultrasound-guided systematic biopsy

For systematic biopsies, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland regardless of the approach used. Sextant biopsy is no longer considered adequate. At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc [3]. Ten to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive [300, 301].

Additional cores should be obtained from suspect areas identified by DRE or on pre-biopsy MRI; multiple (3–5) cores should be taken from each MRI-visible lesion (see Section 5.2.4.2.7.2). They can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique over another [250, 302-305].

##### 5.2.7.1.2 Ultrasound-guided saturation biopsy

In the setting of a positive MRI with targeted biopsy cores being taken, the addition of template cores may increase the detection of significant cancer slightly, but also increases the detection of insignificant cancer [103, 307]. The rationale for this must be carefully considered on an individual patient basis.

##### 5.2.7.1.3 MRI-directed targeted biopsy

Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique over another [250, 302-305]. However, regarding approach, the only systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%) [306]. This benefit was especially pronounced for anterior tumours. Multiple (3–5) cores should be taken from each lesion (see Section 5.2.4.2.7.2).

##### 5.2.7.1.4 Towards 'extended' MRI-directed biopsy?

As detailed in Section 5.2.4.2.6.2, the added value of systematic biopsy is partially explained by the fact that they compensate for guiding imprecisions of targeted biopsy. Therefore, biopsy strategies with multiple perilesional (regional) targeted cores obtained in addition of MRI-directed targeted cores are being investigated [261, 262, 307-310]. Prospective clinical trials are needed to evaluate whether these strategies can replace the combination of systematic and targeted biopsy currently recommended as the diagnostic work-up in men with positive MRI scans.

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

Summary of evidence	LE
Literature review including multiple biopsy schemes suggests that a 10 to 12-core scheme is optimal in the majority of initial and repeat biopsy patients, dependent on prostate size. These biopsy schemes should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [3].	3
A systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%).	2
Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique (cognitive guidance, US/MR fusion software or direct in-bore guidance) over the other.	2

Recommendations	Strength rating*
At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc and 10 to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive.	Strong
Transperineal biopsies are preferred over transrectal biopsies.	Strong
Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak

### 5.2.8.1 Antibiotics prior to biopsy

#### 5.2.8.1.1 Transperineal prostate biopsy

A total of seven randomised studies including 1,330 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (37 events among 657 men) compared to transperineal biopsy (22 events among 673 men) (RR: 1.81 [range 1.09–3.00], 95% CI) [311–318]. In addition, a systematic review including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [319]. Finally, a population-based study from the UK, including 486,467 biopsies over more than a decade from 2008–2019, showed lower rates of sepsis and infection with transperineal vs. transrectal biopsy (0.53% vs. 0.31%,  $p \leq 0.001$ ) [320]. The available evidence demonstrates that the transrectal approach should be abandoned in favour of the transperineal approach despite any possible logistical challenges.

To date, no RCT has been published investigating different antibiotic prophylaxis regimens for transperineal prostate biopsy. However, as it is a clean procedure that avoids rectal flora, quinolones or other antibiotics to cover rectal flora may not be necessary. A single dose of cephalosporin only to cover skin commensals has been shown to be sufficient in multiple single cohort series [299, 321]. Prior negative mid-stream urine test and routine surgical disinfecting preparation of the perineal skin are mandatory. In one of the largest studies to date, 1,287 patients underwent transperineal biopsy under local anaesthesia only [322]. Antibiotic prophylaxis consisted of a single oral dose of either cefuroxime or cephalexin. Patients with cardiac valve replacements received amoxicillin and gentamicin, and those with severe penicillin allergy received sulphamethoxazole. No quinolones were used. Only one patient developed a UTI with positive urine culture and there was no urosepsis requiring hospitalisation.

In another study of 577 consecutive patients undergoing transperineal biopsy using single dose IV cephazolin prophylaxis, one patient (0.2%) suffered prostatitis not requiring hospitalisation [299]. There were no incidences of sepsis. In a further study of 485 patients using only cephazolin, 4 patients (0.8%) suffered infectious complications [323].

#### 5.2.8.1.2 Transrectal prostate biopsy

Meta-analysis of eight RCTs including 1,786 men showed that use of a rectal povidone-iodine preparation before biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications (RR: 0.55, 95% CI: 0.41–0.72) [318, 324–329]. Single RCTs showed no evidence of benefit for perineal skin disinfection [330], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [331].

A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications (RR: 0.96, 95% CI: 0.64–1.54) [318, 332–334].

A meta-analysis of 26 RCTs with 3,857 patients found no evidence that use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than no injection (RR: 1.07, 95% CI: 0.77–1.48) [318]. A meta-analysis of 9 RCTs including 2,230 patients found that extended biopsy templates showed comparable infectious complications to standard templates (RR: 0.80, 95% CI: 0.53–1.22) [318]. Additional meta-analyses found no difference in infectious complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. non-coaxial), needle size (large vs. small), and number of injections for peri-prostatic nerve block (standard vs. extended) [318].

A meta-analysis of eleven studies including 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control (RR: 0.56, 95% CI: 0.40–0.77) [335].

Fluoroquinolones have been traditionally used for antibiotic prophylaxis in this setting; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones resulting in the suspension of the indication for peri-operative antibiotic prophylaxis including prostate biopsy [336].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, or augmented prophylaxis (combination of two or more different classes of antibiotics) is recommended [335]. In countries where use of fluoroquinolones are suspended, cephalosporins or aminoglycosides can be used as individual agents with comparable infectious complications based on a meta-analysis of two RCTs [335]. A meta-analysis of three RCTs reported that fosfomycin trometamol was superior to fluoroquinolones (RR: 0.49, 95% CI: 0.27–0.87) [335], but routine general use should be critically

assessed due to the relevant infectious complications reported in non-randomised studies [337]. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swab/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See figure 5.1 for prostate biopsy workflow to reduce infections complications.

Based on a meta-analysis, suggested antimicrobial prophylaxis before transrectal biopsy may consist of:

1. Targeted prophylaxis - based on rectal swab or stool culture.
2. Augmented prophylaxis - two or more different classes of antibiotics (of note: this option is against antibiotic stewardship programmes).
3. Alternative antibiotics:
  - fosfomycin trometamol (e.g., 3 g before and 3 g 24–48 hrs. after biopsy);
  - cephalosporin (e.g., ceftriaxone 1 g i.m; cefixime 400 mg p.o for 3 days starting 24 hrs. before biopsy) aminoglycoside (e.g., gentamicin 3 mg/kg i.v.; amikacin 15 mg/kg i.m).

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

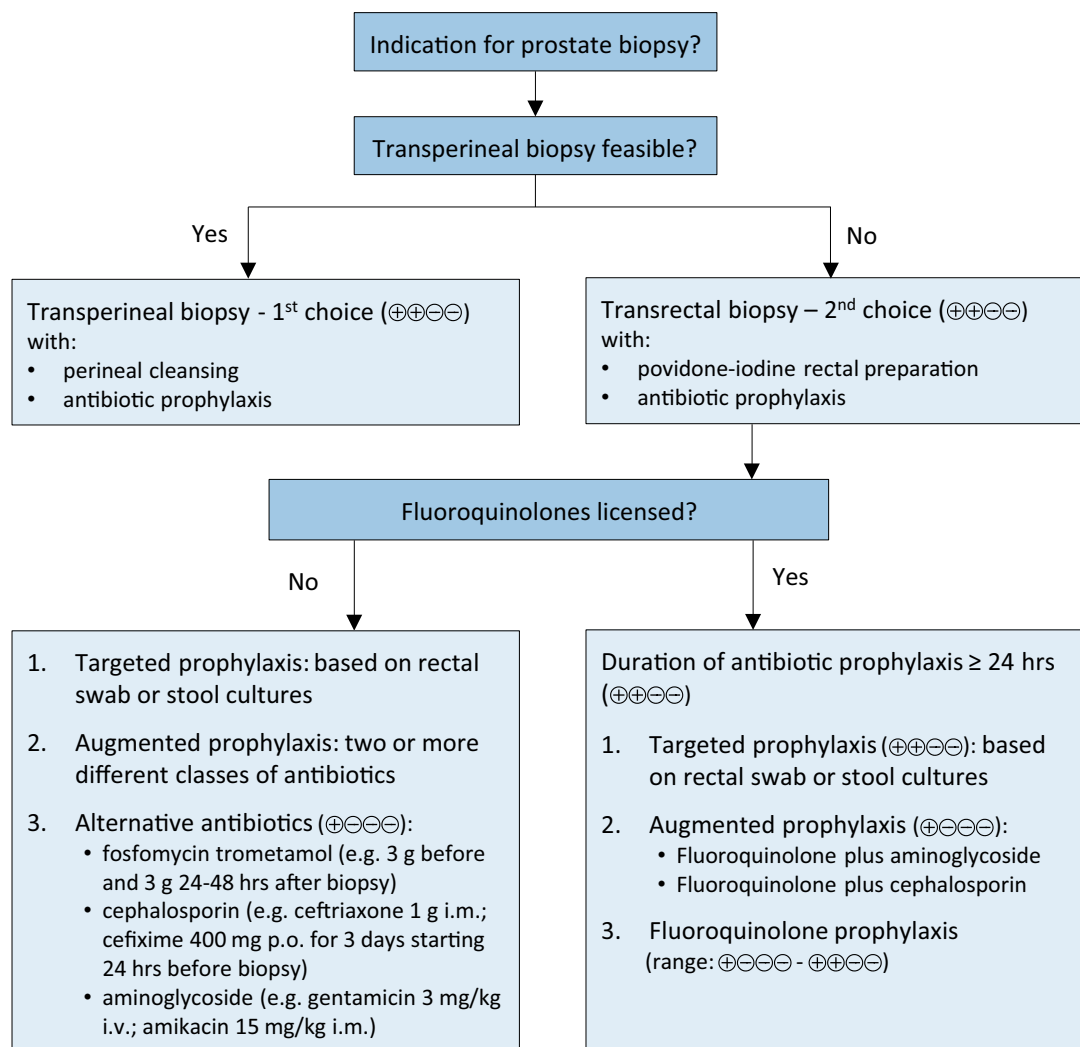
Summary of evidence	LE
A meta-analysis of seven studies including 1,330 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight RCTs including 1,786 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

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

\*Note on strength ratings:

*The above strength ratings are explained here due to the major clinical implications of these new recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its Strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy as, although quality of data is low, the clinical benefit is high and practical application simple. A ‘Strong’ rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.*

**Figure 5.1: Prostate biopsy workflow to reduce infectious complications\***



GRADE Working Group grades of evidence.

- High certainty: (⊕⊕⊕⊕) very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: (⊕⊕⊕⊖) moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: (⊕⊕⊖⊖) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

\*Figure adapted from Pilatz et al., [338] with permission from Elsevier.

### 5.2.8.3 Local anaesthesia prior to biopsy

Ultrasound-guided peri-prostatic block is recommended [339]. It is not important whether the depot is apical or basal. Intra-rectal instillation of local anaesthesia is inferior to peri-prostatic infiltration [340]. Local anaesthesia can also be used effectively for MRI-targeted and systemic transperineal biopsy [341]. 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]) [342]. In a randomised comparison a combination of peri-prostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to peri-prostatic anaesthesia only [343]. Targeted biopsies can then be taken via a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [341, 344, 345].

### 5.2.8.4 Complications

Complications of TRUS biopsy are listed in Table 5.6 [316]. Mortality after prostate biopsy is extremely rare and most are consequences of sepsis [126]. Low-dose aspirin is no longer an absolute contraindication [346].



A systematic review found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haematospermia and urinary retention [347]. 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 [348].

**Table 5.6: Percentage of complications per TRUS biopsy session, irrespective of the number of cores**

Complications	Percentage of patients affected
Haematospermia	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

#### 5.2.8.5 Seminal vesicle biopsy

Indications for SV (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20–25% [349]. A SV staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent RT. Its added value compared with MRI is questionable.

#### 5.2.8.6 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to MRI-detected lesions or repeat biopsies [350].

### 5.2.9 Pathology of prostate needle biopsies

#### 5.2.9.1 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 [351]. 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 [352, 353]. To optimise detection of small lesions and improve accuracy of grading, paraffin blocks should be cut at three levels and intervening unstained sections may be kept for immunohistochemistry (IHC) [354].

#### 5.2.9.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [354-356]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [354]. Section 5.2.8.3 lists the recommended terminology for reporting prostate biopsies [352]. Type and subtype of PCa should be reported such as for instance acinar adenocarcinoma (> 95% of PCa), ductal adenocarcinoma (< 5%) and poorly differentiated small or large cell neuroendocrine carcinoma (< 1%), even if representing a small proportion of the PCa. The distinct aggressive nature of ductal adenocarcinoma and small/large cell neuroendocrine carcinoma should be commented upon in the pathology report [352]. Considerable evidence has been accumulated in recent years supporting that among the Gleason grade 4 patterns, the expansile cribriform pattern carries an increased risk of biochemical recurrence, metastatic disease and death of disease [357, 358]. Reporting of this sub-pattern based on established criteria) is recommended [89, 359]. Intraductal carcinoma, defined as an extension of cancer cells into pre-existing prostatic ducts and acini, distending them, with preservation of basal cells [89], should be distinguished from high-grade PIN [360] as it conveys unfavourable prognosis in terms of biochemical recurrence and cancer-specific survival (CSS) [361, 362]. Its presence should be reported, whether occurring in isolation or associated with adenocarcinoma [89].

### 5.2.9.2.1 Recommended terminology for reporting prostate biopsies [287]

Recommendations	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, provide type and subtype, and presence or absence of cribriform pattern.	
Intraductal carcinoma.	

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2014 grade [88]. For MRI targeted biopsies consisting of multiple cores per target the aggregated (or composite) ISUP grade and percentage of high-grade carcinoma should be reported per targeted lesion [89]. If the targeted biopsies are negative, presence of specific benign pathology should be mentioned, such as dense inflammation, fibromuscular hyperplasia or granulomatous inflammation [89, 363]. A global ISUP grade comprising all systematic (non-targeted) and targeted biopsies is also reported (see Section 4.2). The global ISUP grade takes into account all biopsies positive for carcinoma, by estimating the total extent of each Gleason grade present. For instance, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site of Gleason grade 4 only, the global ISUP grade would be 2 (i.e. GS 7[3+4]) or 3 (i.e. GS 7[4+3]), dependent on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the 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 [364] and BCR [365].

Lymphovascular invasion (LVI) and EPE must each be reported, if identified, since both carry unfavourable prognostic information [366-368].

The proportion of systematic (non-targeted) carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP grade, tumour volume, surgical margins and 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 SV invasion after RP and RT failure [369-371]. 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 [372]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [373] triggering immediate treatment vs. AS in patients with ISUP grade 1 (see Section 6.1.1.2).

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);
- International Society of Urological Pathology grade (global);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (per biopsy site);
- if present: EPE, SV invasion, LVI, intraductal carcinoma/cribriform pattern, peri-neural invasion;
- For MRI-targeted biopsies with multiple cores report aggregate (or composite) ISUP grade and percentage high-grade carcinoma per targeted site;
- For carcinoma-negative MRI-targeted biopsy report specific benign pathology, e.g., fibromuscular hyperplasia or granulomatous inflammation, if present [89].

### 5.2.9.3 Tissue-based prognostic biomarker testing

After a comprehensive literature review and several panel discussions an ASCO-EAU-AUA multidisciplinary expert panel made recommendations regarding the use of tissue-based PCa biomarkers. The recommendations were limited to 5 commercially available tests (Oncotype Dx<sup>®</sup>, Prolaris<sup>®</sup>, Decipher<sup>®</sup>, Decipher PORTOS and ProMark<sup>®</sup>) with extensive validation in large retrospective studies and evidence that their test results might actually impact clinical decision-taking [374].



The selected commercially available tests significantly improved the prognostic accuracy of clinical multivariable models for identifying men who would benefit of AS and those with csPCa requiring curative treatment, as well as for guidance of patient management after RP. In addition, a few studies showed that tissue biomarker tests and MRI findings independently improved the detection of csPCa in an AS setting, but it remains unclear which men would benefit of both tests. Since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa scheduled for RT to decide on treatment intensification with hormonal therapy (HT).

#### 5.2.9.4 Histopathology of radical prostatectomy specimens

##### 5.2.9.4.1 Processing of radical prostatectomy specimens

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most widely accepted method includes complete embedding of the posterior prostate and a single mid-anterior left and right section. Compared with total embedding, partial embedding with this method missed 5% of positive margins and 7% of extraprostatic extension [375].

The entire RP specimen should be inked upon receipt in the laboratory to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin which provides more homogeneous fixation and sectioning after 24 hours [376]. 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 [87]. The remainder of the specimen is cut in transverse, 3–4 mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with pre-operative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

##### 5.2.9.4.1.1 Guidelines for processing prostatectomy specimens

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

##### 5.2.9.4.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.7). 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 5.8). Synoptic reporting results in more transparent and complete pathology reporting [377].

**Table 5.7: 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 and/or cribriform carcinoma.
Tumour (sub)staging and surgical margin status: location and extent of EPE, presence of bladder neck invasion, laterality of EPE or SV 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 5.8: Example checklist: reporting of prostatectomy specimens**

<b>Histopathological (sub)type</b>
Type of carcinoma, e.g. conventional acinaradenocarcinoma, (small cell) neuroendocrine cell carcinoma or ductal
Subtype, e.g. conventional acinar, ductal, mucinous
<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>
<ul style="list-style-type: none"> <li>• indicate whether it is focal or extensive (see Section 5.2.9.4.4);</li> <li>• specify sites;</li> <li>• indicate whether there is seminal vesicle invasion.</li> </ul>
<i>If applicable, regional lymph nodes:</i>
<ul style="list-style-type: none"> <li>• location;</li> <li>• number of nodes retrieved;</li> <li>• number of nodes involved.</li> </ul>
<b>Surgical margins</b>
<i>If carcinoma is present at the margin:</i>
<ul style="list-style-type: none"> <li>• specify sites;</li> <li>• Extent: focal or extensive (see Section 5.2.9.4.6)</li> <li>• (highest) grade at margin.</li> </ul>
<b>Other</b>
Presence of lymphovascular/angio-invasion
Location of dominant tumour
Presence of intraductal carcinoma/cribriform architecture

#### 5.2.9.4.3 ISUP grade in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [88]. The ISUP grade is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [378].

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 GS 6. 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. In a carcinoma almost entirely composed of Gleason grade 3 the presence of a minor (< 5%) Gleason pattern 4 component is not included in the GS (ISUP grade 1), but its presence is commented upon.

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, if > 5% of the PCa volume, is an unfavourable prognostic indicator for BCR and should be incorporated in the ISUP grade. If less than 5% its presence should be mentioned in the report as minor grade component [89, 379].

#### 5.2.9.4.4 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 [380].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [381] or < 1 high-power field in one or at most two sections [382] whereas others measure the depth of extent in millimetres [383].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e. not as pT4, because it does not carry independent prognostic significance for PCa recurrence and should be recorded as EPE (pT3a) [384, 385]. Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [386].

#### 5.2.9.4.5 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [382, 387-390]. Nevertheless, a cut-off of 0.5 mL is traditionally used to distinguish insignificant from clinically relevant cancer [387]. 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 [391].

#### 5.2.9.4.6 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 [388] 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 [392].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [393]. There is evidence for a relationship between margin extent and recurrence risk [394, 395]. However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in mm of involvement: focal,  $\leq 1$  mm vs. extensive,  $> 1$  mm [396], or number of blocks with positive margin involvement. Gleason score at the positive margin was found to correlate independently with outcome, and should be reported [394, 397].

### 5.3 Diagnosis - Clinical Staging

#### 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 [398].

##### 5.3.1.1 TRUS

Transrectal US is no more accurate at predicting organ-confined disease than DRE [399]. 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 [400, 401].

##### 5.3.1.2 MRI

T2-weighted imaging remains the most useful method for local staging on MRI. Pooled data from a meta-analysis showed a sensitivity and specificity of 0.57 (95% CI: 0.49–0.64) and 0.91 (95% CI: 0.88–0.93), 0.58 (95% CI: 0.47–0.68) and 0.96 (95% CI: 0.95–0.97), and 0.61 (95% CI: 0.54–0.67) and 0.88 (95% CI: 0.85–0.91), for EPE, SVI, and overall stage T3 assessment, respectively [402].

Detection of EPE and SVI seems more accurate at high field strength (3 Tesla) [402], while the added value of functional imaging remains debated [402, 403].

In 552 men treated by RP at seven different Dutch centres, MRI showed significantly higher sensitivity (51% vs. 12%;  $p < 0.001$ ), and lower specificity (82% vs. 97%;  $p < 0.001$ ) than DRE for non-organ confined disease. All risk groups redefined using MRI findings rather than DRE findings showed better BCR-free survival due to improved discrimination and the Will Roger's phenomenon [404].

Traditionally, EPE/SVI is diagnosed on MRI using direct qualitative signs (e.g., irregular bulging of the prostate, capsular disruption, visible tumour within periprostatic fat, obliteration of the rectoprostatic angle, asymmetry of the neurovascular bundles or focal low signal intensity in the SVs) [405]. With such subjective reading, experience of the reader remains of paramount importance [406] and the inter-reader agreement is moderate with kappa ( $\kappa$ ) values ranging from 0.41 to 0.68 [407]. The length of tumour capsule contact (LCC) is also a significant predictor of EPE; it has the advantage of being quantitative, although the ideal cut-off value remains debated [408]. Several grading systems combining subjective qualitative signs and/or LCC into a score have shown good sensitivity for EPE (0.68–0.82) with substantial inter-reader agreement ( $\kappa = 0.63$ –0.74), but at the expense of decreased specificity (0.71–0.77); none of these scores has shown definitive superiority over the others [409].

Magnetic resonance imaging findings can improve the prediction of the pathological stage when combined with clinical and biopsy data. As a result, several groups developed multivariate risk calculators for predicting

EPE/SVI or positive surgical margins [410]. In external validation cohorts, these risk calculators showed significantly better discrimination than nomograms without MRI-based features [411-413]. However, they remain limited by substantial miscalibration and therefore their results must be interpreted with care.

Given its low sensitivity for focal (microscopic) EPE, MRI is not recommended for local staging in low-risk patients [414-416]. However, MRI can still be useful for treatment planning.

### 5.3.2 **N-staging**

#### 5.3.2.1 *Computed tomography 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 [417, 418]. Computed tomography and MRI sensitivity is less than 40% [419, 420]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade < 4 cancer, PSA < 20 ng/mL, or localised disease [421-423].

Diffusion-weighted MRI (DW-MRI) may detect metastases in normal-sized nodes, but a negative DW-MRI cannot rule out the presence of LN metastases, and DW-MRI provides only modest improvement for LN staging over conventional imaging [424].

#### 5.3.2.2 *Risk calculators incorporating MRI findings and clinical data*

Because CT and MRI lack sensitivity for direct detection of positive LNs, nomograms combining clinical and biopsy findings have been used to estimate the risk of patients harbouring positive LNs [425-427]. Although these nomograms are associated with good performance, they have been developed using systematic biopsy findings and may therefore not be appropriate for patients diagnosed with combined MRI-targeted biopsy and systematic biopsy.

Two models incorporating MRI-targeted biopsy findings and MRI-derived findings recently underwent external validation [428, 429]. One model was tested on an external cohort of 187 patients with a prevalence of LN invasion of 13.9% (vs. 16.9% in the development cohort). The C-index was 0.73 (vs. 0.81 in the development cohort); at calibration analysis, the model tended to overpredict the actual risk [428]. The other model was validated in an external multi-centre cohort of 487 patients with a prevalence of 8% of LN invasion (vs. 12.5% in the development cohort). The AUC was 0.79 (vs. 0.81 in the development cohort). Using a risk cut-off of 7% would have avoided LN dissection in 273 (56% of the cohort), while missing LN invasion in 7 patients (2.6% of the patients below the 7% threshold; 18% of the 38 patients with LN invasion) [430]. Therefore, this nomogram and a 7% threshold should be used after MRI-targeted biopsy to identify candidates for extended lymph node dissection (eLND).

#### 5.3.2.3 *Choline PET/CT*

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51–66%) and 92% (95% CI: 89–94%), respectively [431]. 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 [432]. 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 [433]. Comparisons between choline PET/CT and DW-MRI yielded contradictory results [432, 434-436].

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

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

Prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT uses several different radiopharmaceuticals; most published studies used <sup>68</sup>Ga-labelling for PSMA PET imaging, but some used <sup>18</sup>F-labelling. At present there are no conclusive data about comparison of such tracers, with additional new radiotracers being developed. Prostate-specific membrane antigen is also an attractive target because of its specificity for prostate tissue, even if the expression in other non-prostatic malignancies or benign conditions may cause incidental false-positive findings [437-441].

A prospective, multi-centre study addressed the use of <sup>68</sup>Ga-PSMA PET/CT in patients with newly diagnosed PCa and negative bone scan findings. 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 [442]. Another prospective multi-centre trial

investigated the diagnostic accuracy of  $^{18}\text{F}$ -DCFPyL PET/CT for LN staging in 117 patients with primary PCa, prior to RP with ePLND.  $^{18}\text{F}$ -DCFPyL PET/CT showed a high specificity (94.0%; CI: 86.9–97.5%), and a limited sensitivity (41.2%, CI: 19.4–66.5%) for the detection of pelvic LN metastases [443]. Comparable results were demonstrated in a phase II/III prospective, multi-centre study (OSPREY). In 252 evaluable patients with high risk of PCa who underwent RP with PLND,  $^{18}\text{F}$ -DCFPyL PET/CT showed a median specificity of 97.9% (95% CI: 94.5–99.4%) and median sensitivity of 40.3% (28.1–52.5%) for pelvic nodal involvement [444]. This suggests that current PSMA-based PET/CT imaging cannot yet replace diagnostic ePLND.

Prostate-specific antigen may be a predictor of a positive PSMA PET/CT. In the primary staging cohort from a meta-analysis, however, no robust estimates of positivity were found [445]. The tracer uptake is also influenced by the ISUP grade. Similarly, patients with PSA levels  $\geq 10$  ng/mL showed significantly higher uptake than those with PSA levels  $< 10$  ng/mL [446].

Comparison between PSMA PET/CT and MRI was performed in a systematic review and meta-analysis including 13 studies ( $n = 1,597$ ) [447].  $^{68}\text{Ga}$ -PSMA was found to have a higher sensitivity and a comparable specificity for staging pre-operative LN metastases in intermediate- and high-risk PCa. Another prospective trial reported superior sensitivity of PSMA PET/CT as compared to MRI for nodal staging of 36 high-risk PCa patients [448].

PSMA PET/CT has a good sensitivity and specificity for LN involvement, possibly impacting clinical decision-making. In a review and meta-analysis including 37 articles, a subgroup analysis was performed in patients undergoing PSMA PET/CT for primary staging. On a per-patient-based analysis, the sensitivity and specificity of  $^{68}\text{Ga}$ -PSMA PET were 77% and 97%, respectively, after eLND at the time of RP. On a per-lesion-based analysis, sensitivity and specificity were 75% and 99%, respectively [445].

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

#### 5.3.2.5 *Risk calculators incorporating MRI and PSMA findings*

Recently, an international, multi-centre study incorporated PSMA PET into existing nomograms in order to predict pelvic LN metastatic disease in PCa patients. Performance of 3 nomograms was assessed in 757 patients undergoing RARP and ePLND. Addition of PSMA PET to the nomograms substantially improved the discriminative ability of the models yielding cross-validated AUCs of 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively [449].

### 5.3.3 **M-staging**

#### 5.3.3.1 *Bone scan*

$^{99\text{m}}\text{Tc}$ -Bone scan is a highly sensitive conventional imaging technique, evaluating the distribution of active bone formation in the skeleton related to malignant and benign disease. A meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%) at patient level [450]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade [417, 451]. A retrospective study investigated the association between age, PSA and GS in 703 newly diagnosed PCa patients who were referred for bone scintigraphy. The incidence of bone metastases increased substantially with rising PSA and upgrading GS [452]. In two studies, a dominant Gleason pattern of 4 was found to be a significant predictor of positive bone scan [453, 454]. Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP grade or clinical stage [417].

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

$^{18}\text{F}$ -sodium fluoride ( $^{18}\text{F}$ -NaF) PET or PET/CT, similarly to bone scintigraphy, only assesses the presence of bone metastases.  $^{18}\text{F}$ -NaF PET or PET/CT was reported to have similar specificity and superior sensitivity to bone scintigraphy for detecting bone metastases in patients with newly diagnosed high-risk PCa [455, 456]. However, in a prospective study  $^{18}\text{F}$ -NaF PET showed no added value over bone scintigraphy in patients with newly diagnosed intermediate- or high-risk PCa and negative bone scintigraphy results [457]. Recently, the interobserver agreement for the detection of bone metastases and the accuracy of  $^{18}\text{F}$ -NaF PET/CT in the diagnosis of bone metastases were investigated. Bone metastases were identified in 211 out of 219 patients with an excellent interobserver agreement, demonstrating that  $^{18}\text{F}$ -NaF PET/CT is a robust tool for the detection of osteoblastic lesions in patients with PCa [458].

It remains unclear whether choline PET/CT is more sensitive than bone scan but it has higher specificity with fewer indeterminate bone lesions [446, 459, 460]. Choline PET/CT has also the advantage of detecting visceral and nodal metastases.

Diffusion-weighted whole-body and axial skeleton MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa. Whole-body MRI can also



detect visceral and nodal metastases; it was shown to be more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [461].

A meta-analysis found that whole-body MRI is more sensitive than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity [450].

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

A systematic review including 12 studies (n = 322) reported high variation in <sup>68</sup>Ga-PSMA PET/CT sensitivity for initial staging (range 33–99%; median sensitivity on per-lesion analysis 33–92%, and on per-patient analysis 66–91%), with good specificity (per-lesion 82–100%, and per-patient 67–99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [462]. Table 5.9 reports the data of the 5 studies including histopathologic correlation.

**Table 5.9: PSMA PET/CT results in primary staging alone [462]**

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 multi-centre 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 [463]; management changes occurred in 21% of patients. A retrospective review investigated the risk of metastases identified by <sup>68</sup>Ga-PSMA at initial staging in 1,253 patients (high-risk disease in 49.7%) [464]. Metastatic disease was identified by PSMA PET/CT 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 ePLND. Bone 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.

In the PSMA PET/CT prospective multi-centre study in patients with high-risk PCa before curative-intent surgery or RT (proPSMA), 302 patients were randomly assigned to conventional imaging with CT and bone scintigraphy or <sup>68</sup>Ga-PSMA-11 PET/CT. The primary outcome focused on the accuracy of first-line imaging for the identification of pelvic LN or distant metastases, using a predefined reference standard consisting of histopathology, imaging, and biochemistry at 6-month follow-up. Accuracy of <sup>68</sup>Ga-PSMA PET/CT was 27% (95% CI: 23–31) higher than that of CT and bone scintigraphy (92% [88–95] vs. 65% [60–69]; p < 0.0001). Conventional imaging had a lower sensitivity (38% [24–52] vs. 85% [74–96]) and specificity (91% [85–97] vs. 98% [95–100]) than PSMA PET/CT. Furthermore, <sup>68</sup>Ga-PSMA PET/CT scan prompted management change more frequently as compared to conventional imaging (41 [28%] men [21–36] vs. 23 [15%] men [10–22], p = 0.08), with less equivocal findings (7% [4–13] vs. 23% [17–31]) and lower radiation exposure (8.4 mSv vs. 19.2 mSv; p < 0.001) [465]. In a small study <sup>18</sup>F-PSMA-1007 PET/CT proved superior to whole-body MRI with DWI and Single-photon Emission Computed Tomography (SPECT) CT [466].

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

The field of non-invasive N- and M-staging of PCa patients is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN- and bone metastases than the classical work-up with bone scan and abdominopelvic CT. In view of the evidence offered by the randomised, multi-centre proPSMA trial [465], replacing bone scan and abdominopelvic CT by more sensitive imaging modalities may be a consideration in patients with high-risk PCa undergoing initial staging. However, in absence of prospective studies demonstrating survival benefit, caution must be used when taking therapeutic decisions [467]. The prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. In particular, it is unclear whether patients with metastases detectable only with PET/CT or whole-body MRI should be managed using systemic therapies, or whether they should be subjected to aggressive local and metastases-directed therapies [468].

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 [469].



### 5.3.5 Summary of evidence and guidelines for staging of prostate cancer

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

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

## 5.4 Estimating life expectancy and health status

### 5.4.1 Introduction

Evaluation of life expectancy and health status is important in clinical decision-making for screening, diagnosis, and treatment of PCa. Prostate cancer is common in older men (median age 68) and diagnoses in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the USA [470, 471].

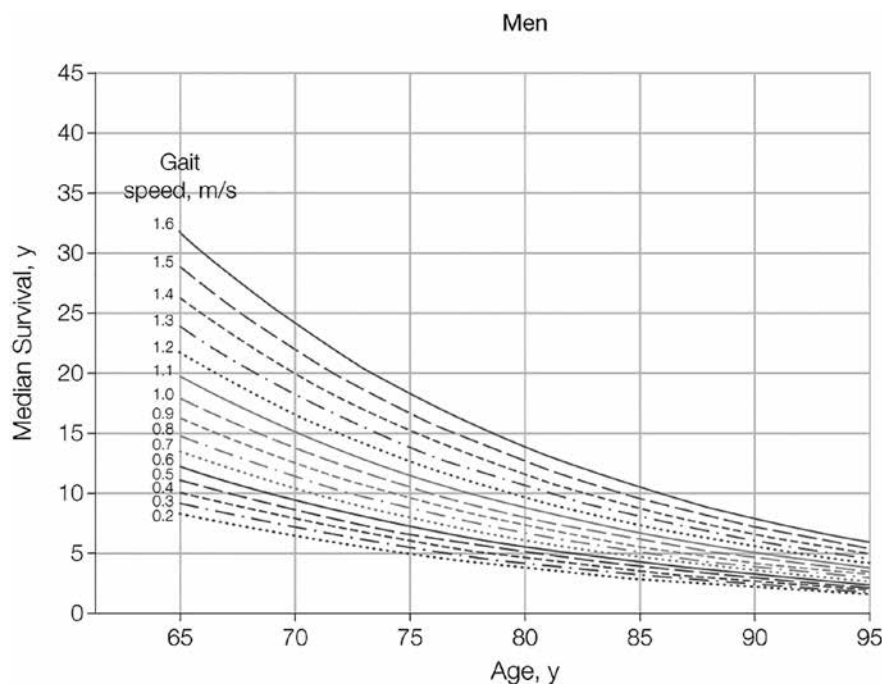
Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over 10 years life expectancy is considered mandatory for any benefit from local treatment and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCa-specific mortality (PCSM) and life expectancy of surgery vs. AS [472]. 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) [473]. External beam RT shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [474].

Older men have a higher incidence of PCa and may be under-treated despite the high overall mortality rates [475, 476]. Of all PCa-related deaths 71% occur in men aged > 75 years [477], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [478-480]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease received curative treatment compared to 88% aged 65-74 [481].

### 5.4.2 Life expectancy

Life expectancy tables for European men are available online: <https://ec.europa.eu/eurostat/web/productsdatasets/-/tps00205>. Survival may be variable and therefore estimates of survival must be individualised. Gait speed is a good single predictive method of life expectancy (from a standing start, at usual pace, generally over 6 meters). For men at age 75, 10-year survival ranged from 19% < 0.4 m/s to 87%, for  $\geq 1.4$  m/s [482].

**Figure 5.2: Predicted Median Life Expectancy by Age and Gait Speed for males\* [482]**



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

#### 5.4.3 Health status screening

Heterogeneity increases with advancing age, so it is important to use measures other than just age or performance status (PS) when considering treatment options. The International SIOG PCa Working Group recommends that treatment for adults over 70 years of age should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (see Table 5.10) [151]. This tool helps to discriminate between those who are fit and those with frailty, a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and negative side effects of cancer treatment [483]. Healthy patients with a G8 score > 14 or vulnerable patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Frail patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (see Figure 5.3) [151]. Patients with a G8 score ≤ 14 should undergo a comprehensive geriatric assessment (CGA) as this score is associated with 3-year mortality. A CGA is a multi-domain assessment that includes co-morbidity, nutritional status, cognitive and physical function, and social supports to determine if impairments are reversible [484]. A systematic review of the effect of geriatric evaluation for older cancer patients showed improved treatment tolerance and completion [485].

The Clinical Frailty Scale (CFS) is another screening tool for frailty (see Figure 5.4) [486]. Although not frequently used in the cancer setting, it is considered to be a common language for expressing degree of frailty. The scale runs from 1 to 9, with higher scores indicating increasing frailty. Patients with a higher CFS score have a higher 30-day mortality after surgery and are less likely to be discharged home [487].

It is important to use a validated tool to identify frailty, such as the G8 or CFS, as clinical judgement has been shown to be poorly predictive of frailty in older patients with cancer [488].

##### 5.4.3.1 Co-morbidity

Co-morbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [489, 490]. Ten years after not receiving active treatment for PCa, most men with a high co-morbidity score had died from competing causes, irrespective of age or tumour aggressiveness [489]. Measures for co-morbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [491, 492] (Table 5.11) and Charlson Co-morbidity Index (CCI) [493].

##### 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) [494].

#### 5.4.3.3 Cognitive function

Cognitive impairment can be screened for using the mini-COG (<https://mini-cog.com/>) which consists of three-word recall and a clock-drawing test and can be completed within 5 minutes. A score of  $\leq 3/5$  indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an increasingly important factor in health status assessment [495-497]. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [498].

#### 5.4.3.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [499]. 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) [500-502].

#### 5.4.3.5 Shared decision-making

The patient's own values and preferences should be taken into account as well as the above factors. A shared decision-making process also involves anticipated changes to QoL, functional ability, and a patient's hopes, worries and expectations about the future [503]. Particularly in older and frail patients, these aspects should be given equal importance to disease characteristics during the decision-making process [504]. Older patients may also wish to involve family members, and this is particularly important where cognitive impairment exists.

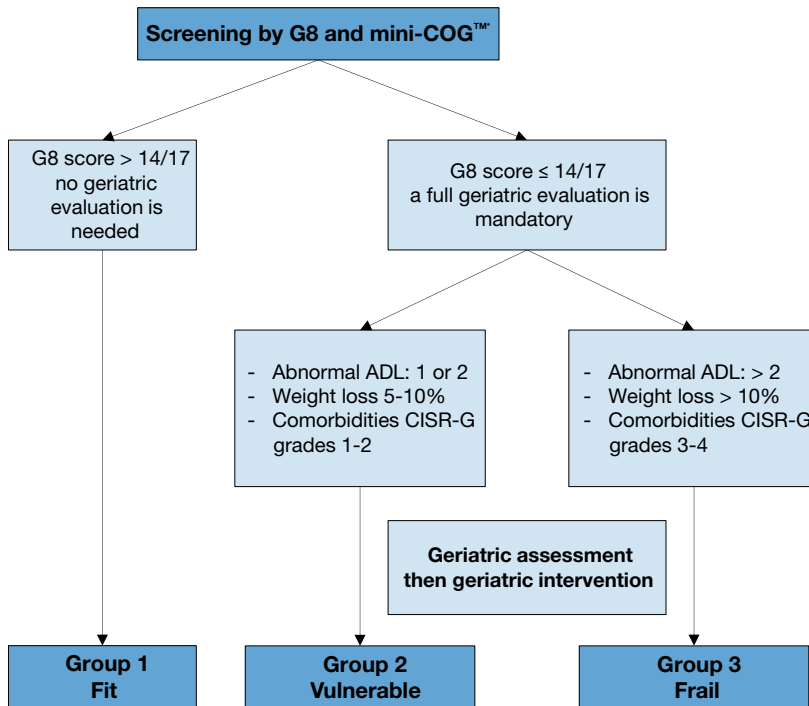
#### 5.4.4 Conclusion

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

**Table 5.10: G8 screening tool (adapted from [505])**

	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 $\geq$ 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 = $\geq$ 85
		1 = 80-85
		2 = < 80
		<b>Total score</b>

Figure 5.3: Decision tree for health status screening (men > 70 years)\*\* [151]



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.

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Figure 5.4: The Clinical Frailty Scale version 2.0 [486]\*

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

SCORING FRAILTY IN PEOPLE WITH DEMENTIA	
The degree of frailty generally corresponds to the degree of dementia. Common symptoms in <b>mild dementia</b> include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.	In <b>moderate dementia</b> , recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In <b>severe dementia</b> , they cannot do personal care without help. In <b>very severe dementia</b> they are often bedfast. Many are virtually mute.

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[www.geriatricmedicineresearch.ca](http://www.geriatricmedicineresearch.ca)

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

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**Table 5.11: Cumulative Illness Score Rating-Geriatrics (CISR-G)**

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

#### 5.4.5 Guidelines for evaluating health status and life expectancy

Recommendations	Strength rating
Use individual life expectancy, health status, and co-morbidity in PCa management.	Strong
Use the Geriatric-8, Clinical Frailty Scale or 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 active treatment. Data are available on patients who did not undergo local treatment with up to 25 years of follow-up, with endpoints of OS and CSS. Several series have shown a consistent CSS rate of 82–87% at 10 years [506–511], and 80–95% for T1/T2 and ISUP grade  $\leq$  2 PCas [512]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [508, 510, 511], and two reported 20-year CSS rates of 57% and 32%, respectively [508, 510]. The observed heterogeneity in outcomes is due to differences in inclusion criteria, with some older studies from the pre-PSA era showing worse outcomes [510]. 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 [512]. Observation was most effective in men aged 65–75 years with low-risk PCa [513].

Co-morbidity is as important as age in predicting life expectancy in men with PCa. Increasing co-morbidity greatly increases the risk of dying from non-PCa-related causes and for those men with a short life expectancy. In an analysis of 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI score  $\geq 2$  had died from competing causes at 10 years follow-up regardless of their age at time of diagnosis. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score  $\leq 1$  had a low risk of death at 10 years, especially for well- or moderately-differentiated lesions [489]. This highlights the importance of assessing co-morbidity before considering a biopsy.

In screen-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 [514]. 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 [515]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up consisting of PSA testing, clinical examination, MRI imaging and repeat prostate biopsies, with curative treatment being prompted by pre-defined thresholds indicative of potentially life-threatening disease, which is still potentially curable, while considering individual life expectancy.

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

**Table 6.1.1: Definitions of active surveillance and watchful waiting [514]**

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

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

#### 6.1.1.2 Active surveillance

No formal RCT is available comparing this modality to standard treatment. The 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 [516].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review [517]. More recently, the largest prospective series of men with low-risk PCa managed by AS was published [518]. Table 6.1.2 summarises the results of selective AS cohorts. It is clear that the long-term OS and CSS of patients on AS are extremely good. However, more than one-third of patients are ‘reclassified’ during follow-up, most of whom undergo curative treatment due to disease upgrading, increase in disease extent, disease stage, progression or patient preference. There is considerable variation and heterogeneity between studies regarding patient selection and eligibility, follow-up policies (including frequency and type of imaging such as MRI imaging, type and frequency of repeat prostate biopsies, such as MRI-targeted biopsies or transperineal template biopsies, use of PSA kinetics and density, and frequency of clinical follow-up), when active treatment should be instigated (i.e. reclassification criteria) and which outcome measures should be prioritised [515]. These will be discussed further in section 6.2.1.



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

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, <i>et al.</i> 2008 [519]	326	22	8/18 (44%)	98	100
Carter, <i>et al.</i> 2007 [520]	407	41	10/49 (20%)	98	100
Adamy, <i>et al.</i> 2011 [521]	533-1,000	48	4/24 (17%)	90	99
Soloway, <i>et al.</i> 2010 [522]	99	45	0/2	100	100
Roemeling, <i>et al.</i> 2007 [523]	278	41	-	89	100
Khatami, <i>et al.</i> 2007 [524]	270	63	-	n.r.	100
Klotz, <i>et al.</i> 2015 [525]	993	77	-	85	98.1
Tosoian, <i>et al.</i> 2015 [518]	1,818	60	-	93	99.9
<b>Total</b>	<b>4,724-5,191</b>	<b>46.5</b>	<b>-</b>	<b>93</b>	<b>99</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 was a RCT from the pre-PSA era, randomising patients to either WW or RP (Table 6.1.3) [526]. The study found RP to provide superior CSS, OS and PFS compared to WW at a median follow-up of 23.6 years (range 3 weeks–28 years). However, the benefit in favour of RP over WW was only apparent after 10 years. The PIVOT trial was a RCT conducted in the early PSA era and made a similar comparison between RP vs. WW in 731 men (50% with non-palpable disease) but in contrast to the SPCG-4, it found little, to no, benefit of RP (cumulative incidence of all-cause death, RP vs. observation: 68% vs. 73%; RR: 0.92, 95% CI: 0.84–1.01) within a median follow-up period of 18.6 years (interquartile range, 16.6 to 20 years) [527]. Exploratory subgroup analysis showed that the borderline benefit from RP was most marked for intermediate-risk disease (RR: 0.84, 95% CI: 0.73–0.98) but there was no benefit in patients with low- or high-risk disease. Overall, no adverse effects on health-related QoL (HRQoL) and psychological well-being was apparent in the first 5 years [528]. However, one of the criticisms of the PIVOT trial is the relatively high overall mortality rate in the WW group compared with more contemporary series. A Cochrane review performed a pooled analysis of RCTs comparing RP vs. WW [529]. Three studies were included (including the Veteran's Administration Cooperative Urological Research Group [VACURG] study which was conducted in the pre-PSA era [530], SPCG-4 and PIVOT). The authors found RP had lower overall mortality (HR: 0.79, 95% CI: 0.70–0.90) and lower cancer-specific mortality (HR: 0.57, 95% CI: 0.44–0.73) compared with WW at 29 years' follow-up. Radical prostatectomy also had lower risk of progression (HR: 0.43, 95% CI: 0.35–0.54) and lower risk of metastatic disease (HR: 0.56, 95% CI: 0.46–0.70). However, RP was associated with higher rates of urinary incontinence (RR: 3.97, 95% CI 2.34–6.74) and erectile dysfunction (ED) (RR: 2.67, 95% CI: 1.63–4.38).

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

**Table 6.1.3: Outcome of SPCG-4 at a median follow-up of 23.6 years [526]**

	RP (n = 348) (%)	Watchful waiting (n = 348) (%)	Relative risk (95% CI)	p-value
Disease-specific mortality	19.6	31.3	0.55 (0.41–0.74)	< 0.001
Overall mortality	71.9	83.8	0.74 (0.62–0.87)	< 0.001
Metastatic progression	26.6	43.3	0.54 (0.42–0.70)	< 0.001

CI = confidence interval; RP = radical prostatectomy.

#### 6.1.1.4 The ProtecT trial

The ProtecT trial randomised 1,643 patients into three arms: active treatment with either RP or EBRT, and active monitoring (AM) [525]. 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 had mainly intermediate-risk disease. After 10 years of follow-up, 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 was that AM was as effective as active treatment at 10 years, at a cost of increased progression and double the metastatic risk. Metastases remained 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 represented an intermediate approach between contemporary AS protocols and WW in terms of a monitoring strategy based almost entirely on PSA measurements alone; there was no use of MRI scan, either at recruitment or during the monitoring period, nor were there any protocol-mandated repeat prostate biopsies at regular intervals. In addition, approximately 40% of randomised patients had intermediate-risk disease. Nevertheless, the ProtecT study has reinforced the role of deferred active treatment (i.e., either AS or some form of initial AM) as a feasible alternative to active curative interventions in patients with low-grade and low-stage disease. Beyond 10 years, no data is available, as yet, although AS is likely to give more reassurance especially in younger men, based on more accurate risk stratification at recruitment and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must be evaluated before considering any active treatment in low-risk patients and in those with up to 10 years' individual life expectancy [531].

Recently, Bryant *et al.*, performed a comprehensive characterisation of the ProtecT study cohort, stratifying patients at baseline according to risk of progression using clinical stage, grade at diagnosis and PSA level [531]. Additionally, detailed clinico-pathological information on participants who received RP were analysed. The authors aimed to test the hypothesis that the clinico-pathological features of participants with disease progression differed from those with stable disease in order to identify prognostic markers. The results showed that out of all patients who had been randomised (n = 1,643), 34% (n = 505) had intermediate- or high-risk disease, and 66% (n = 973) had low-risk disease. Out of all patients who had received AM, RP or RT within 12 months of randomisation (n = 1,607), at a median follow-up of 10 years, 12% of patients (n = 198) developed progression, of which 72% (n = 142) had undergone AM. Treatment received, age (65–69 vs. 50–64 years), PSA, GG at diagnosis, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs. 3.0 mm), aggregate length of tumour (median 8.0 vs. 4.0 mm), and presence of perineural invasion were each associated with increased risk of disease progression (p < 0.001 for each). However, these factors could not reliably predict progression in individuals. Notably, 53% (n = 105) of patients who progressed had biopsy GG 1 disease, although, conversely, none of the participants who received RP and subsequently progressed had pathological GG 1 tumours. This discrepancy can be explained by inadequate sampling by PSA testing and 10-core TRUS-guided biopsies.

## 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 [532]. The procedure involves removing the entire prostate with its capsule intact and SVs, followed by vesico-urethral anastomosis. Surgical approaches have expanded from perineal and retropubic open approaches to laparoscopic and robotic-assisted techniques; anastomoses have evolved from Vest approximation sutures to continuous suture watertight anastomoses under direct vision and mapping of the anatomy of the dorsal venous complex (DVC) and cavernous nerves has led to excellent visualisation and potential for preservation of erectile function [533]. The main results from multi-centre 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	Treatment period	Median FU (mo)	Risk category	CSS (%)
Bill-Axelsson, <i>et al.</i> 2018 [526]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and Intermediate risk	80.4 (at 23 yr.)
Wilt, <i>et al.</i> 2017 [534]	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 [516]	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 [535]. Augmentation of standard verbal and written educational materials such as use of interactive multimedia tools [536, 537] and pre-operative patient-specific 3D printed prostate models has been shown to improve patient understanding and satisfaction and should be considered to optimise patient-centred care [538].

#### 6.1.2.2.2 Pre-operative pelvic floor exercises

Although many patients who have undergone RP will experience a return to urinary continence [539], temporary urinary incontinence is common early after surgery, reducing QoL. Pre-operative pelvic floor exercises (PFE) with, or without, biofeedback have been used with the aim of reducing this early post-operative incontinence. A systematic review and meta-analysis of the effect of pre-RP PFE on post-operative urinary incontinence showed a significant improvement in incontinence rates at 3 months post-operatively with an OR of 0.64 ( $p = 0.005$ ), but not at 1 month or 6 months [540]. Pre-operative PFE may therefore provide some benefit, however the analysis was hampered by the variety of PFE regimens and a lack of consensus on the definition of incontinence.

#### 6.1.2.2.3 Prophylactic antibiotics

Prophylactic antibiotics should be used; however, no high-level evidence is available to recommend specific prophylactic antibiotics prior to RP (See EAU Urological Infections Guidelines [541]). In addition, as the susceptibility of bacterial pathogens and antibiotic availability varies worldwide, any use of prophylactic antibiotics should adhere to local guidelines.

#### 6.1.2.2.4 Neoadjuvant androgen deprivation therapy

Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of these using a 3-month period. The main findings were summarised in a Cochrane review [542]. 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 acetate plus prednisone (AAP) prior to RP in 65 localised high-risk PCa patients [543]. Patients in the combination arm were found to have both significantly lower tumour volume and significantly lower BCR at > 4 years follow-up ( $p = 0.0014$ ). A pooled analysis of 3 RCTs, including 117 patients and assessing the impact of intense neoadjuvant deprivation therapy has reported a complete pathological response rate of 9.4%, with improved BCR outcomes in complete responders [544]. Further supportive evidence is required before recommending combination neoadjuvant therapy including abiraterone prior to RP. Another RCT (CALGB 90203), comparing RP alone to RP with neoadjuvant chemo-hormonal therapy (CHT) including docetaxel for clinically high-risk localised PCa did not meet the study's primary endpoint of biochemical PFS at 3 years post-operatively, due to contamination with early salvage RT. As a result, CHT is not currently recommended unless longer-term data show a survival benefit using clinical endpoints [545].

### 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 [533] but suffered from a lack of access to pelvic LNs. If lymphadenectomy is required during perineal RP it must be done via a separate open retropubic (RRP) or laparoscopic approach. The open retropubic approach was popularised by Walsh in 1982 following his anatomical description of the DVC, enabling its early control and of the cavernous nerves, permitting a bilateral nerve-sparing procedure [546]. This led to the demise in popularity of perineal RP and eventually to the first laparoscopic RP reported in 1997 using retropubic principles but performed transperitoneally [547]. The initial 9 cases averaged 9.4 hours, an indication of the significant technical and ergonomic difficulties of the technique. Most recently, RARP was introduced using the da Vinci Surgical System® by Binder in 2002 [548]. 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, when available.

In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss, but not earlier (12 weeks) functional or oncological outcomes compared to open RP [549]. An updated analysis with follow-up at 24 months did not reveal any significant differences in functional outcomes between the approaches [550]. Increased surgical experience has lowered the complication rates of RP and improved

cancer cure [510-513]. 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 [551-553]. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [509, 528, 534, 554]. A systematic review and meta-analysis of non-RCTs demonstrated that RARP had lower peri-operative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy (LRP), although there was considerable methodological uncertainty [555]. 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 ED outcomes. Another systematic review and meta-analysis included two small RCTs comparing RARP vs. LRP [556]. The results suggested higher rates of return of erectile function (RR: 1.51, 95% CI: 1.19–1.92) and return to continence function (RR: 1.14, 95% CI: 1.04–1.24) in the RARP group. However, a Cochrane review comparing either RARP or LRP vs. open RP included two RCTs and found no significant differences between the comparisons for oncological-, urinary- and sexual function outcomes, although RARP and LRP both resulted in statistically significant improvements in duration of hospital stay and blood transfusion rates over open RP [557]. Therefore, no surgical approach can be recommended over another.

Outcome after prostatectomy has been shown to be dependent on both surgeon [558] as well as hospital volume [559]. Although various volume criteria have been set worldwide, the level of evidence is insufficient to pinpoint a specific lower volume limit.

#### 6.1.2.3.1 Robotic anterior versus Retzius-sparing dissection

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

Galfano *et al.*, first described RS-RARP in 2010 [560]. This approach commences dissection posteriorly at the pouch of Douglas, first dissecting the SVs and progressing caudally behind the prostate. All of the anterior support structures are avoided, giving rise to the hypothetical mechanism for improved early post-operative continence. Retzius-sparing-RARP thus offers the same potential advantage as the open perineal approach, but without disturbance of the perineal musculature.

Retzius-sparing-RARP has been recently investigated in RCTs leading to four systematic reviews and meta-analyses [561-563] including a 2020 Cochrane systematic review [564] and a large propensity score matched analysis [565]. The Cochrane review used the most rigorous methodology and analysed 5 RCTs with 502 patients. It found with moderate certainty that RS-RARP improved continence at 1 week post catheter removal compared to standard RARP (RR: 1.74). Continence may also be improved at 3 months post-operatively (RR: 1.33), but this was based on low-certainty data. Continence outcomes appeared to equalise by 12 months (RR: 1.01). These findings matched those of the other systematic reviews. However, a significant concern was that RS-RARP appears to increase the risk of positive margins (RR: 1.95) but this was also low-certainty evidence. A single-surgeon propensity score matched analysis of 1,863 patients reached the same conclusion as the systematic reviews regarding earlier return to continence but did not show data on margin status [565].

Based on these data, recommendations cannot be made for one technique over another. However, the trade-offs between the risks of a positive margin vs. earlier continence recovery should be discussed with prospective patients. Furthermore, no high-level evidence is available on high-risk disease with some concerns that RS-RARP may confer an increased positive margin rate based on pT3 results. In addition, RS-RARP may be more technically challenging in various scenarios such as anterior tumours, post-TURP, a grossly enlarged gland, or a bulky median lobe [566].

#### 6.1.2.3.2 Pelvic lymph node dissection

A systematic review demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [567]. Moreover, two RCTs have failed to show a benefit of an extended approach vs. a limited PLND on early oncologic outcomes [568, 569]. However, it is generally accepted that eLND provides important information for staging and prognosis which cannot be matched by any other currently available procedure [567].

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 [570].

The individual risk of patients harbouring positive LNs can be estimated based on validated nomograms. The Briganti nomogram [426, 427], the Roach formula [571] or the Partin and MSKCC nomograms [572] have

shown similar diagnostic accuracy in predicting LN invasion. These nomograms have all been developed in the pre-MRI setting based on systematic random biopsy. A risk of nodal metastases over 5% can be used to identify candidates for nodal sampling by eLND during RP [573-575].

An updated nomogram has been externally validated in men diagnosed based on MRI followed by MRI-targeted biopsy [427]. Based on this nomogram patients can be spared an ePLND if their risk of nodal involvement is less than 7%; which would result in missing only 1.5% of patients with nodal invasion [427, 430]. This 7% cut-off is comparable to the 5% cut-off of the Briganti nomogram in patients diagnosed by systematic random biopsy alone. Therefore, this novel nomogram and a 7% threshold should be used after MRI-targeted biopsy to identify candidates for eLND [429].

#### 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 [576].

Intraprostatic injections of indocyanine green (ICG) have 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 [577]. A systematic review showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at eLND [578]. However, there is still insufficient high-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) [579-585]. This lymphoid tissue is present in 5.5–10.6% of cases and contains metastatic PCa in up to 1.3% of intermediate- and high-risk patients.

When positive, the PAFP is often the only site of LN metastasis. The PAFP is therefore a rare but recognised route of spread of disease. Unlike PLND, there is no morbidity associated with removal of the PAFP. The PAFP is always removed at RP for exposure of the endopelvic fascia and should be sent for histologic analysis as per all removed tissue.

#### 6.1.2.3.5 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 [546]. In the open setting, blood loss and transfusion rates have been found to be significantly reduced when ligating the DVC prior to transection [586]. 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 [587]. In another study, mean blood loss was significantly less with prior DVC ligation (184 vs. 176 mL,  $p = 0.033$ ), however it is debatable whether this was clinically significant [588]. 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 [589].

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 [590, 591].

Although age and pre-operative function may remain the most important predictors for post-operative erectile function, nerve-sparing has also been associated with improved continence outcomes and



may therefore still be relevant for men with poor erectile function [592, 593]. 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 [592].

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 [594-597]. Furthermore, many different techniques are propagated such as retrograde approach after anterior release (vs. antegrade), and athermal and traction-free handling of bundles [598-600]. Nerve-sparing does not compromise cancer control if patients are carefully selected depending on tumour location, size and grade [601-603].

#### 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 [604]. 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 SVs. For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen [605]. 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 [606]. However, a RCT comparing nerve-sparing RP with and without a SV-sparing approach found no difference in margin status, PSA recurrence, continence or erectile function outcomes. 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 [607]. 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 [608].

The development of laparoscopic- and robotic-assisted techniques to perform RP have facilitated the introduction of new suturing techniques for the anastomosis. A systematic review and meta-analysis compared unidirectional barbed suture vs. conventional non-barbed suture for vesico-urethral anastomosis during robotic-assisted laparoscopic prostatectomy (RALP) [609]. The review included 3 RCTs and found significantly reduced anastomosis time, operative time and posterior reconstruction time in favour of the unidirectional barbed suture technique, but there were no differences in post-operative leak rate, length of catheterisation and continence rate. However, no definitive conclusions could be drawn due to the relatively low quality of the data. In regard to suturing technique, a systematic review and meta-analysis compared continuous vs. interrupted suturing for vesico-urethral anastomosis during RP [610]. The study included only one RCT with 60 patients [611]. Although the review found slight advantages for continuous suturing over interrupted suturing in terms of catheterisation time, anastomosis time and rate of extravasation, the overall quality of evidence was low and no clear recommendations were possible. A recent RCT [612] compared the technique of suturing using a single absorbable running suture vs. a double-needle single-knot running suture (i.e. Van Velthoven technique) in laparoscopic RP [613]. 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 [608-619].

#### 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 with the aim of securing a mucosa-to-mucosa vesico-urethral anastomosis and avoiding anastomotic stricture. Whilst bringing bladder and urethral mucosa together by the everted bladder mucosa covering the bladder muscle layer, this



step may actually delay healing of the muscle layers. An alternative is to simply ensure bladder mucosa is included in the full thickness anastomotic sutures. A non-randomised study of 211 patients with and without bladder neck mucosal eversion showed no significant difference in anastomotic stricture rate [620]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [621].

#### *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 [622]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. A RCT assessing continence recovery at 12 months and 4 years showed improved objective and subjective urinary continence in both the short- and long term without any adverse effect on oncological outcome [623]. These findings were confirmed by a systematic review [624]. 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 [622]. This study was inconclusive, but it would be sensible to exercise caution when considering bladder neck preservation if significant cancer is known to be at the prostate base. Bladder neck preservation should be performed routinely when the cancer is distant from the base. However, bladder neck preservation cannot be performed in the presence of a large median lobe or a previous TURP.

#### 6.1.2.3.11 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 [625]. Therefore, it is likely that preservation of as much urethral length as possible during RP will maximise the chance of early return to continence. It may also be useful to measure urethral length pre-operatively to facilitate counselling of patients on their relative likelihood of early post-operative continence.

#### 6.1.2.3.12 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 SOC before catheter removal 8 to 10 days after surgery [626]. 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 [627, 628]. Contrast-enhanced transrectal US is an alternative [629].

#### 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 vesicourethral anastomosis heals. Compared to a traditional catheter duration of around 1 week, some centres remove the transurethral catheter early (post-operative day 2–3), usually after thorough anastomosis with posterior reconstruction or in patients selected peri-operatively on the basis of anastomosis quality [630–633]. 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 [634]. 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 [635].

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 [636–640], while others did not find any differences [641, 642]. 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 [643, 644]. 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. Systematic reviews have documented complication rates after RALP [555, 645–648], and can be compared with contemporaneous reports after radical RRP [649]. A prospective controlled non-RCT of patients undergoing RP in 14 centres using RALP or RRP showed that 12 months after RALP, 21.3% of patients were incontinent, as were 20.2% after RRP (adjusted OR: 1.08, 95% CI: 0.87–1.34) [650]. 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) [650].

A systematic review and meta-analysis of unplanned hospital visits and re-admissions post-RP analysed 60 studies with over 400,000 patients over a 20-year period up to 2020. It found an emergency room visit rate of 12% and a hospital re-admission rate of 4% at 30 days post-operatively [651].

A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at 2 years [549]. 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 8.3.2.1).

##### 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 [652, 653]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to 1 pad per day (median 18 vs. 30 days,  $p = 0.024$ ) [654]. 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 [655].

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 [656]. 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%,  $p = 0.609$ ) [657]. 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 [658]. 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%,  $p = 0.313$ ) [659]. 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 [660]. 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 [555])**

Predicted probability of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep-vein thrombosis	0.6	0.2	1.4
Predicted rates of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Clavien 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 [567]. 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 [661]. 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%) [662, 663]. Briganti *et al.*, [664] 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.

### 6.1.3 Radiotherapy

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

#### 6.1.3.1 External beam radiation therapy

##### 6.1.3.1.1 Technical aspects

Intensity-modulated EBRT and volumetric arc external-beam RT (VMAT) employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. Viani *et al.*, show significantly reduced acute and late grade  $\geq 2$  genito-urinary (GU) and gastro-intestinal (GI) toxicity in favour of IMRT, while BCR-free rates did not differ significantly when comparing IMRT with three-dimensional conformal radiation therapy (3D-CRT) in a RCT comprising 215 patients [665]. A meta-analysis by Yu *et al.*, (23 studies, 9,556 patients) concluded that IMRT significantly decreases the occurrence of grade 2–4 acute GI toxicity, late GI toxicity and late rectal bleeding, and achieves better PSA relapse-free survival in comparison with 3D-CRT. Intensity-modulated EBRT and 3D-CRT show comparable acute rectal toxicity, late GU toxicity and OS, while IMRT slightly increases the morbidity of acute GU toxicity [666]. Wortel *et al.*, concluded that, as compared to 3D-CRT, image-guided IMRT was associated with significantly reduced late GI toxicity whereas GU toxicities remained comparable (242 IMRT patients vs. 189 3D-CRT patients) [667]. Finally, Zapatero *et al.*, found, based on 733 consecutive patients (295 IMRT vs. 438 3D-CRT), that compared with 3D-CRT, high-dose IMRT/IGRT is associated with a lower rate of late urinary complications despite a higher radiation dose [668]. In conclusion, IMRT plus IGRT remain the SOC for the treatment of PCa.

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

With dose escalation using IMRT/VMAT, organ movement becomes a critical issue in terms of both tumour control and treatment toxicity. Techniques will therefore combine IMRT/VMAT with some form of IGRT (usually gold marker or cone-beam CT), in which organ movement can be visualised and corrected for in real time, although the optimum means (number of applications per week) of achieving this is still unclear [669, 670].

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

Local control is a critical issue for the outcome of RT of PCa. It has been shown that local failure due to insufficient total dose is prognostic for death from PCa as a second wave of metastases is seen 5 to 10 years later on [671]. Several RCTs have shown that dose escalation (range 74–80 Gy) has a significant impact on 10-year biochemical relapse as well as metastases and disease-specific mortality [672-679]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant HT has varied (see Table 6.1.6). The best evidence of an OS benefit in patients with intermediate- or high-risk PCa, but not with low-risk PCa, derives from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database including a total of 42,481 patients [680]. The concept of a focal boost to the dominant intraprostatic lesion in the MRI has been successfully validated in a RCT of 571 intermediate- and high-risk patients [681]. Patients were randomised between 77 Gy in 35 fractions of 2.2 Gy and the same dose plus a focal boost up to 18 Gy. Additional ADT was given to 65% of patients in both arms. However, the duration of the ADT was not reported. With a median follow-up of 72 months there was a moderate improvement of biochemical PFS (primary endpoint) only. No significant difference for late GU- or GI toxicity grade  $\geq 2$  (23% and 12% vs. 28% and 13%) was documented. For grade  $\geq 3$  GU-toxicity these numbers were 3.5% and 5.6% ( $p > 0.05$ ). However, longer follow-up is needed to assess late GU-toxicity. Of note, there was a clear decrease in biochemical failure with increasing boost dose, individually given up to 18 Gy. In everyday practice, a minimum dose of  $> 74$  Gy is recommended for EBRT plus HT, with no different recommendations according to the patient's risk group. If IMRT/VMAT and IGRT are used for dose escalation, rates of severe late side effects ( $>$  grade 3) for the rectum are 2–3% and for the GU tract 2–5% [674, 677, 682-695].

**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 [679]	301	T1-T3, N0, M0, PSA $\leq 10$ ng/mL PSA 10-20 ng/mL PSA $> 20$ ng/mL	70 vs.78 Gy	15 yr.	DM, DSM, FFF	All patients: 18.9% FFF at 70 Gy 12% FFF at 78 Gy ( $p = 0.042$ ) 3.4% DM at 70 Gy 1.1% DM at 78 Gy ( $p = 0.018$ ) 6.2% DSM at 70 Gy 3.2% DSM at 78 Gy ( $p = 0.043$ ) No difference in OS ( $p > 0.05$ )
PROG 95-09 2010 [673]	393	T1b-T2b PSA $\leq 15$ ng/mL 75% low-risk pts. Low-risk: T1-2a, PSA $< 10$ mg/mL, GS $\leq 6$ Interm-risk: PSA 10-15 ng/mL or GS 7 or T2b High-risk: GS 8-10	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	8.9 yr.	10-yr. ASTRO BCF	All patients: 32% BF at 70.2 Gy 17% BF at 79.2 Gy ( $p < 0.0001$ ) Low-risk patients: 28% BF at 70.2 Gy 7% BF at 79.2 Gy ( $p < 0.0001$ )
MRC RT01 2014 [678]	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 [677]	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 [676]	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 [672]	1,532	T1b-T2b ISUP grade 1 + PSA 10-20 ng/mL or ISUP grade 2/3 + PSA < 15 ng/mL	70.2 vs. 79.2 Gy	100 mo.	OS, DM, BCF (ASTRO)	75% OS at 70.2 Gy 76% OS at 79.2 Gy 6% DM at 70.2 Gy 4% DM at 79.2 Gy (p = 0.05) 47% BCF at 70.2 Gy 31% BCF at 79.2 Gy (p < 0.001; Phoenix, p < 0.001)
FLAME Trial [681]	571	EAU risk classification: Intermediate risk (15%) High risk (84%)	77 Gy (35 fx. 2.2 Gy) vs. 77 Gy (35 Fx.) + focal boost (up to 18 Gy) ADT (65% both arms – duration unknown)	72 mo. (median)	BFS (5 yr.) DSM (5 yr.)	BFS: 92% at 77 Gy + boost 85% at 77 Gy (p < 0.001, HR: 0.45) DSM: p = 0.49

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

#### 6.1.3.1.3 Hypofractionation

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue and slowly proliferating cells are very sensitive to an increased dose per fraction [696]. 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 [697]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at lower cost.

Moderate HFX is defined as RT with 2.5–3.4 Gy/fx. Several studies report on moderate HFX applied in various techniques also including HT in part [698-708]. A systematic review concluded that studies on moderate HFX (2.5–3.4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy but long-term efficacy data are still lacking [707]. These results were confirmed by a recent Cochrane review on moderate HFX for clinically localised PCa [709]. Eleven studies were included (n = 8,278) with a median follow-up of 72 months showing little or no difference in PCa-specific survival (HR: 1.00). Based on 4 studies (n = 3,848), hypofractionation probably makes little or no difference to late radiation GU toxicity (RR: 1.05) or GI toxicity (RR: 1.1), but this conclusion is based on relatively short follow-up, and 10 to 15-year data will be required to confirm these findings [709].

Moderate HFX should only be done by experienced teams using high-quality EBRT using IGRT and IMRT/VMAT and published phase III protocols should be adhered to (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 [702]	550 542	low risk	None	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	<b>5 yr. DFS 86.3%</b> (n.s.) <b>5 yr. DFS 85.3%</b>
Dearnaley, <i>et al.</i> CHHiP 2012 [698] and 2016 [703]	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	<b>5 yr. BCDF 85.9% (19 fx)</b> <b>90.6% (20 fx)</b> <b>88.3% (37 fx)</b>



Aluwini, <i>et al.</i> , 2016 & De Vries, <i>et al.</i> , 2020 [704, 710]	403 392	30% ISUP grade 1 45% ISUP grade 2-3, 25% ISUP grade 4-5	None	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	89	<b>8-yr. OS 80.8% vs. 77.6%</b> (p = 0.17)  <b>8 yr. TF 24.4% vs. 26.3%</b>
Catton, <i>et al.</i> 2017 [706]	608	intermediate risk 53% T1c 46% T2a-c	None	60 Gy/20 fx	77.1	72	<b>5 yr. BCDF both arms 85%</b> 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; ISUP = International Society of Urological Pathology; mo. = month; n = number of patients; NCCN = National Comprehensive Cancer Network; n.s. = not significant; TF = treatment failure; yr. = year.

Ultra-HFX has been defined as RT with > 3.4 Gy per fraction [708]. It requires IGRT and stereotactic body RT (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 full long-term side effects may not yet be known [707, 711, 712]. 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 [713]. 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 biochemical recurrence-free survival (BRFS) rates were 95.3% and 93.7%, respectively, and estimated late grade  $\geq 3$  GU and GI toxicity rates were 2.0% and 1.1%, respectively [714]. The authors conclude that there is sufficient evidence to support SBRT as a standard treatment option for localised PCa, even though the median follow-up in this review was only 39 months and it included at least one trial (HYPO-RT-PC) which used 3D-CRT in 80% and IMRT/VMAT in the remainder for ultra-HFX. In their review on SBRT, Cushman 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 [715]. In the Intensity-modulated fractionated RT vs. stereotactic body RT for PCa (PACE-B) trial, acute grade  $\geq 2$  GU or GI toxicities did not differ significantly between conventional fractionation and ultra-HFX [716]. Adopting planning dose constraints to the penile bulb might minimise ED, especially in younger patients [717].

First results of a small (n = 30) randomised phase-II trial in intermediate-risk PCa of 'ultra-high single dose RT' (SDRT) with 24 Gy compared with an extreme hypofractionated stereotactic body RT regime with 5x9 Gy to the prostate, have been published recently (see Table 6.1.8) [718]. The primary endpoint was toxic effects. With a median follow-up of 48 months SDRT was relatively well tolerated even though there was a trend towards a higher rate of GU side effects after SDRT at all time points. Longer follow-up should be awaited before any conclusion from this approach can be drawn. In conclusion, 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**

Study	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark <i>et al.</i> 2019 HYPO-RT-PC [713]	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 [716]	847	variable	8% low 92% intermediate	78 Gy / 39 fx, 8 wk. 36.25 Gy / 5 fx, 1-2 wk. SBRT	Grade $\geq$ 2 acute GI 12% vs. 10%, p = 0.38 Grade $\geq$ 2 acute GU 27% vs. 23%, p = 0.16
Greco <i>et al.</i> , 2021 PROSINT Randomised phase 2 [718]	30	48	100% intermediate	24 Gy (single dose) 45 Gy, 5 fx, daily SBRT No ADT	Primary endpoint: 'toxic effects'  Grade 1 late GU: HR: 0.41 (in favour of SBRT) Grade $\geq$ 2 late GU: HR: 1.07  Grade 1 late GI: HR: 0.37 (in favour of SBRT)

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

#### 6.1.3.1.4 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with LHRH ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [719-723] (Table 6.1.9). The main message is that for all intermediate-risk disease a short duration of around 6 months is optimal while a longer one, around 3 years, is needed for high-risk patients, as per NCCN definition (see Section 4.2). The OS impact of adding short-term ADT for favourable intermediate-risk disease, however, remains a matter of debate [91].

A meta-analysis based on individual patient data from two RCTs (RTOG 9413 and Ottawa 0101) has compared neoadjuvant/concomitant vs. adjuvant ADT (without substratifying between favourable- and unfavourable intermediate-risk disease) in conjunction with prostate RT and reported superior PFS with adjuvant ADT [724]. This is an important observation, which should influence future clinical trial design and evaluation of outcomes. However, there are differences between the two trials in patient characteristics, exact scheduling of neoadjuvant +/- concomitant ADT, hormonal preparation, and RT schedule. At present, either neoadjuvant or adjuvant ADT remain acceptable options for patients requiring short-term ADT in conjunction with EBRT.

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

Study	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [720]	T3 or N1 M0	977	EBRT $\pm$ ADT	Orchiectomy or LHRH agonist 15% RP	65–70 Gy	<b>Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade 2-5</b>
RTOG 94-13 2007 [725]	T1c–4 N0–1 M0	1,292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	<b>No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)</b>
RTOG 86-10 2008 [721]	T2–4 N0–1	456	EBRT $\pm$ ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65–70 Gy RT	<b>No significant difference at 10 yr.</b>

D'Amico AV, <i>et al.</i> 2008 [722]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	<b>Significant benefit that may pertain only to men with no or minimal co-morbidity</b> (HR: 0.55, 95% CI: 0.34–0.90, p = 0.01)
RTOG 92-02 2008 [726]	T2c–4 N0–1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65–70 Gy	p = 0.73, p = 0.36 <b>overall</b> ; <b>significant benefit</b> (p = 0.044) (p = 0.0061) <b>in subset with ISUP grade 4–5</b>
EORTC 22961 2009 [727]	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	<b>Better result with 3 yr. treatment than with 6 mo.</b> (3.8% improvement in survival at 5 yr.)
EORTC 22863 2010 [719]	T1–2 poorly differentiated and M0, or T3–4 N0–1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70 Gy RT	<b>Significant benefit at 10 yr. for combined treatment</b> (HR: 0.60, 95% CI: 0.45–0.80, p = 0.0004).
TROG 96-01 2011 [723]	T2b–4 N0 M0	802	Neoadjuvant ADT Duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	<b>No significant difference in OS reported; benefit in PCa-specific survival</b> (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 [728]	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	<b>67 vs. 68%</b> , 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 by 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**

Study	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [729]	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 [730] and 2015 [731]	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, <i>et al.</i> 2020 [732]	T3–4 N0 M0	273	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr. OS 71.4% vs. 71.5%

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

#### 6.1.3.1.5 Combined dose-escalated radiotherapy and androgen-deprivation therapy

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. Three-dimensional conformal RT or IMRT were administered [733]. 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 (69%), 456 intermediate-risk (42%) and 170 low-risk (30%) PCa 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. Four RCTs have shown that the benefits of ADT are independent of dose escalation, and that the use of ADT would not compensate for a lower RT dose:

1. The GICOR study shows a better biochemical DFS in high-risk patients for 3D-CRT radiation dose > 72 Gy when combined with long-term ADT [687].
2. DART01/05 GICOR shows improved biochemical control and OS in high-risk patients if 2 years of adjuvant ADT is combined with high-dose RT [734].
3. EORTC trial 22991 shows that 6 months ADT improves biochemical and clinical DFS irrespective of the dose (70, 74, 78 Gy) in intermediate-risk and low-volume high-risk localised PCa patients [735].
4. A Canadian trial of 600 intermediate-risk patients showed that the addition of ADT to EBRT reduced biochemical failure and PCa deaths, in patients treated with either 70 Gy or 76 Gy [736].

A *post-hoc* meta-analysis of two RCTs has suggested that concomitant/adjuvant ADT may be superior to neoadjuvant ADT, but their heterogeneity means that this observation is hypothesis-generating only [724]. However, a Canadian two-arm dose-escalated (76 Gy) RCT compared neoadjuvant and concomitant with adjuvant short-term ADT in 432 patients with intermediate-risk PCa. After 10 years no significant difference in OS or RT-related grade  $\geq 3$  GI or GU toxicity was seen [737]. Therefore both regimen in combination with dose escalation are reasonable standards [737].

#### 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 [673]. Thus, unequivocal information showing an advantage of protons over IMRT photon therapy is still not available. Studies from the SEER database and from Harvard describing toxicity and patient-reported outcomes do not point to an inherent superiority of protons [738, 739]. In terms of longer-term GI toxicity, proton therapy might even be inferior to IMRT [739].

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

#### 6.1.3.3 Spacer during external beam radiation therapy

Biodegradable spacer insertion involves using a liquid gel or balloon to increase the distance between the prostate and rectum and consequently reduce the amount of radiation reaching the rectum. Various materials have been used with most evidence available for CE-marked hydrogel spacers [740]. A meta-analysis including one RCT and six cohort studies using the hydrogel spacer demonstrated a 5–8% reduction in the rectal volume receiving high-dose radiation, although heterogeneity between studies is found [741]. In the final analysis of the RCT with a median follow-up of 37 months and with approximately two-thirds of patients evaluable, those treated with spacer *in situ* had no deterioration from baseline bowel function whilst those treated without spacer had a lower mean bowel summary score of 5.8 points which met the threshold for a minimally important difference of 4–6 points [742].

This meta-analysis highlights inconsistent reporting of procedural complications. In addition, with more widespread clinical use safety reports describe uncommon, but severe and life changing, complications including prostatic abscess, fistulae and sepsis [743]. Implantation is associated with a learning curve and should only be undertaken by teams with experience of TRUS and transperineal procedures with robust audit reporting in place [744]. Its role in the context of moderate or extreme hypofractionation is as yet unclear.

#### 6.1.3.4 Brachytherapy

##### 6.1.3.4.1 Low-dose rate brachytherapy

Low-dose rate (LDR) brachytherapy uses radioactive seeds permanently implanted into the prostate. There is a consensus on the group of patients with the best outcomes after LDR monotherapy [745] for low- or favourable intermediate-risk and good urinary function defined as an International Prostatic Symptom Score (IPSS)  $\leq 12$  and maximum flow rate  $> 15$  mL/min on urinary flow tests, as per NCCN definition (see Section 4.2) [746]. In addition, with due attention to dose distribution, patients having had a previous TURP can undergo brachytherapy without an increase in risk of urinary toxicity. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the postero-lateral sides of the prostate and there should be at least a 3-month interval between TURP and brachytherapy to allow for adequate healing [747-750].

The only available RCT comparing RP and LDR brachytherapy as monotherapy was closed due to poor accrual [751]. Outcome data are available from a number of large population cohorts with mature follow-up [752-759]. The biochemical DFS for ISUP grade 1 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [752-759]. A significant correlation has been shown between the implanted dose and biochemical control [760]. A D90 (dose covering 90% of the prostate volume) of  $> 140$  Gy leads to a significantly higher biochemical control rate (PSA  $< 1.0$  ng/mL) after 4 years (92 vs. 68%). There is no OS benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [761].

Low-dose rate brachytherapy can be combined with EBRT in unfavourable intermediate-risk PCa (See Section 4.2) and high-risk patients. External beam RT (total dose of 78 Gy) has been compared with EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy) in intermediate-risk and high-risk patients in the ASCENDE-RT randomised trial with 12 months of ADT in both arms [762]. The LDR boost resulted in 5- and 7-year PSA PFS increase (89% and 86%, respectively, compared to 84% and 75%). This improvement was achieved at a cost of increased late grade 3+ GU toxicity (18% compared to 8%) [763]. Toxicity resulted mainly in the development of urethral strictures and incontinence and great care should be taken during treatment planning.

##### 6.1.3.4.2 High-dose rate brachytherapy

High-dose rate (HDR) brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in Table 6.1.11. The use of the GEC (Groupe Europeen de Curietherapie)/ESTRO Guidelines is strongly recommended [764]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [765]. A systematic review of non-RCTs and data from population studies suggest outcomes with EBRT plus HDR brachytherapy are superior to EBRT alone [766, 767].

A single centre RCT of EBRT (55 Gy in 20 fractions) vs. EBRT (35.75 Gy in 13 fractions), followed by HDR brachytherapy (17 Gy in two fractions over 24 hours) has been reported [768]. In 218 patients with T1-3 N0M0 PCa the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical disease-free rate ( $p = 0.04$ ) at 5 and 10 years (75% and 46% compared to 61% and 39%). However, an unexpectedly high rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to a dose lower than the current standard used [768].

Supporting, but not definitive, evidence of the benefit of HDR boost is available from the TROG 03.04 RADAR trial. This multi-centre study had upfront radiation dose escalation (non-randomised) with dosing options of 66, 70, or 74 Gy EBRT, or 46 Gy EBRT plus HDR brachytherapy boost and randomised men with locally-advanced PCa to 6 or 18 months ADT. After a minimum follow-up of 10 years HDR boost significantly reduced distant progression, the study primary endpoint (sub HR: 0.68, 95% CI: 0.57-0.80;  $p < 0.0001$ ), when compared to EBRT alone and, independent of duration of ADT, HDR boost was associated with increased IPSS of 3 points at 18 months post-treatment resolving by 3 years but decreased rectal symptoms when compared to EBRT [769].

Although radiation dose escalation using brachytherapy boost provides much higher biological doses, the TROG 03.04 RADAR RCT and systematic reviews show ADT use independently predicts better outcomes regardless of radiation dose intensification [761, 769, 770]. Omitting ADT may result in inferior OS and based on current evidence ADT use and duration should be in line with that used when delivering EBRT alone.

Fractionated HDR brachytherapy as monotherapy can be offered to patients with low- and intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres. Five-year PSA control rates of 97.5% and 93.5% for low- and intermediate-risk PCa, respectively, are reported, with late grade 3+ GU toxicity rates  $< 5\%$  and no, or very minimal, grade 3+ GI toxicity rates [771]. Single fraction HDR monotherapy should not be used as it has inferior biochemical control rates compared to fractionated HDR monotherapy [772].

**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), Palladium-103 (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>

#### 6.1.3.5 Acute side effects of external beam radiotherapy and brachytherapy

Gastro-intestinal and urinary side effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of grade 1, 20% of grade 2, and 2% grade 3. In the same trial, approximately 30% of patients reported acute grade 1 GI toxicity, 10% grade 2, and less than 1% grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [686]. 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 [762]. 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 [773]. Similar findings are reported using HFX; in a pooled analysis of 864 patients treated using extreme HFX and stereotactic RT, declines in urinary and bowel domains were noted at 3 months which returned to baseline, or better, by 6 months [774].

### 6.1.4 Hormonal therapy

#### 6.1.4.1 Introduction

##### 6.1.4.1.1 Different types of hormonal therapy

Androgen deprivation can be achieved by suppressing the secretion of testicular androgens in different ways. This can be combined with inhibiting the action of circulating androgens at the level of their receptor which has been known as complete (or maximal or total) androgen blockade (CAB) using the old-fashioned anti-androgens [775].

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

###### 6.1.4.1.1.1.1 Castration level

The castration level of testosterone is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15 ng/dL [776]. 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 [777-779]. 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 [780].

###### 6.1.4.1.1.1.3 Oestrogens

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [781]. 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 [782-784].



#### 6.1.4.1.1.4 Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly, basis. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the ‘testosterone surge’ or ‘flare-up’ phenomenon which starts two to three days after administration and lasts for about one week. This may lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [785]. 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 [786, 787].

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 [788]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [789]. So far, no survival difference between LHRH agonists and orchiectomy has been reported due to the lack of high-quality trials [790].

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.

#### 6.1.4.1.1.5 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone-releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available. Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [788]. A phase III RCT compared degarelix to monthly leuprorelin following up patients for 12 months, suggesting a better PSA PFS for degarelix 240/80 mg compared to monthly leuprorelin [791]. A systematic review did not show a major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond 12 months as well as the lack of survival data [792]. Its definitive superiority over the LHRH analogues remains to be proven. Short-term follow-up data from a meta-analysis indicate that the use of GnRH antagonist is associated with significantly lower overall mortality and cardiovascular events as compared with agonists. On the other hand, other adverse effects such as decreased libido, hot flushes, ED, weight gain, and injection site reactions are seen less often with the agonists [793, 794].

Relugolix is an oral gonadotropin-releasing hormone antagonist. It was compared to the LHRH agonist leuprolide in a randomised phase III trial [795]. The primary endpoint was sustained testosterone suppression to castrate levels through 48 weeks. There was a significant difference of 7.9 percentage points (95% CI: 4.1–11.8) showing non-inferiority and superiority of relugolix. The incidence of major adverse cardiovascular events was significantly lower with relugolix (prespecified safety analysis). Relugolix has been approved by the FDA [796].

#### 6.1.4.1.1.6 Anti-androgens

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g., cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g., nilutamide, flutamide and bicalutamide.

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

##### 6.1.4.1.1.6.1 Steroidal anti-androgens

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

Cyproterone acetate was the first licensed anti-androgen but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31–41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT CPA showed a poorer OS when compared with LHRH analogues [797]. An underpowered RCT comparing CPA monotherapy with flutamide



in M1b PCa did not show any difference in DSS and OS at a median follow-up of 8.6 years [798]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

#### 6.1.4.1.1.1.6.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy with e.g., nilutamide, flutamide or bicalutamide does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [799]. Non-androgen-related pharmacological side effects differ between agents. Bicalutamide shows a more favourable safety and tolerability profile than flutamide and nilutamide [800]. 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, non-steroidal anti-androgen monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [799, 801]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

#### 6.1.4.1.1.2 New androgen pathway targeting agents (ARTA)

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 [802]. This has led to the development of several new compounds targeting the androgen axis. In mCRPC, AAP and enzalutamide have been approved. In addition to ADT (sustained castration), AAP, apalutamide and enzalutamide have been approved for the treatment of metastatic hormone sensitive PCa (mHSPC) by the FDA and the EMA. For the updated approval status see EMA and FDA websites [803-807]. Finally, apalutamide, darolutamide and enzalutamide have been approved for non-metastatic CRPC (nmCRPC) at high risk of further metastases [808-812].

##### 6.1.4.1.1.2.1 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17 $\alpha$ -hydroxylase 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 [803, 806].

##### 6.1.4.1.1.2.2 Apalutamide, darolutamide, enzalutamide (alphabetical order)

These agents are novel non-steroidal anti-androgens with a higher affinity for the AR receptor than bicalutamide. While previous non-steroidal anti-androgens still allow transfer of ARs to the nucleus and would act as partial agonists, all three agents also block AR transfer and therefore suppress any possible agonist-like activity [807-809]. Darolutamide has structurally unique properties [808]. In particular, in preclinical studies, it showed not to cross the blood-brain barrier [813, 814].

#### 6.1.4.1.1.3 New compounds

##### 6.1.4.1.1.3.1 PARP inhibitors

Poly (ADP-ribose) polymerase inhibitors (PARPi) block the enzyme poly ADP ribose polymerase (PARP) and were developed aiming to selectively target cancer cells harbouring *BRCA* mutations and other mutations inducing homologous recombination deficiency and high level of replication pressure with a sensitivity to PARPi treatment. Due to the oncogenic loss of some DNA repair effectors and incomplete DNA repair repertoire, some cancer cells are addicted to certain DNA repair pathways such as Poly (ADP-ribose) polymerase (PARP)-related single-strand break repair pathway. The interaction between *BRCA* and PARP is a form of synthetic lethal effect which means the simultaneously functional loss of two genes lead to cell death, while a defect in any single gene only has a limited effect on cell viability [815]. The therapeutic indication for PCa is discussed in Section 6.5.8.1.

##### 6.1.4.1.1.3.2 Immune checkpoint inhibitors

Immune checkpoints are key regulators of the immune system. Checkpoint proteins, such as B7-1/B7-2 on antigen-presenting cells (APC) and CTLA-4 on T cells, help keep the immune responses in an equilibrium. The binding of B7-1/B7-2 to CTLA-4 keeps the T cells in the inactive state whilst an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and to kill tumour cells.

Approved checkpoint inhibitors target the molecules CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Programmed death-ligand 1 is the transmembrane programmed cell death 1 protein which interacts with PD-L1 (PD-1 ligand 1). Cancer-mediated upregulation of PD-L1 on the cell surface may inhibit T cells. Antibodies that bind to either PD-1 or PD-L1 and therefore block the interaction may allow the T cells to induce cell killing. Examples of PD-1 inhibitors are pembrolizumab and nivolumab; of

PD-L1 inhibitors, atezolizumab, avelumab and durvalumab and an example of CTLA4 inhibitors is ipilimumab [816, 817]. Therapeutic use is discussed in Section 6.5.10.

#### 6.1.4.1.1.3.3 Protein kinase B (AKT) inhibitors

Aberrant activation of the PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase)/AKT pathway, predominately due to PTEN loss (phosphatase and tensin homologue deleted from chromosome 10), is common in PCa (40–60% of mCRPC) and is associated with worse prognosis. The androgen receptor signalling and AKT pathway are reciprocally cross-regulated, so that inhibition of one leads to upregulation of the other. AKT inhibitors are small molecules which are designed to target and bind to all three isoforms of AKT, which is a key component of the PI3K/AKT pathway and a key driver of cancer cell growth. Ipatasertib is an oral, highly specific, AKT inhibitor which shows clinically significant activity when combined with abiraterone acetate in patients with loss of the tumour suppressor protein PTEN (on IHC) within the tumour [818, 819]. The therapeutic indication for PCa is discussed in Section 6.5.6.5.

#### 6.1.4.1.1.3.4 Radiopharmaceutical therapy

Radiopharmaceutical therapy (RPT) is based on the delivery of radioactive atoms to tumour-associated targets. The mechanism of action for RPT is radiation-induced killing of cells. Radionuclides with different emission properties are used to deliver radiation. The most commonly used radionuclides are represented by  $\beta$ -particles (e.g.,  $^{177}\text{Lu}$ ) or  $\alpha$ -particles (e.g.  $^{223}\text{Ra}$ ,  $^{225}\text{Ac}$ ).  $^{177}\text{Lu}$  is increasingly used because of its optimal imaging range (100–200 keV), favourable half time (6.6 days) and appropriate  $\beta$ -particle energy for therapy.

The short path of the  $\beta$ -particles (0.05–0.08 mm) results in minimal toxic effects in adjacent healthy tissue. These properties enable such radionuclides to be used as theranostics (i.e., the same radionuclide may be used for both diagnostic and therapeutic purposes). However, an essential requirement prior to any RPT is to assess the targeting of the agent, mainly using PET techniques which show the tumour expression and the extent of cancer [820].

### 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 [821-824]. 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 (RFA) and electroporation, among others, are considered to be in the early phases of evaluation [825]. In addition, a relatively newer development is focal ablative therapy [825, 826] 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 [821-824]. 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  $-40^{\circ}\text{C}$  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%) [827]. 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 [827].

#### 6.1.5.3 *High-intensity focused ultrasound*

High-intensity focused US consists of focused US waves emitted from a transducer that cause tissue damage by mechanical and thermal effects as well as by cavitation [828]. The goal of HIFU is to heat malignant tissue above  $65^{\circ}\text{C}$  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%) [827]. 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 [827].

#### 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 that men are identified 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 [829–831]. 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 [832–834].

A systematic review and network meta-analysis on ablative therapy in men with localised PCa performed a sub-group analysis of focal therapy vs. RP and EBRT [827]. 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.*, performed a systematic review to summarise the evidence regarding the effectiveness of focal therapy in localised PCa [826]. 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 and 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 between 1<sup>st</sup> January 2000 and 12<sup>th</sup> June 2020 [835]. In brief, out of 1,119 articles identified, 4 primary studies (1 RCT and 3 retrospective cohort studies) [836–840] recruiting 3,961 patients, and 10 systematic reviews were included [827]. Only qualitative synthesis was possible due to clinical heterogeneity. Overall risk of bias (RoB) and confounding were moderate to high. Comparative effectiveness data regarding focal therapy were inconclusive. Data quality and applicability were poor due to clinical heterogeneity, RoB and confounding, lack of long-term data, inappropriate outcome measures and poor external validity. The majority of systematic reviews had a low or critically low confidence rating.

The only identified RCT, Azzouzi *et al.*, deserves discussion [836]. The authors compared 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, that less patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24–0.46), and needed less radical therapy (6% vs. 29%,  $p < 0.0001$ ). 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 showing that these benefits were maintained after four years [837]. 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 which may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy or any MRI scanning, which is not representative of contemporary practice. 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 [841] are needed before unrestricted recommendations in support of focal therapy for routine clinical practice can be made [825, 841, 842]. For now, the available evidence indicates that focal therapy should be performed within the context of a clinical trial setting or well-designed prospective cohort study. It is hoped that more mature and robust data demonstrating long-term efficacy in the next few years will provide the necessary evidence which will facilitate its wider implementation and acceptance.

## 6.1.6 General guidelines for the treatment of prostate cancer

Recommendations	Strength rating
Inform patients that based on robust current data with up to 12 years of follow-up, no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all active local 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, magnetic resonance imaging, or with this information combined into a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
<b>Radiotherapeutic treatment</b>	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease.	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
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or intermediate-risk disease with ISUP grade 2 and ≤ 33% of biopsy cores involved.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10–20 ng/mL.	Weak
Offer LDR or HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak
<b>Active therapeutic options outside surgery or radiotherapy</b>	
Offer whole-gland cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

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

##### 6.2.1.1.1 Active surveillance - inclusion criteria

Guidance regarding selection criteria for AS is limited by the lack of data from prospective RCTs. As a consequence, the Panel undertook an international collaborative study involving healthcare practitioners and patients to develop consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS (DETECTIVE Study) [284], as well as a formal systematic review on the various AS protocols [843]. The criteria most often published include: ISUP grade 1, clinical stage cT1c or cT2a, PSA < 10 ng/mL and PSA-D < 0.15 ng/mL/cc [517, 844]. The latter threshold remains controversial [844, 845]. These criteria were supported by the DETECTIVE consensus. There was no agreement on the maximum number of cores that can be involved with cancer or the maximum percentage core involvement (CI), although there was recognition that extensive disease on MRI should exclude men from AS [284]. A systematic review and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, which included PSA-D, > 2 positive cores, and African-American race [846]. In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were

present: predominant ductal carcinoma (including pure intraductal carcinoma), cribriform histology, sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [382] and perineural invasion [847].

Recently, a multidisciplinary consensus conference on germline testing attempted to develop a genetic implementation framework for the management of PCa [165]. Based on consensus, *BRCA2*-gene testing was recommended for AS discussions. However, the nature of such discussions and how a positive result influences management were beyond the scope of the project. Currently, if included in AS programmes, patients with a *BRCA2* mutation should be cautiously monitored until such time that more robust data are available.

#### 6.2.1.1.2 Tissue-based prognostic biomarker testing

Biomarkers, including Oncotype Dx<sup>®</sup>, Prolaris<sup>®</sup>, Decipher<sup>®</sup>, PORTOS and ProMark<sup>®</sup> are promising (see Section 5.2.8.3). However, further data will be needed before such markers can be used in standard clinical practice [236].

#### 6.2.1.1.3 Magnetic resonance imaging for selection for active surveillance

In men eligible for AS based upon systematic biopsy findings alone who did not have a pre-biopsy MRI, a re-biopsy within 6–12 months (usually referred to as ‘confirmatory biopsy’) seems mandatory to exclude sampling error [844, 848]. Magnetic resonance imaging can also improve the detection of aggressive cancers [849, 850]. A systematic review showed that men with positive baseline MRI have an, approximately, 3-fold higher chance (RR: 2.77, 95% CI: 1.76–4.38) of upgrading to an ISUP grade  $\geq 2$  cancer than men with negative MRI [851]. More recent studies of patients on AS for ISUP 1 cancer confirmed that a positive baseline MRI was a significant predictor of upgrading to ISUP grade  $\geq 2$  cancer and of unfavourable disease at RP [852, 853]. This is also true when upgrading is defined as progression to ISUP grade  $\geq 3$  cancer [854, 855]. Of note, MRI keeps its significant predictive power for upgrading when other strong predictors such as age or PSA-D are accounted for [853, 855, 856].

At confirmatory biopsy, adding MRI-targeted biopsy to systematic biopsy improves upgrade detection rates by increments of 3.3 to 7.9 per 100 men depending on the series [857]. However, systematic biopsy retains substantial added value [851].

A meta-analysis evaluated the proportion of men eligible for AS based on systematic TRUS-guided biopsy in whom the cancer was upgraded by MRI-targeted biopsy (17%) and systematic biopsy (20%) at confirmatory biopsy [851]. Ten percent of patients were upgraded by both biopsy methods, meaning MRI-targeted biopsy upgraded an additional 7% (95% CI: 5–10%) of men, whilst systematic biopsy upgraded an additional 10% of men (95% CI: 8–14%). Even if the analysed series used different definitions for cancer upgrading, combining the two biopsy techniques appears to be 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). After 2 years of follow-up, use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%,  $p = 0.017$ ) and in fewer patients progressing to ISUP grade  $\geq 2$  cancer (9.9% vs. 23%,  $p = 0.048$ ) [858].

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 [284].

#### 6.2.1.1.4 Follow-up during active surveillance

Based on the DETECTIVE consensus study, the follow-up strategy should be based on serial DRE (at least once yearly), PSA (at least once, every 6 months) and repeated biopsy. It was also agreed that PSA progression or change in PSA kinetics alone should lead to reclassification only if accompanied by changes in histology on repeat biopsy [284].

In 2016, the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria were established to standardise the assessment of tumour progression on serial MRI [859]. Progression on MRI, defined using the PRECISE criteria, or not, is a strong predictor of histological upgrading [860]. Two independent meta-analyses assessed the value of MRI progression criteria for predicting histological progression (mostly defined as progression to ISUP grade  $\geq 2$ ). The pooled histological progression rate was 27% in both reviews. If biopsies were triggered only by MRI progression findings, approximately two thirds of the biopsies would be avoided, at the cost of missing 40% of men with histological progression. In addition, at least half of biopsied men would have had negative findings for histological progression and thus would have undergone unnecessary biopsies. If histological progression was restricted to progression to ISUP grade  $\geq 3$ , approximately 30% of histological progression would be missed and approximately 80% of the biopsies performed would be unnecessary. The use of the PRECISE criteria did not seem to change these results [861, 862].

Combining MRI finding with PSA-D [855, 863, 864] or PSA kinetics [850, 865] may improve the prediction of histological progression, prompting, for example, the biopsy of all patients with elevated PSA-D



regardless of MRI findings, or avoiding biopsy only when MRI does not show progression and the PSA level is stable. Combining MRI with other biomarkers may also help selecting patients for follow-up biopsy [866, 867]. Nonetheless, the level of evidence of these studies remains low and therefore, protocol-mandated, untriggered follow-up biopsies seem necessary [284].

A Panel systematic review incorporating 263 surveillance protocols showed that 78.7% of protocols mandated per-protocol confirmatory biopsies within the first 2 years and that 57.7% of the protocols performed repeat-biopsy at least every 3 years for 10 years after the start of AS [843]. In a single centre AS cohort of 514 patients who underwent at least three protocol-mandated biopsies after diagnosis (the confirmatory biopsy and at least two additional surveillance biopsies), men with one negative biopsy (i.e., no cancer at all) at confirmatory or second biopsy, or men with two consecutive negative biopsies had a lower likelihood of positive third biopsy and significantly better 10-year treatment-free survival [868]. This suggests that men with repetitive negative biopsies may pursue AS with at least less frequent untriggered biopsies.

#### 6.2.1.1.5 Active Surveillance - change in treatment

Men may remain on AS whilst they continue to consent, have a life expectancy of > 10 years and the disease remains indolent. Patient anxiety about continued surveillance occurs in around 10% of patients on AS [869] and was recognised as a valid reason for active treatment [284]. More common is the development of other co-morbidities which may result in a decision to transfer to a WW strategy.

A PSA change alone (including PSA-DT < 3 years) should not change management based on its weak link with grade progression [870, 871] but rather trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting that a change in PSA should lead to repeat-MRI and repeat-biopsy. It was also agreed that changes on follow-up MRI needed a confirmatory biopsy before considering active treatment [284].

However, the histopathology criteria required to trigger a change in management in the targeted biopsy era remain debated. Magnetic resonance imaging-targeted biopsy induces a grade shift and ISUP 2-3 cancers detected by MRI-targeted biopsy have, on average, better prognosis than those detected by systematic sampling (see Section 5.2.4.2.6.4). As an increasing number of men with favourable intermediate-risk disease are managed with AS, it seems illogical to use progression to ISUP grade 2 based on targeted biopsies as the sole criterion for reclassification. In addition, as acknowledged in the DETECTIVE consensus meeting, the number of positive cores is not an indicator of tumour volume anymore if targeted biopsies are performed [284, 866]. No agreement could be reached on the pathological criteria required to trigger a change in management during the DETECTIVE consensus meeting [284]. However, based on the findings of a systematic review incorporating 271 reclassification protocols, patients with low-volume ISUP 2 disease at recruitment, and with increased core positivity (> 3 cores) and/or core involvement (> 50% per core) on repeat systematic biopsies not using MRI, should be reclassified [843].

#### 6.2.1.2 Alternatives to active surveillance

In terms of alternatives to AS in the management of patients with low-risk disease there is some data from randomised studies. In the PIVOT trial (Section 6.1.1.3.1) which compared surgery vs. observation, only 42% of patients had low-risk disease [527]. Sub-group analysis revealed that for low-risk disease there was no statistically significant difference in all-cause mortality between surgery vs. observation (RR: 0.93, 95% CI: 0.78–1.11). In the ProtecT study (Section 6.1.1.4) which compared AM vs. surgery vs. EBRT, 56% of patients had low-risk disease [516]. However, no sub-group analysis on disease risk was performed on this population. The study found no difference between the three arms in terms of OS and CSS, but AM had higher metastatic progression compared with surgery or EBRT (6.0% vs. 2.6%). There are no robust data comparing contemporary AS protocols with either surgery or EBRT in patients with low-risk disease. On balance, although AS should be the default management strategy in patients with low-risk disease and a life expectancy > 10 years, it would be reasonable to consider surgery and EBRT as alternatives to AS in patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.

##### 6.2.1.2.1 ADT monotherapy

Data regarding the use of ADT monotherapy in men with low-risk localised disease may be inferred indirectly from the Early Prostate Cancer (EPC) Trial Programme which published its findings in 2006 [872]. The EPC programme comprises three large RCTs including 8,113 men with localised (cT1–2, N0/NxM0) or locally advanced (cT3–4, any N; or any T, N+, M0) PCa. The intervention was oral bicalutamide 150 mg monotherapy vs. placebo following standard care (defined as RP, radical EBRT or WW). The primary endpoints were PFS and OS. Patients were stratified according to clinical stage only; data regarding PSA and Gleason score were not assessed. The authors found in patients with localised disease, ADT monotherapy did not improve PFS nor OS in any of the subgroups, compared with placebo. Instead, there was a statistically insignificant numerical



trend towards worse OS with ADT in the WW sub-group (HR: 1.16, 95% CI: 0.99–1.37; p = 0.07). Although the trial did not directly address men with low-risk disease, it offered some evidence suggesting that otherwise asymptomatic men with localised disease should not receive ADT monotherapy. Currently, there is no evidence supporting the use of ADT monotherapy in asymptomatic men with low-risk disease who are not eligible for any local/radical treatment; these men should simply be offered WW alone.

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

### 6.2.1.3 Summary of evidence and guidelines for the treatment of low-risk disease

Summary of evidence	LE
Systematic biopsies have been scheduled in AS protocols, the number and frequency of biopsies varied, there is no approved standard.	NR

Recommendations	Strength rating
<b>Active surveillance (AS)</b>	
<i>Selection of patients</i>	
Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong
Perform magnetic resonance imaging (MRI) before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
<i>Follow-up of patients</i>	
Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
In case of prostate-specific antigen progression or change in digital-rectal examination or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
<b>Active treatment</b>	
Offer surgery or 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
<i>Pelvic lymph node dissection (PLND)</i>	
Do not perform a PLND.	Strong
<i>Radiotherapeutic treatment</i>	
Offer low-dose rate brachytherapy to patients with low-risk PCa and good urinary function.	Strong
Use intensity-modulated radiation therapy/volumetric modulated arc therapy plus image-guided 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 (ADT).	Strong
<b>Other therapeutic options</b>	
Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Strong
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 [873]. These estimates are based on systematic biopsies and may be overestimated in the era of MRI-targeted biopsies.

#### 6.2.2.1 Active Surveillance

In the ProtecT trial, up to 22% of the randomised patients in the AM arm had ISUP grade > 1 and 10% a PSA > 10 ng/mL [516]. A Canadian consensus group proposes that low volume ISUP grade 2 (< 10% Gleason pattern 4 on systematic biopsies) may also be considered for AS. These recommendations have been endorsed by the American Society of Clinical Oncology (ASCO) [874] and the recent DETECTIVE consensus

meeting [284] for those patients with a PSA < 10 ng/mL and low core positivity. The DETECTIVE Study concluded that men with favourable ISUP 2 cancer (PSA < 10 ng/mL, clinical stage ≤ cT2a and a low number of positive systematic cores) should also be considered for deferred treatment [284]. In this setting, re-biopsy within 6 to 12 months to exclude sampling error is mandatory [844, 848] even if this could be modified in the future [875]. The DETECTIVE consensus group were clear that those with ISUP 3 disease should not be considered for AS. It is clear that the presence of any grade 4 pattern is associated with a 3-fold increased risk of metastases compared to ISUP grade 1, while a PSA up to 20 ng/mL might be an acceptable threshold [848, 876, 877], especially in the context of low PSA-D. In addition, it is likely that MRI and targeted biopsies will detect small foci of Gleason 4 cancer that might have been missed with systematic biopsy. Therefore, care must be taken when explaining this treatment strategy especially to patients with the longest life expectancy.

Enikeev *et al.*, performed a systematic review and meta-analysis to assess the outcomes of AS in patients with intermediate-risk PCa to summarise available data on its oncological outcomes in comparison with low-risk disease [878]. The definition of AS was not provided by the authors; instead the search strategy included 'active surveillance' as a search term, and no *a priori* study protocol was available. The primary outcome was the proportion of patients who remained on AS, whilst secondary outcomes included CSS, OS, and metastasis-free survival. Seventeen studies were included, incorporating 6,591 patients with intermediate-risk disease. Sixteen studies included patients with low- and intermediate-risk disease, hence enabling comparative outcome assessment via pooled analysis. Only one study performed MRI at recruitment and follow-up. There was significant clinical heterogeneity in terms of inclusion criteria for intermediate-risk disease. The results showed the proportion of patients who remained on AS was comparable between the low- and intermediate-risk groups after 10 and 15 years' follow-up (OR: 0.97, 95% CI: 0.83–1.14; and OR: 0.86, 95% CI: 0.65–1.13). Cancer-specific survival was worse in the intermediate-risk group after 10 years (OR: 0.47, 95% CI: 0.31–0.69) and 15 years (OR: 0.34, 95% CI: 0.2–0.58). Overall survival was not statistically significantly different at 5 years' follow-up (OR: 0.84, 95% CI: 0.45–1.57) but was significantly worse in the intermediate-risk group after 10 years (OR: 0.43, 95% CI: 0.35–0.53). Metastases-free survival did not significantly differ after 5 years (OR: 0.55, 95% CI: 0.2–1.53) but was worse in the intermediate-risk group after 10 years (OR: 0.46, 95% CI: 0.28–0.77). The authors concluded that AS could be offered to patients with intermediate-risk disease but they should be informed of a higher rate of progression.

The DETECTIVE Study-related qualitative systematic review aimed to determine appropriate criteria for inclusion of intermediate-risk disease into AS protocols [843]. Out of 371 AS protocols included in the review, more than 50% included patients with intermediate-risk disease on the basis of PSA up to 20 ng/mL (25.3%), ISUP 2 or 3 (27.7%), clinical stage cT2b/c (41.6%) and/or direct use of D'Amico risk grouping of intermediate-risk or above (51.1%).

Consequently, AS can be cautiously considered in patients with low-volume ISUP 2 (defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement CI/per core) or another single element of intermediate-risk disease (i.e. favourable intermediate-risk disease) except ISUP 3 disease, which should be excluded. The monitoring schedule should also be more intensive, given the significantly higher risk of progression, development of regional or distant metastases and death of this group compared with low-risk disease. During monitoring, if repeat non-MRI-based systematic biopsies reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease, patients should be reclassified (i.e. actively treated).

#### 6.2.2.2 Radical prostatectomy

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71, 95% CI: 0.53–0.95), death from PCa (RR: 0.38, 95% CI: 0.23–0.62) and distant metastases (RR: 0.49, 95% CI: 0.32–0.74) were significantly reduced in intermediate-risk PCa at 18 years. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69, 95% CI: 0.49–0.98), but not death from PCa (0.50, 95% CI: 0.21–1.21) at 10 years. A meta-analysis based on the findings of SPCG-4, PIVOT and ProtecT demonstrated a benefit from RP over observation with a significantly decreased risk of death of 9% and of disease progression of 43% [879]. However, no stratification by disease stages was performed. The risk of having positive LNs in intermediate-risk PCa is between 3.7–20.1% [880]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [426] or 7% if using the nomogram by Gandaglia *et al.*, which incorporates MRI-guided biopsies [429]. In all other cases eLND can be omitted, which means accepting a low risk of missing positive nodes. Nerve sparing surgery is discussed in Section 6.1.2.3.6.

#### 6.2.2.3 Radiation therapy

##### 6.2.2.3.1 Recommended IMRT/VMAT for intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT/VMAT with short-term ADT (4–6 months) [881–883]. For patients unsuitable (e.g., due to co-morbidities) or unwilling to accept ADT (e.g. to preserve their sexual health)

the recommended treatment is IMRT/VMAT (76–78 Gy) or a combination of IMRT/VMAT and brachytherapy as described below (see Section 6.2.3.2.3).

#### 6.2.2.3.2 Brachytherapy for intermediate-risk PCa

The authors of a systematic review of LDR brachytherapy recommend that LDR brachytherapy monotherapy can be offered to patients with NCCN favourable intermediate-risk disease and good urinary function (see Section 4.2) [884]. 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 [771]. There are no direct data to inform on the use of ADT in this setting. Trimodality therapy with IMRT plus brachytherapy boost and short-term ADT can be considered for NCCN unfavourable intermediate-risk PCa (see Section 4.2) but patients should be made aware that the potential improvements in biochemical control are accompanied with an increased risk of long-term urinary problems [762, 763, 767].

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

##### 6.2.2.4.1 Focal therapy

A prospective study on focal therapy using HIFU in patients with localised intermediate-risk disease was published but the data was derived from an uncontrolled single-arm case series [842]. 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 [825].

##### 6.2.2.4.2 Androgen deprivation therapy monotherapy

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from the EORTC 30891 trial, which was a RCT comparing deferred ADT vs. immediate ADT in 985 patients with T0–4 N0–2 M0 disease [880]. 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 with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA <10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP grade group 3 disease must be excluded from AS protocols.	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
<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 based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2).	Strong
<b>Radiotherapeutic treatment</b>	
Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
For intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), 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 androgen deprivation therapy (ADT) (4–6 months).	Strong

Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Weak
Offer high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	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 [885]. 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 [886]. 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 [426, 427]. Patients should be aware pre-operatively that surgery may be part of multi-modal treatment, with adjuvant or salvage radiotherapy (SRT) or ADT. Neoadjuvant therapy using ADT with or without new generation hormone therapy or docetaxel is not indicated. (See Section 6.1.2.2.4) [542, 543]. Nerve sparing management is discussed in Section 6.1.2.3.6.

##### 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 [886]. Several retrospective case series have demonstrated CSS rates over 60% at 15 years after RP in the context of a multi-modal approach (adjuvant or salvage ADT and/or RT) in patients with a biopsy ISUP grade 5 [473, 549, 887, 888].

##### 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% [473, 549, 556, 889–891].

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

At 15 years follow-up cN0 patients who undergo RP but who were found to have pN1 were reported to have an overall CSS and OS of 45% and 42%, respectively [892–898]. A systematic review has reported 10-year BCR-free, CSS, and OS rates ranging from 28% to 56%, 72% to 98%, and 60% to 87.6%, respectively, in pN1 patients [899]. These findings highlight that pN1 patients represent a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Sections 6.2.5.2 and 6.2.5.6).

#### 6.2.3.2 External beam radiation therapy

For high-risk localised PCa, a combined modality approach should be used consisting of IMRT/VMAT plus long-term ADT. The duration of ADT has to take into account PS, co-morbidities and the number of poor prognostic factors. It is important to recognise that in several studies EBRT plus short-term ADT did not improve OS in high-risk localised PCa and long-term ADT (at least 2 to 3 years) is currently recommended for these patients [721, 722, 725].

##### 6.2.3.2.1 Lymph node irradiation in cN0

There is low level evidence for prophylactic whole-pelvic irradiation as RCTs so far failed to show that patients benefit from prophylactic irradiation (46–50 Gy) of the pelvic LNs in intermediate- and high-risk disease [900–902].

The long-term results of the NRG/RTOG 9413-trial which randomised intermediate-risk and high-risk localised PCa patients (1,322 cN0 patients were enrolled), showed that neoadjuvant hormonal treatment plus whole pelvic RT improved PFS only compared with neoadjuvant ADT plus prostate RT and whole pelvic RT plus adjuvant ADT [903]. However, at the increased risk of  $\geq$  grade 3 GI-toxicity. There was a suggestion of interaction between ADT and RT and therefore whole pelvic RT should be avoided without neoadjuvant ADT.

A well-conducted RCT compared prostate-only RT (PORT) vs. whole pelvic RT (WPRT) in localised high-risk- and locally advanced tumours (cN0) with a risk of > 20% of positive nodes (Roach formula). With a median follow-up of 68 months there was a significant improvement of distant metastasis-free survival (95.9% vs. 89.2%, HR: 0.35,  $p = 0.01$ ) and DFS (89.5% vs. 77.2%,  $p = 0.02$ ). However, there was a significant higher rate of late GU  $\geq 2$  effects (17.7% vs. 7.5%,  $p = 0.02$ ), the trial was relatively small in size with additional limitations and these findings are therefore insufficient to define a change in practice [904, 905]. The benefits of pelvic nodal irradiation using IMRT/VMAT merit further investigation in large scale RCTs as conducted by the RTOG or the UK National Cancer Research Institute (NCRI). 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 experimental in the absence of high-level evidence.

#### 6.2.3.2.2 Brachytherapy boost

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

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

Currently there is a lack of evidence supporting any other treatment option apart from RP and radical RT in localised high-risk PCa. The use of ADT monotherapy was addressed by the EORTC 30891 trial [880] (see Section 6.2.4.4.2). Immediate ADT may only benefit patients with a PSA-DT < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour [880, 931].

#### 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 (see Section 6.2.4.1).	Strong
<b>Radiotherapeutic treatment</b>	
In patients with high-risk localised disease, use intensity-modulated radiation therapy (IMRT) /volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
<b>Therapeutic options outside surgery or radiotherapy</b>	
Do not offer either whole gland or focal therapy to patients with high-risk localised disease.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

#### 6.2.4 Treatment of locally advanced PCa

In the absence of high-level evidence, a recent systematic review could not define the most optimal treatment option [906]. Randomised controlled trials are only available for EBRT. A local treatment combined with a systemic treatment provides the best outcome, provided the patient is ready and fit enough to receive both.

##### 6.2.4.1 Radical prostatectomy

Surgery for locally advanced disease as part of a multi-modal therapy has been reported [886, 907, 908]. 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 [909]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at 10 years [886, 907, 908, 910-914]. For cT3b–T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [915-917]. 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 [604]. 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) [906]. See Sections 6.1.3.4.1 and 6.1.3.4.2 for LDR and HDR brachytherapy boost in T3N0M0 PCa.

#### 6.2.4.3 Treatment of cN1 M0 PCa

Lymph node metastasised PCa is where options for local therapy and systemic therapies overlap. Approximately 5% to 10% of newly diagnosed PCa patients have synchronous suspected pelvic nodal metastases on conventional imaging (CT/bone scan) without bone or visceral metastases (cN1 M0 stage). Meta-analyses have shown that PSMA-PET/CT prior to primary treatment in advanced PCa detected disease outside the prostate in 32% of cases despite prior negative conventional imaging using bone scan and pelvic CT/MRI [445]. A RCT assessing PSMA-PET/CT as staging tool in high-risk PCa confirmed these findings and showed a 32% increase in accuracy compared with conventional imaging for the detection of pelvic nodal metastases [465]. Notably, more sensitive imaging also causes a stage shift with more cases classified as cN1, but with, on average, lower nodal disease burden.

The management of cN1M0 PCa is mainly based on long-term ADT combined with a local treatment. The benefit of adding local treatment has been assessed in various retrospective studies, summarised in one systematic review [918] including 5 studies only [919-923]. The findings suggested an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT as compared to ADT alone. The main limitations of this analysis were the lack of randomisation, of comparisons between RP and RT, as well as the value of the extent of PLND and of RT fields. Only limited evidence exists supporting RP for 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 [924].

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

The addition of a brachytherapy boost to ADT plus EBRT was not associated with improved OS in a retrospective study of 1,650 cN1 patients after multivariable adjustment and propensity score matching [925].

The intensification of systemic treatment (abiraterone acetate, docetaxel, zoledronic acid) has been assessed in unplanned sub-group analyses from the STAMPEDE multi-arm RCT by stratifying for cN+ and M+ status [40, 922]. The analyses were balanced for nodal involvement and for planned RT use in STAMPEDE at randomisation and at analysis. Abiraterone acetate was associated with a non-significant OS improvement (HR: 0.75, 95% CI: 0.48–1.18) in non-metastatic patients (N0/N+M0), but OS data were still immature with a low number of events. Furthermore, this was an underpowered subgroup analysis and hypothesis generating at best. Moreover, subgroup analyses were performed according to the metastatic/non-metastatic status and to the nodal status (any M) without specific data for the N+M0 population (n = 369; 20% of the overall cohort). The same would apply for the docetaxel arm in the STAMPEDE trial for which no specific subgroup analysis of newly diagnosed N+M0 PCa (n = 171, 14% of the overall cohort) was performed. However, the addition of docetaxel, zoledronic acid, or their combination, did not provide any OS benefit when stratifying by M0 and N+ status.

In the AFU-GETUG 12 trial comparing the impact of docetaxel plus estramustine in addition to ADT, 29% of included high-risk non-metastatic PCa patients had a nodal involvement at randomisation [926]. A non-significant trend towards better relapse survival rates was reported in the treatment arm (HR 0.66; 0.43–1.01) without OS benefit. A meta-analysis of docetaxel trials in N0M0–M1 patients concluded to an 8% 4-year survival advantage for docetaxel compared with ADT alone in terms of failure-free survival without OS benefit [927].

The STAMPEDE trial reported on 1,974 men with *de novo* high-risk/locally-advanced M0 disease, or relapse after primary curative therapy with high-risk features [928]. Eligibility criteria for *de novo* disease were: at least two of T-category clinical T3 or T4, Gleason sum score 8–10, PSA > 40 ng/mL, or node positive. Eligibility



criteria for relapsed patients were any of: node positive; PSA > 4 ng/mL and rising with a doubling time < 6 months; or PSA > 20 ng/mL. Patients were randomised to ADT alone, or ADT plus abiraterone, with or without enzalutamide. Radiotherapy was mandated for N0 disease and recommended for N1 disease. Androgen deprivation therapy was administered for 3 years, and abiraterone/enzalutamide for 2 years.

Four hundred and fifty-nine patients were treated with ADT plus abiraterone, and 527 with ADT plus abiraterone plus enzalutamide. Ninety-seven percent of patients randomised were treated for *de novo* disease. Thirty-nine percent of patients were N+. Radiotherapy was administered in 99% of N0 and 71% of cN1 patients, respectively. The primary outcome measure was metastasis-free survival. With a median follow-up of 72 months, the combination therapy significantly improved metastasis-free survival (HR 0.53,  $p = 2.9 \times 10^{-11}$ ) and OS (HR: 0.60,  $p = 9.3 \times 10^{-7}$ ). Adding enzalutamide did not improve efficacy. Combined ADT (for 3 years) and additional abiraterone (for 2 years), plus prostate and whole pelvic RT in the case of primary therapy, should be a SOC in this group of patients.

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

Study	n	Design	Study period/ follow-up	Treatment arms	Effect on survival
Bryant, <i>et al.</i> 2018 [929]	648	Retrospective (National Veterans Affairs)	2000-2015 61 mo.	ADT ± EBRT	Significant benefit for combined treatment only if PSA levels less than the median (26 ng/mL) All-cause mortality HR: 0.50 CSS, HR: 0.38
Sarkar, <i>et al.</i> 2019 [930]	741	Retrospective (National Veterans Affairs)	2000-2015 51 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for RP All cause mortality HR 0.36 CSS, HR: 0.32  No statistical difference for RP vs. RT ( $p \geq 0.1$ ) All-cause mortality HR: 0.47 CSS, HR: 0.88
Lin, <i>et al.</i> 2015 [920]	983 before propensity score matching	Retrospective (NCDB)	2004-2006 48 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 73% vs. 52% HR: 0.5
Tward, <i>et al.</i> 2013 [919]	1,100	Retrospective (SEER)	1988-2006 64 mo.	EBRT (n = 397) vs. no EBRT (n=703) No information on ADT)	Significant benefit for EBRT 5-yr CSS 78% vs. 71% HR: 0.66 5-yr. OS: 68% vs. 56%, HR: 0.70
Rusthoven, <i>et al.</i> 2014 [923]	796	Retrospective (SEER)	1995-2005 61 mo.	EBRT vs. no EBRT (no information on ADT)	Significant benefit for EBRT 10-yr. OS: 45% vs. 29% HR: 0.58
Seisen, <i>et al.</i> 2018 [921]	1,987	Retrospective (NCDB)	2003-2011 50 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for combined treatment 5-yr. OS: 78.8% vs. 49.2% HR: 0.31 No difference between RP and RT
James, <i>et al.</i> 2016 [922]	177	Unplanned subgroup analysis RCT	2005-2014 17 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr. OS: 93% vs. 71% 2-yr. FFS: 81% vs 53% FFS, HR: 0.48

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

#### 6.2.4.4 Options other than surgery or radiotherapy for primary treatment

##### 6.2.4.4.1 Investigational therapies

Currently cryotherapy, HIFU or focal therapies have no place in the management of locally-advanced PCa.

##### 6.2.4.4.2 Androgen deprivation therapy monotherapy

The deferred use of ADT as single treatment modality has been answered by the EORTC 30891 trial [880]. 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 or those that are symptomatic [880, 931]. The median time to start deferred treatment was 7 years. In the deferred treatment arm 25.6% of patients died without needing treatment.

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

Recommendations	Strength rating
<b>Radical prostatectomy (RP)</b>	
Offer RP to selected patients with locally-advanced PCa as part of multi-modal therapy.	Strong
<b>Extended pelvic lymph node dissection (ePLND)</b>	
Perform an ePLND prior to RP in locally-advanced PCa.	Strong
<b>Radiotherapeutic treatments</b>	
Offer patients with locally-advanced disease intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guide radiation therapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer patients with locally advanced disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Offer long-term ADT for at least 2 years.	Strong
Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or ≥ 2 high-risk factors (cT3–4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong
<b>Therapeutic options outside surgery or radiotherapy</b>	
Do not offer whole gland treatment or focal treatment to patients with locally-advanced PCa.	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 IMRT/VMAT plus IGRT) 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. A post-operative detectable PSA is an indication of persistent prostate cells (see Section 6.2.6). All information listed below refers to patients with a post-operative undetectable PSA.

##### 6.2.5.2 Risk factors for relapse

Patients with ISUP grade > 2 in combination with EPE (pT3a) and particularly those with SV invasion (pT3b) and/or positive surgical margins are at high risk of progression, which can be as high as 50% after 5 years [932]. Irrespective of the pT stage, the number of removed nodes [933–940], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [941]. A LN density (defined as ‘the percentage of positive LNs in relation to the total number of analysed/removed LNs’) of over 20% was found to be associated with poor prognosis [942]. The number of involved nodes seems to be a major factor for predicting relapse [935, 936, 943]; the threshold considered is less than 3 positive nodes from an ePLND [567, 935, 943]. However, prospective data are needed before defining a definitive threshold value.

### 6.2.5.2.1 Biomarker-based risk stratification after radical prostatectomy

The Decipher<sup>®</sup> gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment. A meta-analysis of five studies analysed the performance of the Decipher<sup>®</sup> Genomic Classifier (GC) test on men post-RP. The authors showed in multivariable analysis that Decipher<sup>®</sup> GC remained a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47,  $p < 0.001$ ) per 0.1 unit increase in score and concluded that it can independently improve prognostication of patients post-RP within nearly all clinicopathologic, demographic, and treatment subgroups [944]. A systematic review of the evidence for the Decipher<sup>®</sup> GC has confirmed the clinical utility of this test in post-RP decision-making [945]. Further studies are needed to establish how to best incorporate Decipher<sup>®</sup> GC in clinical decision-making.

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

Four prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]), 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 which presents a major limitation interpreting these findings as patients with a detectable PSA would now be considered for salvage therapy rather than ART [946].

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

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [946]	431	pT3 cN0 ± involved SM	60–64 Gy vs. observation	> 0.4	152	10 yr.: 53% vs. 30% ( $p < 0.05$ )	<b>10 yr.: 74% vs. 66%</b> Median time: 15.2 vs. 13.3 yr., $p = 0.023$
EORTC 22911 2012 [947]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr.: 60.6% vs. 41% ( $p < 0.001$ )	<b>81% vs. 77% n.s.</b>
ARO 96-02 2014 [948]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr.: 56% vs. 35% ( $p = 0.0001$ )	<b>10 yr.: 82% vs. 86% n.s.</b>
FinnProstate Group 2019 [949]	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% ( $p < 0.001$ )	<b>10 yr.: 92% vs. 87% n.s.</b>

\*See Section 6.3.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; n.s. = not significant; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin; SRT = salvage radiotherapy.

### 6.2.5.4 Comparison of adjuvant- and salvage radiotherapy

Two retrospective matched studies (510 and 149 patients receiving ART) failed to show an advantage for metastasis-free survival [950, 951]. However, both studies were underpowered for high-risk patients (pT3b/R1/ISUP grade 4–5 PCa).

In contrast to these studies, a propensity score-matched retrospective analysis of two cohorts of 366 pT3 and/or R1 patients found that compared to SRT at a PSA between 0.1 and 0.5 ng/mL, ART given at an undetectable PSA (< 0.1 ng/mL) improved all three endpoints; BCR, metastasis-free survival, and OS [952].

Both approaches (ART and early SRT) together with the efficacy of adjuvant ADT are compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial [953], the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial [954], and the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG-AFU 17) trial [955]. In addition, a pre-planned meta-analysis of all three trials has been published (Table 6.2.5.2) [956].

Two trials closed early after randomising 333/470 patients (RAVES) and 424/718 (GETUG-AFU-17) patients. RADICALS-RT included 1,396 patients with the option of subsequent inclusion in RADICALS-HT; 154/649 (24%) of patients starting in the adjuvant RT group also received neoadjuvant or adjuvant HT; 90 patients for 6 months/45 for 2 years/19 patients outside RADICALS-HT. From the SRT group, 61/228 (27%) received neoadjuvant or adjuvant HT for 6 months ( $n = 33$ ) and 2 years ( $n = 13$ ). Fifteen of these patients were treated outside the trial [953]. All men in the GETUG-AFU-17 trial ( $n = 424$ ) received 6 months of HT. All together, 684 out of 2,153 patients received additional ADT for at least 6 months across both trials [956]. Radiotherapy to the pelvic lymphatics was allowed in the GETUG-AFU and in the RADICALS-RT trials.

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

It is important to note that the indication for ART changed over the last ten years with the introduction of ultra-sensitive PSA-tests, favouring early SRT. Therefore many patients, randomised in these 3 trials (accruing 2006–2008) are not likely to benefit from ART as there is a low risk of biochemical progression (~20–30%) in, for example, pT3R0 or pT2R1-tumours. The median pre-SRT PSA in all 3 trials was 0.24 ng/mL which is much lower than the conventional cut-off level of PSA  $< 0.5$  ng/mL used to base 'early' SRT on. Therefore, patients with 'low-risk factors' of biochemical progression after RP should be closely followed up with ultra-sensitive assays and SRT should be discussed as soon as PSA starts to rise, which has to be confirmed by a second PSA measurement (see Section 6.3). The proportion of patients with adverse pathology at RP (ISUP grade group 4–5 and pT3 with or without positive margins) in all 3 trials was low (between 10–20%) and therefore even the meta-analysis may be underpowered to show an outcome in favour of SRT [956]. In addition, the side-effect profile may have been impacted with a larger proportion of ART patients receiving treatment with older 3D-treatment planning techniques as compared to SRT patients (GETUG-AFU 17: ART, 69% 3D vs. 46% SRT) and patients treated more recently were more likely to undergo IMRT techniques with a proven lower rate of late side effects [665].

For these reasons, 10-year OS and metastasis-free survival endpoints results should be awaited before drawing final conclusions. Due to the small number of patients with adverse pathology (ISUP grade group 4–5 and pT3) included in these 3 trials (between 10–20%), ART remains a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients') i.e. ISUP grade group 4–5 and pT3 with or without positive margins [936, 957, 958]. This recommendation was supported by a published retrospective multi-centre study comparing ART and SRT in patients with high-risk features (pN1 or ISUP 4–5 and pT3/4-tumours) after RP [959]. After a median follow-up of 8.2 years of the 26,118 men included in the study, 2,104 patients died, 25.62% from PCa ( $n = 539$ ) and 2,424 patients had adverse pathology compared with 23,694 who did not. After excluding men with persistent PSA after RP, ART when compared with early SRT showed a significantly lower acute mortality risk ( $p = 0.02$ , HR: 0.33).

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

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (yr)	BPFS	OS or MFS	Side effects
RAVES TROG 08.03/ ANZUP 2020 [954]	333 target was 470 early closed	pT3a/pT3b any T - SM+ PSA post-RP: < 0.1 ng/mL	64 Gy ART PSA: [< 0.1 ng/mL] vs. 64 Gy early SRT at PSA > 0.2 ng/mL med. pre-SRT: n.r.	> 0.4 post RT	6.1	<b>5 yr.: 86% vs. 87%</b> (p > 0.05)	n.r.	LT grade ≥ GU: 70% vs. 54% (p = 0.002)
RADICALS-RT 2020 [953]	1,396	pT3a/pT3b/pT4 PSA > 10 ng/mL pre-RP any T, SM+ Gleason 7-10 PSA post-RP: < 0.2 ng/mL	52.5 Gy (20 Fx) or 66 Gy (33 Fx) ART early SRT identical at PSA > 0.1 med.pre-SRT: 0.2 ng/mL	> 0.4 or 2 at any time	4.9	<b>5 yr.: 85% vs. 88%</b> (p = 0.56)	n.r.	SR urinary incontinence 1 yr: 4.8 vs. 4 (p = 0.023) urethral stricture grade 3/4 2 yr: 6% vs. 4% (p = 0.02)
GETUG-AFU 17 2020 [955]	424 target was 718 early closed	pT3a/pT3b/pT4a and SM+ PSA post-RP: < 0.1 ng/mL	66 Gy (ART) vs. 66 Gy early SRT at PSA 0.1 both groups: 6 mo. LHRH-A med. pre-SRT 0.24	> 0.4	6.25	<b>5 yr.: 92% vs. 90%</b> (p = 0.42)	n.r.	LT grade ≥ 2 GU 27% vs. 7% (p < 0.001) ED: 28% vs. 8% (p < 0.001)
ARTISTIC-Meta-analysis 2020 [956]	2,153	see above	see above	see above	4.5	<b>5 yr.: 89% vs. 88%</b> p = 0.7	n.r.	n.r.

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

#### 6.2.5.5 Adjuvant 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 [960]. A systematic review showed a possible benefit for PFS but not OS for adjuvant androgen ablation [542].

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (6 cycles) ended prematurely due to poor accrual. A phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally-advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [961]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [962].

#### 6.2.5.6 Adjuvant treatment in pN1 disease

##### 6.2.5.6.1 Adjuvant androgen ablation alone

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% and has been shown to significantly improve CSS and OS in prospective RCTs [963, 964]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and these findings may not apply to men with less extensive nodal metastases.

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

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

surgery irrespective of PSA). The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), ISUP grade 2–5 and pT3–4 or R1, as well as men with 3 to 4 positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [965]. Comparable results were obtained from another retrospective single centre study [966]. These results were confirmed by a US National Cancer Database analysis based on 5,498 patients [967]. Another US National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT plus EBRT (including pelvic LNs) vs. observation and vs. ADT alone in all men with single or multiple adverse pathological features. Men without any adverse pathological features did not benefit from immediate adjuvant therapy [968].

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 [969]. In a SEER retrospective population-based analysis, adding RT to RP showed a non-significant trend for improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [923]. Radiotherapy should be given to the pelvic lymphatics and the prostatic fossa [965, 966, 970, 971]. In a systematic review of the literature, RT with or without ADT was associated with improved survival in men with locally-advanced disease and a higher number of positive nodes [899].

Retrospective data from a multi-centre cohort (1,491 pN1-patients after RP) with a median follow-up of 8.2 years, after excluding patients with persisting PSA, show a significantly lower all-cause mortality risk for adjuvant RT compared with early SRT (p = 0.04, HR: 0.66). No data are available in pN1 patients addressing adjuvant EBRT without ADT [972].

#### 6.2.5.6.3 Observation of pN1 patients after radical prostatectomy and extended lymph node dissection

Several retrospective studies and a systematic review addressed the management of patients with pN1 PCa at RP [899, 943, 965, 966, 973]. A subset of patients with limited nodal disease (1–2 positive LNs) showed favourable oncological outcomes and did not require additional treatment.

An analysis of 209 pN1 patients with one or two positive LNs at RP showed that 37% remained metastasis-free without need of salvage treatment at a median follow-up of 60.2 months [973]. Touijer *et al.*, reported their results of 369 LN-positive patients (40 with and 329 without adjuvant treatment) and showed that higher pathologic grade group and ≥ 3 positive LNs were significantly associated with an increased risk of BCR on multivariable analysis [943]. Biochemical-free survival rates in pN1 patients without adjuvant treatment ranged from 43% at 4 years to 28% at 10 years [899]. Reported CSS rates were 78% at 5 years and 72% at 10 years. The majority of these patients were managed with initial observation after surgery, had favourable disease characteristics, and 63% had only one positive node [899]. Initial observation followed by early salvage treatment at the time of recurrence may represent a safe option in selected patients with a low disease burden [899].

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

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients.	Strong
Only offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) to high-risk patients (pN0) with adverse pathology (ISUP grade group 4–5 and pT3 with or without positive margins).	Strong
Discuss three management options with patients with pN1 disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak

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

Recommendations	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.	Strong



<b>Watchful waiting for locally-advanced prostate cancer</b>	
Offer a deferred treatment policy using androgen deprivation monotherapy to MO 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.	Weak

### 6.2.6 **Persistent PSA after radical prostatectomy**

Between 5 and 20% of men continue to have detectable or persistent PSA after RP (when defined in the majority of studies as detectable post-RP PSA of  $\geq 0.1$  ng/mL within 4 to 8 weeks of surgery) [974, 975]. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue.

#### 6.2.6.1 *Natural history of persistently elevated PSA after RP*

Several studies have shown that persistent PSA after RP is associated with more advanced disease (such as positive surgical margins, pathologic stage  $\geq$  T3a, positive nodal status and/or pathologic ISUP grade > 3) and poor prognosis. Initially defined as  $\geq 0.1$  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 [976, 977]. 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  $\geq 3$  [977]. 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 [976]. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively.

Spratt *et al.*, confirmed that a persistently detectable PSA after RP represents one of the worst prognostic factors associated with oncological outcome [978]. Of 150 patients with a persistent PSA, 95% received RT before detectable metastasis. In a multivariable analysis the presence of a persistently detectable PSA post-RP was associated with a 4-fold increase in the risk of developing metastasis. This was confirmed by data from Preisser *et al.*, who showed that persistent PSA is prognostic of an increased risk of metastasis and death [979]. At 15 years after RP, metastasis-free survival rates, OS and CSS rates were 53.0 vs. 93.2% ( $p < 0.001$ ), 64.7 vs. 81.2% ( $p < 0.001$ ) and 75.5 vs. 96.2% ( $p < 0.001$ ) for persistent vs. undetectable PSA, respectively. The median follow-up was 61.8 months for patients with undetectable PSA vs. 46.4 months for patients with persistent PSA. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR: 3.59,  $p < 0.001$ ), death (HR: 1.86,  $p < 0.001$ ) and cancer-specific death (HR: 3.15,  $p < 0.001$ ).

However, not all patients with persistent PSA after RP experience disease recurrence. Xiang *et al.*, showed a 50% 5-year BCR-free survival in men who had a persistent PSA level > 0.1 but  $\leq 0.2$  ng/mL at 6–8 weeks after RP [980].

Rogers *et al.*, assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [981]. 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.

#### 6.2.6.2 *Imaging in patients with persistently elevated PSA after RP*

Standard imaging with bone scan and MRI has a low pick-up rate in men with a PSA below 2 ng/mL. However, PSMA PET/CT has been shown to identify residual cancer with positivity rates of 33%, 46%, 57%, 82%, and 97%, in men with post-RP PSA ranges of 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and  $\geq 2$  ng/mL, respectively [982–987] which can guide SRT planning [988]. Based on these post-RP PSA ranges, Schmidt-Hegemann *et al.*, studied 129 patients who had either persistent PSA (52%) or BCR (48%) after RP, showing that men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those developing a detectable PSA [989]. In a multi-centre retrospective study including 191 patients,  $^{68}\text{Ga}$ -PSM localised biochemical persistence after RP in more than two-thirds of patients with high-risk PCa features. The obturator and presacral/mesorectal nodes were identified as high risk for residual disease [990]. Another retrospective study included 150 patients with persistent PSA after RARP who were re-staged with both  $^{68}\text{Ga}$ -PSMA and  $^{18}\text{F}$ -DCFPyL PSMA. The authors found that in the presence of persistent PSA the majority of patients already had metastatic pelvic LNs or distant metastases which would support a role of PSMA PET/CT imaging in guiding (salvage) treatment strategies [991]. At present there is uncertainty regarding the best treatment if PSMA PET/CT shows metastatic disease.

### 6.2.6.3 Impact of post-operative RT and/or ADT in patients with persistent PSA

The benefit of SRT in patients with persistent PSA remains unclear due to a lack of RCTs, however, it would appear that men with a persistent PSA do less well than men with BCR undergoing RT.

Preisser *et al.*, compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not [979]. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with SRT vs. no RT, OS rates at 10 years after RP were 86.6 vs. 72.6% in the entire cohort ( $p < 0.01$ ), 86.3 vs. 60.0% in patients with positive surgical margin ( $p = 0.02$ ), 77.8 vs. 49.0% in pT3b disease ( $p < 0.001$ ), 79.3 vs. 55.8% in ISUP grade 1 disease ( $p < 0.01$ ) and 87.4 vs. 50.5% in pN1 disease ( $p < 0.01$ ), respectively. Moreover, CSS rates at 10 years after RP were 93.7 vs. 81.6% in the entire cohort ( $p < 0.01$ ), 90.8 vs. 69.7% in patients with positive surgical margin ( $p = 0.04$ ), 82.7 vs. 55.3% in pT3b disease ( $p < 0.01$ ), 85.4 vs. 69.7% in ISUP grade 1 disease ( $p < 0.01$ ) and 96.2 vs. 55.8% in pN1 disease ( $p < 0.01$ ), for SRT vs. no RT, respectively. In multivariable models, after 1:1 propensity score matching, SRT was associated with lower risk for death (HR: 0.42,  $p = 0.02$ ) and lower cancer-specific death (HR: 0.29,  $p = 0.03$ ). These survival outcomes in patients with persistent PSA who underwent SRT suggest they benefit but outcomes are worse than for men experiencing BCR [992].

It is clear from a number of studies that poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade  $\geq 4$  in the RP histology and pT3b disease [993-998]. Fossati *et al.*, suggested that only men with a persistent PSA after RP and ISUP grade  $\leq 3$  benefit significantly [999], although this is not supported by Preisser *et al.* [979]. The current data do not allow making any clear treatment decisions.

Addition of ADT may improve PFS [994]. Choo *et al.*, studied the addition of 2-year ADT to immediate RT to the prostate bed in patients with pathologic T3 disease (pT3) and/or positive surgical margins after RP [994]. Twenty-nine of the 78 included patients had persistently detectable post-operative PSA. The relapse-free rate was 85% at 5 years and 68% at 7 years, which was superior to the 5-year progression-free estimates of 74% and 61% in the post-operative RT arms of the EORTC and the SWOG studies, respectively, which included patients with undetectable PSA after RP [946, 947]. Patients with persistently detectable post-operative PSA comprised approximately 50% and 12%, respectively, of the study cohorts in the EORTC and the SWOG studies.

In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only (66 Gy per protocol [arm C]). The 10-year clinical relapse-free survival was 63% [993]. The GETUG-22 trial comparing RT with RT plus short-term ADT for post-RP PSA persistence (0.2–2.0 ng/mL) reported good tolerability of the combined treatment. The oncological endpoints are yet to be published [1000].

Two systematic reviews addressing persistent PSA confirmed a strong correlation of PSA persistence with poor oncologic outcomes [974, 975]. Ploussard *et al.*, also reported that SRT was associated with improved survival outcomes, although the available evidence is of low quality [975].

### 6.2.6.4 Conclusion

The available data suggest 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.

### 6.2.6.5 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 prostate-specific antigen $> 0.2$ ng/mL if the results will influence subsequent treatment decisions.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

## 6.3 Management of PSA-only recurrence after treatment with curative intent

Follow-up will be addressed in Chapter 7 and is not discussed in this section.

### 6.3.1 Background

Between 27% and 53% of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily

lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

### 6.3.2 **Controversies in the definitions of clinically relevant PSA relapse**

The PSA level that defines treatment failure depends on the primary treatment. Patients with rising PSA after RP or primary RT have different risks of subsequent symptomatic metastatic disease based on various parameters, including the PSA level. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [1001-1003]. 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' [1004]. Clinicians should interpret a PSA rise in light of the EAU BCR risk groups (see Section 6.3.3).

After HIFU or cryotherapy no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments [1005].

### 6.3.3 **Natural history of biochemical recurrence**

Once a PSA recurrence has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. A systematic review and meta-analysis investigated the impact of BCR on hard endpoints and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, PCa-specific and overall mortality [1005]. 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) [1006, 1007]. After primary RT, OS rates are approximately 20% lower at 8 to 10 years follow-up even in men with minimal co-morbidity [1008, 1009]. Still, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality.

The risk of subsequent metastases, PCa-specific- and overall mortality may be predicted by the initial clinical and pathologic factors (e.g., T-category, PSA, ISUP grade) and PSA kinetics (PSA-DT and interval to PSA failure), which was further investigated by the systematic review [1005].

For patients with BCR after RP, the following outcomes were found to be associated with significant prognostic factors:

- distant metastatic recurrence: positive surgical margins, high RP specimen pathological ISUP grade, high pT category, short PSA-DT, high pre-SRT PSA;
- prostate-cancer-specific mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure as defined by investigators, short PSA-DT;
- overall mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure, high PSA-DT.

For patients with BCR after RT, the corresponding outcomes are:

- distant metastatic recurrence: high biopsy ISUP grade, high cT category, short interval to biochemical failure;
- prostate-cancer-specific mortality: short interval to biochemical failure;
- overall mortality: high age, high biopsy ISUP grade, short interval to biochemical failure, high initial (pre-treatment) PSA.

Based on this meta-analysis, proposal is to stratify patients into '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 [1010].

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

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

#### 6.3.4.1 *Assessment of metastases*

##### 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 [937, 1011], the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [1012]. In men with PSA-only recurrence after RP the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [1013, 1014]. Only 11–14% of patients with BCR after RP have a positive CT [1013]. 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 [1015].

##### 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 [1016, 1017].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [1018] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [1019]. The specificity of choline PET/CT is also higher than bone scan with fewer false-positive and indeterminate findings [450]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.3). Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [459, 1020, 1021]. 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 [1022–1024].

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

##### 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 [1025]. However, <sup>18</sup>F-NaF PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [1026].

##### 6.3.4.1.4 Fluciclovine PET/CT

<sup>18</sup>F-Fluciclovine PET/CT has been approved in the U.S. and Europe and it is therefore one of the PCa-specific radiotracers widely commercially available [1027–1029].

<sup>18</sup>F-Fluciclovine PET/CT has a slightly higher sensitivity than choline PET/CT in detecting the site of relapse in BCR [1030]. In a multi-centre 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%; lesions could be visualised either at local level (38.7%) or in LNs and bones (9%) [1031]. As for choline PET/CT, fluciclovine PET/CT sensitivity is dependent on the PSA level, with a sensitivity likely inferior to 50% at PSA < 1 ng/mL.

In a prospective RCT evaluating the impact of <sup>18</sup>F-fluciclovine PET/CT on SRT management decisions in patients with recurrence post-prostatectomy, in 28 of 79 (35.4%) patients overall radiotherapeutic management changed following <sup>18</sup>F-fluciclovine PET/CT [1032]. <sup>18</sup>F-Fluciclovine PET/CT had a significantly higher positivity rate than conventional imaging (abdominopelvic CT or MRI plus bone scan) for whole body (79.7% vs. 13.9%,  $p < 0.001$ ), prostate bed (69.6% vs. 5.1%,  $p < 0.001$ ), and pelvic LNs (38.0% vs. 10.1%,  $p < 0.001$ ) [1032]. However, as yet, no data demonstrating that these changes translate into a survival benefit are available.

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

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 based on a high-volume series (see Table 6.3.1) [982]. High sensitivity (75%) and specificity (99%) were observed on per-lesion analysis.

**Table 6.3.1: PSMA-positivity separated by PSA level category [982]**

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

PSA = prostate-specific antigen; <sup>68</sup>Ga-PSMA PET = Gallium-68 prostate-specific membrane antigen positron emission tomography.

Prostate-specific membrane antigen PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL [1033, 1034]. In a study of 314 patients with BCR after treatment and a median PSA level of 0.83 ng/mL, <sup>68</sup>Ga-PSMA PET/CT was positive in 197 patients (67%) [1035]. In another prospective multi-centre trial including 635 patients with BCR after RP (41%), RT (27%), or both (32%), PPV for <sup>68</sup>Ga-PSMA PET/CT was 0.84 (95% CI: 0.75–0.90) by histopathologic validation (primary endpoint, n = 87) and 0.92 (95% CI: 0.75–0.90) by a composite reference standard. Detection rates significantly increased with PSA value [1036].

A prospective multi-centre, multi-reader, open-label, phase II/III trial (OSPREY) evaluated the diagnostic performance of <sup>18</sup>F-DCFPyL in patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging [444]. Median sensitivity and median PPV 95.8% (95% CI: 87.8%–99.0%) and 81.9% (95% CI: 73.7%–90.2%), respectively.

Another prospective study evaluated the diagnostic performance of <sup>18</sup>F-DCFPyL in 208 men with BCR after RP or RT. The primary endpoint, the correct localisation rate was achieved, demonstrating positive findings on DCFPyL PET/CT in the setting of negative standard imaging [1037]. At present there are no conclusive data about comparison of such tracers [1038].

#### 6.3.4.1.6 Whole-body and axial MRI

Whole body MRI has not been widely evaluated in BCR because of its limited value in the detection of early metastatic involvement in normal-sized LNs [461, 1039]. In a prospective series of 68 patients with BCR, the diagnostic performance of DW-MRI was significantly lower than that of <sup>68</sup>Ga-PSMA PET/CT and <sup>18</sup>NaF PET/CT for diagnosing bone metastases [1040].

#### 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 [1012], 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.

Magnetic resonance imaging can detect local recurrences in the prostatic bed but its sensitivity in patients with a PSA level < 0.5 ng/mL remains controversial [1041, 1042]. Choline PET/CT is less sensitive than MRI when the PSA level is < 1 ng/mL [1043]. In a retrospective study of 53 patients with BCR after RP (median PSA level 1.5 ng/mL) who underwent <sup>18</sup>F-choline whole body hybrid PET/MRI, MRI identified more local relapses while PET detected more regional and distant metastases [1044].

The detection rates of <sup>68</sup>Ga-PSMA PET/CT in patients with BCR after RP increase with the PSA level [1045]. Prostate-specific membrane antigen PET/CT studies showed that a substantial part of recurrences after RP were located outside the prostatic fossa even at low PSA levels [983, 1046]. Combining <sup>68</sup>Ga-PSMA PET and MRI may improve the detection of local recurrences, as compared to <sup>68</sup>Ga-PSMA PET/CT [1047–1049].

The EMPIRE-1, a single-centre, open-label, phase II/III RCT evaluated the role of <sup>18</sup>F-fluciclovine-PET/CT compared with conventional imaging for salvage RT. Three hundred and sixty five patients with detectable PSA after RP, but negative results on conventional imaging were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow-up was 3.5 years. In adjusted analyses, the study group was significantly associated with event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1050].



#### 6.3.4.2.2 Local recurrence after radiation therapy

In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained 18–24 months after initial treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [1012].

Transrectal US is not reliable in identifying local recurrence after RT. In contrast, MRI has yielded excellent results and can be used for biopsy targeting and guiding local salvage treatment [1012, 1051-1054], even if it slightly underestimates the volume of the local recurrence [1055]. Detection of recurrent cancer is also feasible with choline PET/CT [1056], but choline PET/CT has not yet been compared to MRI. Prostate-specific membrane antigen PET/CT can also play a role in the detection of local recurrences after RT [982].

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

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

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

Recommendations	Strength rating
<b>Prostate-specific antigen (PSA) recurrence after radical prostatectomy</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.	Weak
In case PSMA PET/CT is not available, and the PSA level is $\geq$ 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 magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

#### 6.3.5 Treatment of PSA-only recurrences

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

##### 6.3.5.1 Treatment of PSA-only recurrences after radical prostatectomy

###### 6.3.5.1.1 Salvage radiotherapy for PSA-only recurrence after radical prostatectomy (cTxcN0M0, without PET/CT)

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al.*, reported a 75% reduced risk of systemic progression with SRT when comparing 856 SRT patients with 1,801 non-SRT patients [1057]. 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% [953, 1058].

The PSA level at BCR was shown to be prognostic [1057]. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [1059-1062], corresponding to a ~80% chance of being progression-free 5 years later [1063]. 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 [1064].

The EAU BCR definitions have been externally validated and may be helpful for individualised treatment decisions [1010]. Despite the indication for salvage RT, a ‘wait and see’ strategy remains an option for the EAU BCR ‘Low-Risk’ group [1005, 1065]. For an overview see Table 6.3.2.



Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence; metastatic disease, disease-specific and OS are more meaningful endpoints to support clinical decision-making. A systematic review and meta-analysis on the impact of BCR after RP reports SRT to be favourable for OS and 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 [1005]. An international multi-institutional analysis of pooled data from RCTs has suggested that metastasis-free survival is the most valid surrogate endpoint with respect to impact on OS [1066, 1067]. Table 6.3.3 summarises results of recent studies on clinical endpoints after SRT.

**Table 6.3.2: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy PSA level\* (cTxcN0M0, without PET/CT)**

Study	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, et al. 2018 [1068]	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Soto, et al. 2012 [1069]	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16
Stish, et al. 2016 [1059]	1,106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Tendulkar, et al. 2016 [1070]	2,460	60	0.5	66 Gy 16% ADT	56% (5)	Pre-SRT PSA 71% 0.01–0.2 ng/mL 63% 0.21–0.5 ng/mL 54% 0.51–1.0 ng/mL 43% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

\*Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival'. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.

ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up; mo = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen; SRT = salvage radiotherapy; yr = year.

**Table 6.3.3: Recent studies reporting clinical endpoints after SRT (cTxcN0M0, without PET/CT)**  
(the majority of included patients did not receive ADT)

Study	n	Median FU (mo)	Regimen	Outcome
Bartkowiak, et al. 2018 [1068]	464	71	66.6 (59.4-72) Gy no ADT	5.9 yr. OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p = 0.005
Jackson, et al. 2014 [1071]	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> 2016 [1059]	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> 2016 [1070]	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10-yr. DM (19% all patients) Pre-SRT PSA 9% 0.01–0.2 ng/mL 15% 0.21–0.5 ng/mL 19% 0.51–1.0 ng/mL 20% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

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

#### 6.3.5.1.2 Salvage radiotherapy combined with androgen deprivation therapy (cTxN0, without PET/CT)

Data from RTOG 9601 suggest both CSS and OS benefit when adding 2 years of bicalutamide (150 mg o.d.) to SRT [1072]. According to GETUG-AFU 16 also 6-months treatment with a LHRH-analogue can significantly improve 10-year BCR, biochemical PFS and, modestly, metastasis-free survival. However, SRT combined with either goserelin or placebo showed similar DSS and OS rates [1073]. Table 6.3.4 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 BCR risk classification may offer guidance in this respect [1005, 1010].

One of these RCTs reports improved OS (RTOG 96-01) and the other improved metastasis-free survival 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. In a sub-analysis of men with a PSA of 0.61 to 1.5 (n = 253) there was an OS benefit associated with anti-androgen assignment (HR: 0.61, 95% CI: 0.39–0.94). In those receiving early SRT (PSA 0.6 ng/mL, n = 389), there was no improvement in OS (HR: 1.16, 95% CI: 0.79–1.70), with increased other-cause mortality (sub-distribution HR: 1.94, 95% CI: 1.17–3.20, p = 0.01) and increased odds of late grades 3–5 cardiac and neurologic toxic side-effects (OR: 3.57, 95% CI: 1.09–15.97, p = 0.05). These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of anti-androgen treatment with SRT. In patients receiving late SRT (PSA > 0.6 ng/mL), hormone therapy was associated with improved outcomes. In men receiving early SRT (PSA < 0.6 ng/mL), long-term anti-androgen treatment was not associated with improved OS [1074].

A 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 [1075]. In a retrospective multi-centre-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 [1076]. 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 [1077].

**Table 6.3.4: Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone**

Study	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 2019 [1073]	369 RT + ADT 374 RT	ISUP grade ≤ 2/3 89%  ISUP grade ≥ 4 11% cN0	112	66 Gy + 6 mo. GnRH analogue 6 mo. 66 Gy	<b>10-yr.</b> <b>PFS: RT + ADT, 64%</b> <b>PFS: RT, 49%</b> p < 0.0001 <b>MFS: RT + ADT, 75%</b> <b>MFS: RT, 69%</b> p = 0.034
RTOG 9601 2017 [1072]	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy + bicalutamide 24 mo. 64.8 Gy + placebo	<b>12-yr.</b> <b>cumulative DM</b> <b>RT + ADT: 14%</b> <b>RT + placebo: 23%</b> p = 0.005 <b>OS</b> <b>RT + ADT: 76%</b> <b>RT + placebo: 71%</b> p = 0.04 <b>DSM</b> <b>RT + ADT: 5.8%</b> <b>RT + placebo: 13.4%</b> p < 0.001

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

#### 6.3.5.1.2.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for ‘clinical target volumes’ of PCa [1078-1081] and for organs at risk of normal tissue complications [1082]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS but not metastasis-free survival has been reported in patients receiving whole pelvis SRT (± ADT) but the advantages must be weighed against possible side effects [1083].

The optimal SRT dose has not been well defined. It should be at least 64 Gy to the prostatic fossa (± the base of the SVs, depending on the pathological stage after RP) [958, 1060, 1084]. In a systematic review, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that the treatment dose above 70 Gy should be administered at the lowest possible PSA level [1085]. 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 [950, 1086, 1087]. 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 [1088]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [1070].

Two RCT’s were recently published (Table 6.3.5). Intensity-modulated radiation therapy plus IGRT was used in 57% of the patients in the SAKK-trial [958] and in all patients of the Chinese trial [1089]. No patient had a PSMA PET/CT before randomisation. The primary endpoint in both trials was ‘freedom from biochemical progression’, which was not significantly improved with higher doses. However, in the Chinese trial a subgroup analysis showed a significant improvement of this endpoint for patients with Gleason 8-10 tumours (79.7% vs. 55%, p = 0.049). In this trial, patients were treated with ART or SRT and the number of patients was relatively small (n = 144). At this time it seems difficult to draw final conclusions about the optimal total RT-dose and longer follow-up should be awaited.

**Table 6.3.5: Randomized trials investigating dose escalation for SRT without ADT and without PET-CT**

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
SAKK 09/10 trial, 2021 [958]	350	pT2a-3b R0 – R1 pN0 or cN0 PSA post-op undetectable (< 0.1 ng/mL) or persistent (> 0.1 ng/mL < 0.4 ng/mL)	64 Gy vs.70 Gy  No ADT allowed  VMAT + IGRT: 57% 3-D planning: 43%	6.2 yr.	Primary endpoint: FFBP	<b>6 yr. FFBP: 62% vs. 61%</b> <b>OS: no difference</b>  <b>Late side effects:</b> <b>GI grade 2: 7.3% vs. 20%</b> <b>GI grade 3: 4.2% vs. 2.3%</b> p for ≥ grade 2/3: 0.009
Phase-III-Trial Qi X, <i>et al.</i> , 2020 [1089]	144 ART: 33% SRT: 67%	pT2-4 R0-R1 pN0 or cN0 Med. PSA pre-RT: 0.2 ng/mL	66 Gy vs. 72 Gy All patients VMAT + IGRT No ADT allowed  High risk (pT3–4, GS: 8–10, PSA > 20 ng/mL): whole pelvis RT: 126 (87.5%)	49 mo.	Primary endpoint: FFBP	<b>4 yr. FFBP: 75.9% vs. 82.6%</b> (p > 0.05) <b>High risk (GS: 8–10): 55.7% vs. 79.7%</b> (p < 0.049)  <b>Late side effects:</b> <b>GI + GU grade 2 p &gt; 0.05</b> <b>No grade 3</b>

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

Salvage RT is associated with toxicity. In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late grade 3 reactions of the GI tract, but overall, severe GU tract toxicity was not observed. Late grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [1068].

In a RCT on dose escalation for SRT (n = 350), acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastro-intestinal tract grades 2 and 3 toxicity occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy. Late effects have yet to be reported [1090, 1091]. Late grade 2 and 3 GI toxicity was significantly increased with higher doses but without significant differences in QoL. In this study, however, the rectal wall dose constraints were rather permissive and in 44% of the patients outdated 3-D-techniques were used [958].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side effects, especially GU symptoms, clearly increases, even with newer planning and treatment techniques [1092, 1093]. In particular, when compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02) but no effect on the relatively high level of GU toxicity was shown (5-year, 3D-CRT 15.8% vs. IMRT 16.8%) [1092]. However, in a RCT comparing 66 Gy and 72 Gy with all patients having IMRT plus IGRT (n = 144), no significant differences for GI and GU-toxicity was demonstrated [1089]. After a median salvage IMRT dose of 76 Gy however, the 5-year risk of grade 2–3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [1093]. Doses of at least 64 Gy and up to 72 Gy in patients without PET/CT can be recommended [1068, 1090].

#### 6.3.5.1.2.2 Salvage RT with or without ADT (cTx CN0/1) with PET/CT

In a prospective multi-centre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [463]. A prospective study

in a subgroup of 119 BCR patients with low PSA (< 0.5 ng/mL) reported a change in the intended treatment in 30.2% of patients [983]; 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 (0.2–1 ng/mL) [985].

A single-centre study retrospectively assessed 164 men from a prospective 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 [1094]. 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. As there are no prospective phase III data (in particular not for PCa-specific survival or OS) these results have to be confirmed before a recommendation can be provided.

A single-centre open-label, phase II/III RCT (EMPIRE-1) evaluated the role of <sup>18</sup>F-fluciclovine-PET/CT compared with conventional imaging for salvage RT. Three hundred and sixty five patients with detectable PSA after RP but negative results on conventional imaging, were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow-up was 3.5 years. In adjusted analyses, the study group was significantly associated with event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1050].

#### 6.3.5.1.2.3 Metastasis-directed therapy for rcN+ (with PET/CT)

Radiolabelled PSMA PET/CT is increasingly used as a diagnostic tool to assess metastatic disease burden in patients with BCR following prior definitive therapy. A review including 30 studies and 4,476 patients showed overall estimates of positivity in a restaging setting of 38% in pelvic LNs and 13% in extra-pelvic LN metastases [982]. The percentage positivity of PSMA PET/CT was proven to increase with higher PSA values, from 33% (95% CI: 16–51) for a PSA of < 0.2 ng/mL, to 45% (39–52), 59% (50–68), 75% (66–84), and 95% (92–97) for PSA subgroup values of 0.2–0.49, 0.5–0.99, 1.00–1.99, and > 2.00 ng/mL, respectively [982]. Results of this review demonstrated high sensitivity and specificity of <sup>68</sup>Ga-PSMA PET in advanced PCa with a per-lesion-analysed sensitivity and specificity of 75% and 99%, respectively.

In patients relapsing after a local treatment (including cN+ and highly selected M1 patients), a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. Metastasis-directed (MDT) therapy in PET/CT detected nodal oligo-recurrent PCa after RP was assessed in a large retrospective multi-institutional study (263 patients received MDT and 1,816 patients SOC as control group [matched 3:1]). Metastasis-targeting therapy consisted of salvage LN resection (n = 166) and stereotactic ablation RT (SABR) (n = 97). After a median follow-up of 70 months, the MDT-group showed significantly better CSS (5-year survival 98.6% vs. 95.7%, p < 0.01, respectively), however, these results should be viewed with caution as this was a retrospective study, the findings of which require further validation in prospective trials [1095].

Another retrospective study compared SABR with elective nodal irradiation (ENRT) in PET/CT-detected nodal oligo-recurrent PCa (n = 506 patients, 365 of which with N1 pelvic recurrence). With a median follow-up of 36 months, ENRT (n = 197) was associated with a significant reduction of nodal recurrences compared with SABR (n = 309) of 2% vs. 18%, respectively, but at the cost of higher side effects of ENRT [1096]. These results have to be confirmed in prospective trials before any recommendations can be made. In these situations SABR should be used in highly selected patients in prospective cohorts or clinical trials only. For MDT in M1-patients see Section 6.4.7.

A phase II trial assessed the biochemical response after <sup>18</sup>F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1097].

Phillips and colleagues reported outcomes of the phase II ORIOLE (Observation vs. Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer) clinical trial in patients with hormone-sensitive oligometastatic PCa randomised to receive SABR or observation alone [1098]. The primary outcome was the proportion of patients with disease progression at 6 months. Fifty-four patients were randomised and progression at 6 months occurred in 19% of patients receiving SABR and in 61% undergoing observation. In a *post-hoc* analysis, total consolidation of PSMA-positive disease decreased the risk of new lesions at 6 months (16% vs. 63%; p = 0.006).



A review on new generation imaging modalities (whole-body MRI and PET with choline or fluciclovine or sodium fluoride or PSMA) for the detection of recurrent oligometastatic hormone-sensitive PCa showed that PSMA and choline PET can contribute to guiding MDT [1099]. However, such studies should still be considered as experimental as no data demonstrating the clinical significance of any outcomes are available. For MDT in M1-patients see Section 6.4.7.

#### 6.3.5.1.3 Salvage lymph node dissection

The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [1100-1102] and a systematic review [1103]. The reported 5-year BCR-free survival rates ranged from 6% to 31%. Five-year OS was approximately 84% [1103]. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [1104]. Addition of RT to the lymphatic template after salvage LN dissection may improve the BCR rate [1105]. In a multi-centre retrospective study long-term outcomes of salvage LN dissection were reported to be worse than previously described in studies with shorter follow-up [1106]. Biochemical recurrence-free survival at 10 years was 11%. Patients with a PSA response after salvage LN dissection and patients receiving ADT within 6 months from salvage LN dissection had a lower risk of death from PCa [1106]. High-level evidence for the oncological value of salvage LN dissection is still lacking [1103].

#### 6.3.5.1.4 Comparison of adjuvant- and salvage radiotherapy

Section 6.2.5.4 is referred to for more details. Main findings are that after RP the vast majority of patients do not need ART which is supported by the results of 3 phase III RCTs comparing adjuvant RT and early salvage RT with a median follow-up of 5 years [953-957].

However, longer term (10-year) results and results of metastasis-free survival endpoints are needed before final conclusions can be drawn. Due to the small number of patients with adverse pathology (ISUP grade group 4–5 and pT3) included in these 3 trials (only approximately 20%) ART remains a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients') i.e. ISUP grade group 4–5 and pT3 with or without positive margins. This is supported by retrospective studies [957, 959].

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

Therapeutic options in these patients are ADT or salvage local procedures. A systematic review and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage HIFU, salvage cryotherapy, SBRT, salvage LDR brachytherapy, and salvage HDR brachytherapy in the management of locally recurrent PCa after primary radical EBRT [1107]. The outcomes were BCR-free survival at 2 and 5 years. No significant differences with regards to recurrence-free survival (RFS) between these modalities was found. Five-year RFS ranged from 50% after cryotherapy to 60% after HDR brachytherapy and SBRT. The authors reported that severe GU toxicity exceeded 21% for HIFU and RP, whereas it ranged from 4.2% to 8.1% with re-irradiation. Differences in severe GI toxicity also appeared to favour re-irradiation, particularly HDR brachytherapy [1107]. Due to the methodological limitations of this review (the majority of the included studies were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes) the available evidence for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made. The following is an overview of the most important findings for each of these techniques.

##### 6.3.5.2.1 Salvage radical prostatectomy

Salvage RP after RT is associated with a higher likelihood of adverse events (AEs) compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation [1108].

##### 6.3.5.2.1.1 Oncological outcomes

In a systematic review of the literature, Chade, *et al.*, showed that SRP provided 5- and 10-year BCR-free survival estimates ranging from 47–82% and from 28–53%, respectively. The 10-year CSS and OS rates ranged from 70–83% and from 54–89%, respectively. The pre-SRP PSA value and prostate biopsy ISUP grade were the strongest predictors of the presence of organ-confined disease, progression, and CSS [1109]. In a multi-centre analysis including 414 patients, 5-year BCR-free survival, CSS and OS were 56.7%, 97.7% and 92.1%, respectively [1110]. Pathological T stage  $\geq$  T3b (OR: 2.348) and GS (up to OR 7.183 for GS > 8) were independent predictors for BCR (see Table 6.3.6).



**Table 6.3.6: Oncological results of selected salvage radical prostatectomy case series**

Study	n	Median FU (mo)	Pathologic Organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability
Chade, <i>et al.</i> 2011 [1111]	404	55	55	25	16	37	83	10 yr.
Mandel, <i>et al.</i> 2016 [1112]	55	36	50	27	22	49	89	5 yr.
Ogaya-Pinies, <i>et al.</i> 2018 [1113]	96	14	50	17	8	85*	-	14 mo.
Marra, <i>et al.</i> 2021 [1110]	414	36	46	30	16	57	98	5 yr.

\*Percentage of patients without BCR.

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

#### 6.3.5.2.1.2 Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [1114]. In more recent series, these complications appear to be less common [1108, 1109, 1112].

Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients (see Table 6.3.7) [1109, 1112].

**Table 6.3.7: Peri-operative morbidity in selected salvage radical prostatectomy case series**

Study	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5 (%)	Blood loss, mL, mean, range
Ward, <i>et al.</i> 2005 [1115]	138	5	22	-	-
Sanderson, <i>et al.</i> 2006 [1116]	51	2	41	6	-
Gotto, <i>et al.</i> 2010 [1114]	98	9	41	25	-
Gontero, <i>et al.</i> 2019 [1108]	395	1.6	25	3.6	10.1

n = number of patients.

#### 6.3.5.2.1.3 Summary of salvage radical prostatectomy

In general, SRP should be considered only in patients with low co-morbidity, a life expectancy of at least 10 years, a pre-SRP PSA < 10 ng/mL and initial biopsy ISUP grade ≤ 2/3, no LN involvement or evidence of distant metastatic disease pre-SRP, and those whose initial clinical staging was T1 or T2 [1109].

A meta-analysis and systematic review of local salvage therapies after RT for PCa has suggested that re-irradiation with SBRT, HDR brachytherapy or LDR brachytherapy appears to result in less severe GU toxicity than RP, and re-irradiation with HDR brachytherapy in less severe GI toxicity than RP [1107].

#### 6.3.5.2.2 Salvage cryoablation of the prostate

##### 6.3.5.2.2.1 Oncological outcomes

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to salvage RP, as it has a potentially lower risk of morbidity and equal efficacy.

In a systematic review a total of 32 studies assessed SCAP, recruiting a total of 5,513 patients. The overwhelming majority of patients (93%) received whole-gland SCAP. The adjusted pooled analysis for 2-year BCR-free survival for SCAP was 67.49% (95% CI: 61.68–72.81%), and for 5-year BCR-free survival was 50.25% (95% CI: 44.10–56.40%). However, the certainty of the evidence was low. Table 6.3.8 summarises the results of a selection of the largest series on SCAP to date in relation to oncological outcomes (BCR only) [1107].

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

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Ginsburg, <i>et al.</i> 2017 [1117]	898	19.0	5	71.3%	Phoenix criteria
Spiess, <i>et al.</i> 2010 [1118]	450	40.8	3.4	39.6%	PSA > 0.5 ng/mL
Li, <i>et al.</i> 2015 [1119]	486	18.2	5	63.8%	Phoenix criteria
Kovac, <i>et al.</i> 2016 [1120]	486	18.2	5	75.5% (nadir PSA < 0.4 ng/mL); 22.1% (nadir PSA ≥ 0.4 ng/mL)	Phoenix criteria
Ahmad, <i>et al.</i> 2013 [1121]	283	23.9	3	67.0% (nadir PSA ≤ 1 ng/mL); 14.0% (nadir PSA > 1 ng/mL)	Phoenix criteria
Pisters, <i>et al.</i> 2008 [1122]	279	21.6	5	58.9% (ASTRO) 54.5% (Phoenix)	ASTRO and Phoenix criteria

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

#### 6.3.5.2.2.2 Morbidity

The main adverse effects and complications relating to SCAP include urinary incontinence, urinary retention due to bladder outflow obstruction, recto-urethral fistula, and ED. A systematic review and meta-analysis showed an adjusted pooled analysis for severe SCAP-related GU toxicity of 15.44% (95% CI: 10.15–21.54%) [1107]. As before, the certainty of the evidence was low. Table 6.3.9 summarises the results of a selection of the largest series on SCAP to date in relation to GU outcomes.

**Table 6.3.9: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage cryoablation case series, including at least 100 patients**

Study	n	Time point of outcome measurement (mo)	Incontinence (%)	Obstruction/Retention (%)	Rectourethral fistula (%)	ED (%)
Li, <i>et al.</i> 2015 [1119]	486	12	33.3	21.7	4.7	71.3
Ahmad, <i>et al.</i> 2013 [1121]	283	12	12.0	8.1	1.8	83.0
Pisters, <i>et al.</i> 2008 [1122]	279	12	4.4	3.2	1.2	NA
Cespedes, <i>et al.</i> 1997 [1123]	143	Median 27.0	28.0	14.0	NA	NA
Chin, <i>et al.</i> 2001 [1124]	118	Median 18.6	6.7	NA	3.3	NA

ED = erectile dysfunction; mo = months; n = number of patients.

#### 6.3.5.2.2.3 Summary of salvage cryoablation of the prostate

In general, the evidence base relating to the use of SCAP is poor, with significant uncertainties relating to long-term oncological outcomes, and SCAP appears to be associated with significant morbidity. Consequently, SCAP should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study.

#### 6.3.5.2.3 Salvage re-irradiation

##### 6.3.5.2.3.1 Salvage brachytherapy for radiotherapy failure

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

In a systematic review a total of 16 studies (4 prospective) and 32 studies (2 prospective) assessed salvage HDR and LDR brachytherapy, respectively, with the majority (> 85%) receiving whole-gland brachytherapy rather than focal treatment [1107]. The adjusted pooled analysis for 2-year BCR-free survival for HDR was 77% (95% CI: 70–83%) and for LDR was 81% (95% CI: 74–86%). The 5-year BCR-free survival for

HDR was 60% (95% CI: 52–67%) and for LDR was 56% (95% CI: 48–63%). As noted above, brachytherapy techniques are associated with lower rates of severe GU toxicity when compared to RP or HIFU, at 8% for HDR (95% CI: 5.1–11%) and 8.1% for LDR (95% CI: 4.3–13%). Rates of severe GI toxicity are reported to be very low at 0% for HDR (95% CI: 0–0.2%) and 1.5% for LDR (95% CI: 0.2–3.4%). High-dose-rate or LDR brachytherapy are effective treatment options with an acceptable toxicity profile. However, the published series are small and likely under-report toxicity. Consequently, this treatment should be offered in experienced centres ideally within randomised clinical trials or prospective registry studies (see Table 6.3.10).

**Table 6.3.10: Treatment-related toxicity and BCR-free probability in selected salvage brachytherapy studies including at least 100 patients.**

Study	Study design	n and BT type	Median FU (mo)	Treatment toxicity	BCR-free probability
Lopez, <i>et al.</i> 2019 [1125]	multi-centre retrospective	75 HDR 44 LDR	52	23.5% late G3+ GU	5 yr. 71% (95% CI: 65.9-75.9%)
Crook, <i>et al.</i> 2019 [1126]	multi-centre prospective	100 LDR	54	14% late G3 combined GI/GU	n.r.
Smith, <i>et al.</i> 2020 [1127]	single-centre retrospective	108 LDR	76	15.7%/2.8% late G3 GU/GI	5 yr. 63.1% 10 yr. 52%
Lyczek, <i>et al.</i> 2009 [1128]	single-centre retrospective	115 HDR	n.r.	12.2%/0.9% late G3+ GU/GI	60% at 40 mo.

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

#### 6.3.5.2.3.2 Salvage stereotactic ablative body radiotherapy for radiotherapy failure

##### 6.3.5.2.3.2.1 Oncological outcomes and morbidity

Stereotactic ablative body radiotherapy (CyberKnife® or linac-based treatment) is a potentially viable new option to treat local recurrence after RT. Carefully selected patients with good IPSS-score, without obstruction, good PS and histologically proven localised local recurrence are potential candidates for SABR. In a meta-analysis and systematic review five mostly retrospective studies including 206 patients were treated with CyberKnife® or linac-based treatment showing 2-year RFS estimates (61.6%, 95% CI: 52.6–69.9%) [1107]. In a retrospective multi-centre study (n = 100) the median pre-salvage PSA was 4.3 ng/mL with 34% of patients having received ADT for twelve months (median). All recurrences were biopsy proven. Patients were treated with the CyberKnife® with a single dose of 6 Gy in six daily fractions (total dose 36 Gy). With a median follow-up of 30 months the estimated 3-year second BCR-free survival was 55% [1129].

In a smaller retrospective series including 50 men with histologically proven local recurrence with a median pre-salvage PSA of 3.9 ng/mL only 15% had received additional ADT. The estimated 5-year second BCR-free survival was 60% (median follow-up of 44 months) which is an outcome comparable to series treating patients with RP, HIFU or brachytherapy [1130]. Table 6.3.11 summarises the results of the two larger SABR series addressing oncological outcomes and morbidity.

**Table 6.3.11: Treatment-related toxicity and BCR-free survival in selected SABR studies including at least 50 patients**

Author	Study design	n and RT-type	Median FU (mo)	Fractionation (SD/TD)	ADT	Treatment toxicity	BCR-free survival
Fuller, <i>et al.</i> 2020 [1130]	single-centre retrospective	50 Cyber Knife	44	SD 6.8 Gy TD 34 Gy	7/50	5 yr.: 8% late G3+ GU	5 yr. 60%
Pasquier, <i>et al.</i> 2020 [1129]	multi-centre retrospective	100 Cyber Knife	30	SD 6 Gy TD 36 Gy	34/100 median 12 mo.	3 yr. grade 2+ GU 20.8% GI 1%	3 yr. 55%

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

##### 6.3.5.2.3.2.2 Morbidity

In a retrospective single-centre study with 50 consecutive patients chronic significant toxicity was only seen for the GU domain with 5-year grade 2+ and grade 3+ GU rates of 17% and 8%, respectively. No GI toxicity > grade 1 was seen. Of note, of the fifteen patients who were sexually potent pre-salvage SBRT, twelve

subsequently lost potency [1130]. In a retrospective French (GETUG) multi-centre series (n = 100) the 3-year late grade 2+ GU and GI toxicity was 20.8% (95% CI: 13–29%) and 1% (95% CI: 0.1–5.1%), respectively [1129].

#### 6.3.5.2.3.2.3 Summary of salvage stereotactic ablative body radiotherapy

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

#### 6.3.5.2.4 Salvage high-intensity focused ultrasound

##### 6.3.5.2.4.1 Oncological outcomes

Salvage HIFU has emerged as an alternative thermal ablation option for radiation-recurrent PCa. Being relatively newer than SCAP the data for salvage HIFU are even more limited. A systematic review and meta-analysis included 20 studies (n = 1,783) assessing salvage HIFU [1107]. The overwhelming majority of patients (86%) received whole-gland salvage HIFU. The adjusted pooled analysis for 2-year BCR-free survival for salvage HIFU was 54.14% (95% CI: 47.77–60.38%) and for 5-year BCR-free survival 52.72% (95% CI: 42.66–62.56%). However, the certainty of the evidence was low. Table 6.3.12 summarises the results of a selection of the largest series on salvage HIFU to date in relation to oncological outcomes (BCR only).

**Table 6.3.12: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients**

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Crouzet, <i>et al.</i> 2017 [1131]	418	39.6	5	49.0%	Phoenix criteria
Murat, <i>et al.</i> 2009 [1132]	167	Mean 18.1	3	25.0% (high-risk) 53.0% (low-risk)*	Phoenix criteria or positive biopsy or initiation of post-HIFU salvage therapy
Kanthabalan, <i>et al.</i> 2017 [1133]	150	35.0	3	48.0%	Phoenix criteria
Jones, <i>et al.</i> 2018 [1134]	100	12.0	1	50.0%	Nadir PSA > 0.5 ng/mL or positive biopsy

\*Results stratified by pre-EBRT D'Amico risk groups

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

##### 6.3.5.2.4.2 Morbidity

The main adverse effects and complications relating to salvage HIFU include urinary incontinence, urinary retention due to bladder outflow obstruction, rectourethral fistula and ED. The systematic review and meta-analysis showed an adjusted pooled analysis for severe GU toxicity for salvage HIFU of 22.66% (95% CI: 16.98–28.85%) [1107]. The certainty of the evidence was low. Table 6.3.13 summarises the results of a selection of the largest series on salvage HIFU to date in relation to GU outcomes.

**Table 6.3.13: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage HIFU case series, including at least 100 patients**

Study	n	Time point of outcome measurement (yr)	Incontinence* (%)	Obstruction/retention (%)	Rectourethral fistula (%)	ED (%)
Crouzet, <i>et al.</i> 2017 [1131]	418	Median 39.6	42.3	18.0	2.3	n.r.
Murat, <i>et al.</i> 2009 [1132]	167	Median 18.1	49.5	7.8	3.0	n.r.
Kanthabalan, <i>et al.</i> 2017 [1133]	150	24	12.5	8.0	2.0	41.7

Jones, <i>et al.</i> 2018 [1134]	100	12	42.0	49.0	5.0	74.0
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\*Incontinence was heterogeneously defined; figures represent at least 1 pad usage.  
ED = erectile dysfunction; n.r. = not reported; n = number of patients.

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

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

#### 6.3.6 Hormonal therapy for relapsing patients

The Panel conducted a systematic review including studies published from 2000 onwards [1135]. 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) [1136]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [1137]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic workup and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. Predictive factors for poor outcomes were; CRPC, distant metastases, CSS, OS, short PSA-DT, high ISUP grade, high PSA, increased age and co-morbidities. In some studies, such as the Boorjian, *et al.*, study [1065], high-risk patients, mainly defined by a high ISUP grade and a short PSA-DT (most often less than 6 months) seem to benefit most from (early) HT, especially men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [1064]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [1138]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors. Based on the lack of definitive efficacy and the undoubtedly associated significant side effects, patients with recurrence after primary curative therapy should not receive standard HT since only a minority of them will progress to metastases or PCa-related death. The objective of HT should be to improve OS, postpone distant metastases, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with co-morbidities the side effects of HT may even decrease life expectancy; in particular cardiovascular risk factors need to be considered [1139, 1140]. Early HT should be reserved for those at the highest risk of disease progression defined mainly by a short PSA-DT at relapse (< 6–12 months) or a high initial ISUP grade (> 2/3) and a long life expectancy.

#### 6.3.7 Observation

In unselected relapsing patients the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [937]. For patients with EAU Low-Risk BCR features (see Section 6.3.3), unfit patients with a life expectancy of less than 10 years or patients unwilling to undergo salvage treatment, active follow-up may represent a viable option.

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

Local salvage treatment	Strength rating
<b>Recommendations for biochemical recurrence (BCR) after radical prostatectomy</b>	
Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises.	Strong
A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with BCR.	Weak

<b>Recommendations for BCR after radiotherapy</b>	
Offer monitoring, including PSA to EAU Low-Risk BCR patients.	Weak
Only offer salvage radical prostatectomy (RP), brachytherapy, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
<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 with ADT alone, however, it is highly variable since the M1 population is heterogeneous [1141]. 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 [1142-1145].

'Volume' of disease as a potential predictor was introduced by CHARTED (Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) [1145-1147] and has been shown to be predictive in a powered subgroup analysis for benefit of addition of prostate RT ADT [1148].

'Metachronous' metastatic disease vs. synchronous (or *de novo*) metastatic disease has also been shown to have a better prognosis [1149].

Based on a large SWOG 9346 cohort, the PSA level after 7 months of ADT was used to create 3 prognostic groups (see Table 6.4.2) [1150]. 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 CHARTED study independent of the addition of docetaxel [1151].

**Table 6.4.1 Definition of high- and low-volume and risk in CHARTED [1145-1147] and LATITUDE [812]**

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

\*Lymph nodes are not considered as visceral metastases.

**Table 6.4.2: Prognostic factors based on the SWOG 9346 study [1150]**

<b>PSA after 7 months of castration</b>	<b>Median survival on ADT monotherapy</b>
< 0.2 ng/mL	75 months
0.2 $\leq$ 4 ng/mL	44 months
> 4 ng/mL	13 months

### 6.4.3 First-line hormonal treatment

Primary ADT has been the SOC for over 50 years [775]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, neither for orchiectomy nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist, therefore patients with impending spinal cord compression or other potential impending complications from the cancer should be treated with either a bilateral orchidectomy or LHRH antagonists as the preferred options.

There is a suggestion in some studies that cardiovascular side effects are less frequent in patients



treated with LHRH antagonists vs. in patients treated with LHRH agonists [795, 1152, 1153]; therefore patients with pre-existing cardiovascular disease or other cardio-vascular risk factors might be considered to be treated with antagonists if a chemical castration is chosen.

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

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to 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 AEs [1154]. 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 [1155-1157] and two meta-analyses [1158, 1159] 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 [1160]. 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) [1155]. 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 review of the available phase III trials highlighted the limitations of most trials and suggested a cautious interpretation of the non-inferiority results [1161]. 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 [1162, 1163].

#### 6.4.3.3 *Early versus deferred androgen deprivation therapy*

There is an increasing body of evidence that early start of hormonal treatment also for the newer generation hormonal treatments is beneficial. Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease despite lack of randomised phase III data in this specific setting and specifically not with the combination therapies that are standard nowadays.

A 2002 Cochrane review included four RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [1164]. 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 [1164]. 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 [1165]. Since the analysis included only a very limited number of M1 patients who were not evaluated separately, the benefit of early ADT in this setting remains unproven. All of the trials testing the combination therapies in the metastatic hormone-sensitive setting also included asymptomatic patients.

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side effects. The risk of developing symptoms, and even dying from PCa, without receiving the benefit from hormone treatment with deferred treatment has been highlighted [873, 885], but in the era before next generation imaging was used.

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

### 6.4.4 **Combination therapies**

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

#### 6.4.4.1 *'Complete' androgen blockade with older generation NSAA*

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [1166]. 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) [1167, 1168] beyond 5 years of survival [1169] 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. In addition, the newer combination therapies (see Tables 6.4.3, 6.4.4, 6.4.5) are more effective as shown specifically for enzalutamide vs. NSAA in a phase III trial [1170], therefore combination with NSAAs should only be considered if the other combination therapies are not available.

#### 6.4.4.2 Androgen deprivation combined with other agents

##### 6.4.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [881, 1145, 1171]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within 3 months of ADT initiation). The primary objective in all three studies was to assess OS. The key findings are summarised in Table 6.4.3.

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

	STAMPEDE [881, 1172]		GETUG-AFU 15 [1171]		CHAARTED [1145,1146]	
	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; 78.2 (update M1)		50		54 (update)	
HR (95% CI)	0.78 (0.66-0.93)		1.01 (0.75-1.36)		0.72 (0.59-0.89)	
<b>M1 only</b>						
N	1,086		-		-	
HR (95% CI)	0.81 (0.69-0.95)		-		-	

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

In the GETUG 15 trial, all patients had M1 PCa, either *de novo* or after a primary treatment [1171]. They were stratified based on previous treatment and Glass risk factors [1142]. In the CHAARTED trial the same inclusion criteria applied, and patients were stratified according to disease volume (see Table 6.4.1) [1145].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1 or N1 or having two of the following 3 criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade 4–5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < 6 months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [881]. 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 [1173, 1174].

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 [1174]. 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 [1146, 1147], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [1172]. The effects were less apparent in men who had prior local treatment although the numbers were small and the event rates lower. A systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to SOC improved survival [1174]. The HR of 0.77 (95% CI: 0.68–0.87,  $p < 0.0001$ ) translates into an absolute improvement in 4-year survival of 9% (95% CI: 5–14). Docetaxel in addition to SOC 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 mHSPC was studied [40, 812, 1175]. The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [812]. 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 [40]. 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 [1176].

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 AAP compared to ADT monotherapy (HR: 1.37 [0.82–2.29]). However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%). Based on these data upfront AAP combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug (see Table 6.4.4) [1175].

In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with mHSPC was tested [810, 811, 1170]. In ARCHES the primary endpoint was radiographic PFS (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 [811]. In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were 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 [810].

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients treated had *de novo* metastatic disease and the evidence is most compelling in this situation. In the trials with the new AR antagonists, a proportion of patients had metachronous disease (see Table 6.4.5); therefore, a combination should also be considered for men progressing after radical local therapy. Lastly, whether the addition of a new AR antagonist plus docetaxel adds further OS benefit is currently unclear. Longer follow-up data are needed before a definitive conclusion is possible. At the moment, since toxicity clearly increases, AR antagonists plus docetaxel should not be given outside of clinical trials.

The addition of abiraterone to ADT and docetaxel has been reported to have a benefit in rPFS and in OS in the PEACE-1 trial [1176b]. Formal recommendation will be considered following publication of the data.

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

	STAMPEDE [40]		LATITUDE [812]	
	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	<b>83% (ADT + AA + P)</b> <b>76% (ADT)</b>		<b>66% (ADT + AA + P)</b> <b>49% (ADT + placebo)</b>	
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	FFS (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; FFS = failure-free survival; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo = month; n = number of patients; NA = not available; OS = overall survival; P = prednisone; PFS = progression-free survival; PSA = prostate-specific antigen; yr. = year.

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

	ENZAMET [1170]		TITAN [810]	
	ADT+ older antagonist +/-docetaxel (SOC)	ADT + enzalutamide +/-docetaxel	ADT + placebo	ADT + apalutamide
N	562	563	527	525
Newly diagnosed M+	72.1%	72.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS 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; OS = overall survival; SOC = standard of care; PFS = progression-free survival; yr = year.

#### 6.4.5 **Treatment selection and patient selection**

An ADT-based combination therapy is the SOC for patients with newly diagnosed mHSPC. There are no head-to-head data comparing 6 cycles of docetaxel and the continuous use of AAP or of apalutamide or of enzalutamide in newly diagnosed mHSPC. However, for a period, patients in STAMPEDE were randomised to either the addition of abiraterone or docetaxel to SOC. 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 [1177], patients receiving AAP plus SOC reported clinically meaningful higher global-QoL scores throughout the first two years compared to patients receiving docetaxel but statistical significance was not reached [1178]. A meta-analysis also found no significant OS benefit for either drug [1179]. Limitations of network meta-analyses include variable patient populations with different treatment benefits and follow-up periods. In the STOPCAP systematic review and meta-analysis, AAP was found to have the highest probability of being the most effective treatment [1180]. 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, fitness for docetaxel, availability and cost.

There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the combination therapies has been clearly proven to be superior over another [1181, 1182]. As a consequence, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on non-cancer co-morbidities).

#### 6.4.6 **Treatment of the primary tumour in newly diagnosed metastatic disease**

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [1183]. 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 that RT to the primary tumour did not improve OS in unselected patients [1148]. 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 and it must be highlighted that this benefit was obtained without an increased dose. The doses and template used in STAMPEDE should be considered (55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6-weekly fractions of 6 Gy or a biological equivalent total dose of 72 Gy). Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel and no patients had additional AAP, so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment as results of ongoing trials are awaited.

In a systematic review and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04, p = 0.195) [1184]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases.

#### 6.4.7 **Metastasis-directed therapy in M1-patients**

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There are two randomised phase II trials testing metastasis-directed therapy (MDT) using surgery ± SABR vs. surveillance [1185] or SABR vs. surveillance in men with oligo-recurrent PCa [1098]. Oligo-recurrence was defined as ≤ 3 lesions on choline-PET/CT only [1185] or conventional imaging with MRI/CT and/or bone scan [1098]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1185]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1185]. The primary endpoint in the ORIOLE trial was progression after 6 months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1098]. Currently there is no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as experimental until the results of the ongoing RCT are available [1186, 1187].

#### 6.4.8 Guidelines for the first-line treatment of metastatic disease

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

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 or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy ( $\geq 1$ year) and are willing to accept the increased risk of side effects.	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 (RT) (using the doses and template from the STAMPEDE study) 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 (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

### 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) [1188]. 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 and microsatellite instability-high (MSI-H)/mismatch repair-deficient (*dMMR*) status;
- known histological variants and DNA repair deficiency (consider platinum or targeted therapy like PARPi);
- local approval status of drugs and reimbursement situation;
- available clinical trials;
- The patient and his co-morbidities.



#### 6.5.2.1 *Molecular diagnostics*

All metastatic patients should be offered somatic genomic testing for homologous repair and *MMR* defects, preferably on metastatic carcinoma tissue but testing on primary tumour may also be performed. Alternatively, but still less common, genetic testing on circulating tumour DNA (ctDNA) is an option and has been used in some trials. One test, the FoundationOne® Liquid CDx, has been FDA approved [1189]. Defective *MMR* assessment can be performed by IHC for *MMR* proteins (*MSH2*, *MSH6*, *MLH1* and *PMS2*) and/or by next-generation sequencing (NGS) assays [1190]. Germline testing for *BRCA1/2*, *ATM* and *MMR* is recommended for high-risk and particularly for metastatic PCa if clinically indicated.

Molecular diagnostics should be performed by a certified (accredited) institution using a standard NGS multiplication procedure (minimum depth of coverage of 200 X). The genes and respective exons should be listed; not only DNA for mutations but RNA needs to be examined for fusions and protein expression to obtain all clinically relevant information. A critical asset is the decision support helping to rate the mutations according to their clinical relevance [1191, 1192].

Level 1 evidence for the use of PARP-inhibitors has been reported [1193-1195]. Microsatellite instability (MSI)-high (or *MMR* deficiency) is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA and could be a valuable additional treatment option [1196, 1197].

Germline molecular testing is discussed in Section 5.1.3 - Genetic testing for inherited PCa. Recommendations for germline testing are provided in Section 5.1.4.

#### 6.5.3 **Treatment decisions and sequence of available options**

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel, olaparib and radium-223. In general, sequencing of ARTAs like abiraterone 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 (see detailed discussion in Section 6.5.8.2) [1198, 1199].

The use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence is recommended and should be applied early enough when the patient is still fit for chemotherapy. This is supported by high-level evidence [1198].

#### 6.5.4 **Non-metastatic CRPC**

Frequent PSA testing in men treated with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases within two years, detected by conventional imaging [207].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free survival and OS [207, 1200]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1201]. Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC [1202]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

Three large phase III RCTs, PROSPER [1203], SPARTAN [1204] and ARAMIS [1205], evaluated metastasis-free survival as the primary endpoint in patients with nmCRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide vs. placebo (ARAMIS), respectively (see Table 6.5.1). The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of  $\leq 10$  months were included. Patient characteristics in trials revealed that about two-thirds of participants had a PSA-DT of  $< 6$  months. All trials showed a significant metastasis-free survival benefit. All three trials showed a survival benefit after a follow-up of more than 30 months. In view of the long-term treatment with these AR targeting agents in asymptomatic patients, potential AEs need to be taken into consideration and the patient informed accordingly.

**Table 6.5.1: Randomised phase III controlled trials – nmCRPC**

Study	Intervention	Comparison	Selection criteria	Main outcomes
<b>ARAMIS</b> 2019, 2020 [1205, 1206]	ADT + darolutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	<b>59% reduction of distant progression or death</b> <b>Median MFS: darolutamide 40.4 vs placebo 18.4 mo;</b> <b>31% reduction in risk of death</b> HR = 0.69 (95% CI: 0.53–0.88) p = 0.003
<b>PROSPER</b> 2018, 2020 [1203, 1207]	ADT + enzalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	<b>71% reduction of distant progression or death</b> <b>Median MFS: enzalutamide 36.6 vs placebo 14.7 months;</b> <b>27% reduction in risk of death</b> HR = 0.73 (95% CI: 0.61–0.89) p = 0.001
<b>SPARTAN</b> 2018, 2021 [1204, 1208]	ADT + apalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	<b>72% reduction of distant progression or death</b> <b>Median MFS: apalutamide 40.5 vs placebo 16.2 months;</b> <b>22% reduction in risk of death</b> HR = 0.78 (95% CI: 0.64–0.96) p = 0.0161

ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; nmCRPC = non-metastatic castrate-resistant prostate cancer; PSA-DT = prostate-specific antigen doubling time.

### 6.5.5 Metastatic CRPC

The remainder of this section focuses on the management of men with proven mCRPC on conventional imaging.

#### 6.5.5.1 Conventional androgen deprivation in CRPC

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [1209, 1210]. However, in the absence of prospective data, the modest potential benefits of continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression, therefore, it should be continued in these patients.

### 6.5.6 First-line treatment of metastatic CRPC

#### 6.5.6.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients in the phase III COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [1211]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and rPFS were the co-primary endpoints. After a median follow-up of 22.2 months there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93, p = 0.0033) [1212]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1–2. Subset analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [1213].

#### 6.5.6.2 Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [1214]. 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 endpoints, rPFS (HR: 0.186, CI: 0.15–0.23, p < 0.0001), and OS (HR: 0.706, CI: 0.6–0.84, p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide

was equally effective and well tolerated in men > 75 years [1215] as well as in those with or without visceral metastases [1216]. However, for men with liver metastases, there seemed to be no discernible benefit [1216, 1217].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double blind phase II study (TERRAIN) showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44,  $p < 0.0001$ ) in favour of enzalutamide [1217]. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [1218].

#### 6.5.6.3 Docetaxel

A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxel-based chemotherapy compared to mitoxantrone plus prednisone [1219, 1220]. 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 [1221].

Age by itself is not a contraindication to docetaxel [1222] but attention must be paid to careful monitoring and co-morbidities as discussed in Section 5.4 - Estimating life expectancy and health status [1223]. 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 AEs and a prolonged time to treatment failure [1224].

#### 6.5.6.4 Sipuleucel-T

In 2010 a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [1225]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 ( $p = 0.03$ ). No PSA decline was observed and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related AEs grade 1–2 in the sipuleucel-T group, but the same grade 3–4 AEs in both arms. Sipuleucel-T is not available in Europe.

#### 6.5.6.5 Ipatasertib

The AKT inhibitor ipatasertib in combination with AAP was studied in asymptomatic or mildly symptomatic patients with and without PTEN loss by IHC and previously untreated for mCRPC. The randomised phase III trial (IPAtential) showed a significant benefit for the first endpoint rPFS in the PTEN loss (IHC) population (18.5 vs. 16.5 mo;  $p = 0.0335$ , HR: 0.77, 95% CI: 0.61–0.98). The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhoea [818]. Grade 3 or higher AEs occurred nearly double as often in the combination group and the discontinuation rate due to AEs was 4 times higher. This combination is still investigational [1226].

**Table 6.5.2: Randomised phase III controlled trials - first-line treatment of mCRPC**

Study	Intervention	Comparison	Selection criteria	Main outcomes
<b>DOCETAXEL</b>				
SWOG 99-16 2004 [1227]	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		<b>OS: 17.52 vs. 15.6 mo.</b> ( $p = 0.02$ , HR: 0.80; 95% CI: 0.67-0.97) <b>PFS: 6.3 vs. 3.2 mo.</b> ( $p < 0.001$ )
TAX 327 2004, 2008 [1219, 1228]	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		<b>OS: 19.2 for 3 weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.</b> ( $p = 0.004$ , HR: 0.79, 95% CI: 0.67-0.93)

<b>ABIRATERONE</b>				
COU-AA-302 2013, 2014, 2015 [1211, 1212, 1229]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	<b>OS: 34.7 vs. 30.3 mo.</b> (HR: 0.81, p = 0.0033). <b>FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.</b> (p < 0.0001)
<b>ENZALUTAMIDE</b>				
PREVAIL 2014 [1214]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	<b>OS: 32.4 vs. 30.2 mo.</b> (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) <b>rPFS: 20.0 mo. vs. 5.4 mo.</b> HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)
<b>SIPULEUCEL-T</b>				
IMPACT2010 [1225]	sipuleucel-T	placebo	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	<b>OS: 25.8 vs. 21.7 mo.</b> (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). <b>FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo.</b> (no difference)
2006 [1230]	sipuleucel-T	placebo	- ECOG 0-1. - No visceral met. - No corticosteroids.	<b>OS: 25.9 vs. 21.4 mo.</b> (p = 0.1). FU: 36 mo. <b>PFS: 11.7 vs. 10.0 wk.</b>
<b>IPATASERTIB</b>				
IPAtential150 2021 [1226]	ipatasertib (400 mg/d) + abiraterone (1000 mg/d) + prednisone (5 mg bid)	abiraterone + prednisolone + placebo	Previously untreated for mCRPC, asymptomatic/ mildly symptomatic, with and without PTEN loss by IHC	<b>rPFS in PTEN loss (IHC) population: 18.5 vs. 16.5 mo.</b> (p = 0.0335, HR: 0.77 95% CI: 0.61-0.98)

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

### 6.5.7 Second-line treatment for mCRPC and sequence

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.3. High-level evidence exists for second-line treatments after first-line treatment with docetaxel and for third-line therapy.

#### 6.5.7.1 Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [1231]. 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 endpoint which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months, p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3–4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) but also non-haematological (57.4 vs. 39.8%, p < 0.0002) toxicity [1232]. 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 [1233, 1234]. 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 [1235].

#### 6.5.7.2 *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 [1236] and confirmed by the final analysis [1237]. A total of 1,195 patients with mCRPC were randomised 2:1 to AAP or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary endpoint was OS, with a planned HR of 0.8 in favour of AAP. After a median follow-up of 20.2 months, the median survival in the AAP group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74,  $p < 0.0001$ ). The benefit was observed in all subgroups and all the secondary objectives were in favour of AAP (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3–4 AEs did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the AAP group, mainly grade 1–2 (fluid retention, oedema and hypokalaemia).

#### 6.5.7.3 *Enzalutamide after docetaxel*

The planned interim analysis of the AFFIRM study was published in 2012 [1238]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary endpoint was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63,  $p < 0.001$ ). This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [1218]. Enzalutamide was active also in patients with visceral metastases.

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

#### 6.5.7.4 *Radium-223*

The only bone-specific drug that is associated with a survival benefit is the  $\alpha$ -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 SOC. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70,  $p < 0.001$ ) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [1239]. 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 [1239]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [1240]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent [1241]. In particular, the use of radium-223 in combination with AAP showed significant safety risks related to fractures and more deaths. This was most striking in patients without the concurrent use of anti-resorptive agents [1242].

#### 6.5.8 **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 supported by the best data. The CARD trial, an open label randomised phase III trial, evaluated cabazitaxel after docetaxel and one line of ARTA (either AAP or enzalutamide) [1198]. 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 [1243]. 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 [1244, 1245] and there is evidence of cross-resistance between enzalutamide and abiraterone [1246, 1247].

In this context, radioligand therapy has been discussed for many years. In pre-treated and highly selected patients, based on PSMA- and FDG PET scan results,  $^{177}\text{Lu}$ -PSMA-617 was compared with cabazitaxel in a randomised phase II trial. The primary endpoint PSA reduction  $\geq 50\%$  was in favour of the radioligand therapy [1248]. Pivotal phase III data for  $^{177}\text{Lu}$ -PSMA-617 are discussed in Section 6.5.9.2.



Poly (ADP-ribose) polymerase inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one ARTA and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate to olaparib [1249] and in another confirmatory trial a confirmed composite response of 54.3% (95% CI: 39.0–69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1–54.6) evaluable patients in the 300 mg cohort [1250].

#### 6.5.8.1 PARP inhibitors for mCRPC

So far, two PARP inhibitors, olaparib and rucaparib, are licenced by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation (e.g., talazoparib, niraparib).

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative 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 [1194, 1195]. Radiographic PFS by blinded independent central review in the *BRCA1/2* or *ATM* mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). The final results for OS demonstrated a significant improvement among men with *BRCA1/2* or *ATM* mutations (Cohort A) ( $p = 0.0175$ ; HR: 0.69, 95% CI: 0.50–0.97). This was not significant in men with any (other) HRR alteration (Cohort B) (HR: 0.96, 95% CI: 0.63–1.49). Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 66% ( $n = 86/131$ ) crossed over to olaparib. When looking specifically at the Cohort B patients, olaparib did not improve rPFS by blinded independent central review (HR: 0.88, 95% CI: 0.58–1.36) or OS (HR: 0.73, 95% CI: 0.45–1.23), however, investigator assessed rPFS demonstrated a benefit for olaparib (HR: 0.60, 95% CI:  $> 0.39$ –0.93) [1195, 1251].

The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary to an AE, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first trial to show a benefit for genetic testing and precision medicine in mCRPC.

The olaparib approval by the FDA is for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1* and *BRCA2* alterations [1252]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib has been approved for patients with deleterious *BRCA* mutations (germline and/or somatic) who have been treated with ARTA and a taxane-based chemotherapy [1253]. Approval was not based on OS data but on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious *BRCA* mutations was 43.5% (95% CI: 31–57) [1254].

#### 6.5.8.2 Sequencing treatment

##### 6.5.8.2.1 ARTA -> ARTA (chemotherapy-naive patients)

The use of sequential ARTAs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial [1255–1262]. In particular in patients who had a short response to the first ARTA for mCRPC ( $< 12$  months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present).

In highly selected patients treated for more than 24 weeks with AAP, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1–8.3) and an unconfirmed PSA response rate of 27% [1263]. In case the patient is unfit for chemotherapy and a PARP inhibitor best supportive care should be considered in case no other appropriate treatment option is available (clinical trial or immunotherapy if MSI-high). An ARTA-ARTA sequence should never be the preferred option but might be considered in such patients if the PS still allows for active treatment and the potential side effects seem manageable.

First prospective cross-over data on an ARTA-ARTA sequence [1255] and a systematic review and meta-analysis suggest that for the endpoints PFS and PSA PFS, but not for OS, abiraterone followed by enzalutamide is the preferred choice [1264].



#### 6.5.8.2.2 ARTA -> PARP inhibitor/olaparib

This sequence in patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial [1195]. A subgroup of patients in this trial was pre-treated with one or two ARTAs and no chemotherapy (35%). The ARTA – docetaxel - PARP inhibitor vs. ARTA – PARP inhibitor - docetaxel sequences are still under investigation.

#### 6.5.8.2.3 Docetaxel for mHSPC -> docetaxel rechallenge

There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mHSPC. Docetaxel seems to be less active than ARTA at progression to mCRPC following docetaxel for mHSPC [1265].

#### 6.5.8.2.4 ARTA -> docetaxel or docetaxel -> ARTA followed by PARP inhibitor

Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARTA and docetaxel in either sequence [1195, 1253].

#### 6.5.8.2.5 ARTA before or after docetaxel

There is level 1 evidence for both sequences (see Table 6.5.3).

#### 6.5.8.2.6 ARTA -> docetaxel -> cabazitaxel or docetaxel -> ARTA -> cabazitaxel

Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high-level evidence favouring cabazitaxel vs. a second ARTA after docetaxel and one ARTA. CARD is the first prospective randomised phase III trial addressing this question (see Table 6.5.3) [1198].

**Table 6.5.3: Randomised controlled phase II/III - second-line/third-line trials in mCRPC**

Study	Intervention	Comparison	Selection criteria	Main outcomes
<b>ABIRATERONE</b>				
COU-AA-301 2012 [1237]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	<b>OS: 15.8 vs. 11.2 mo.</b> ( $p < 0.0001$ , HR: 0.74, 95% CI: 0.64–0.86; $p < 0.0001$ ). FU: 20.2 mo. <b>rPFS: no change</b>
COU-AA-301 2011 [1236]				<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>				
ALSYMPCA 2013 [1239]	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 endpoints show a benefit over best SOC.
<b>CABAZITAXEL</b>				
TROPIC 2013 [1266]	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: -
TROPIC 2010 [1231]				<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)

CARD 2019 [1198]	cabazitaxel (25 mg/m <sup>2</sup> Q3W) + prednisone + G-CSF	ARTA: abiraterone + prednisone OR enzalutamide	Previous docetaxel. Progression ≤ 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>				
AFFIRM 2012 [1238]	enzalutamide	placebo	Previous docetaxel. ECOG 0-2.	<b>OS: 18.4 vs. 13.6 mo.</b> (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>				
PROfound 2020 [1194, 1195, 1251]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARTA, alterations in HRR mutated genes	<b>rPFS: 7.39 vs. 3.55 mo.</b> (p < 0.0001, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). <b>OS: 19.1 mo vs. 14.7 mo.</b> (in pts with <i>BRCA1/2</i> , <i>ATM</i> alterations) (p = 0.0175; HR 0.69, 95% CI: 0.5–0.97).
<b>Radioligand therapy</b>				
VISION 2021 [1267]	<sup>177</sup> Lu-PSMA-617	<sup>177</sup> Lu-PSMA-617 + SOC or SOC alone	Previous at least 1 ARTA and one or two taxane regimens; Mandatory: PSMA- positive gallium-68 ( <sup>68</sup> Ga)-labelled PSMA-PET scan	<b>Imaging-based PFS: 8.7 vs. 3.4 mo.</b> (p < 0.001; HR 0.40; 99.2% CI: 0.29–0.57) <b>OS: 15.3 vs. 11.3 mo.</b> (p < 0.001; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [1248]	<sup>177</sup> Lu-PSMA-617 (8.5 GBq i.v.q 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	<sup>177</sup> Lu-PSMA-617 1:1 randomisation cabazitaxel (20 mg/m <sup>2</sup> i.v.q 3-weekly, up to 10 cycles)	mCRPC post docetaxel, suitable for cabazitaxel	<b>PSA reduction of &gt; 50%:</b> 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016).

\*Only studies reporting survival outcomes as primary endpoints have been included.

ARTA = androgen receptor targeting agents; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; HR = hazard ratio; Lu = lutetium; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr = year; HRR= homologous recombination repair.

### 6.5.9 Second-line treatment for mCRPC and sequencing of therapy

#### 6.5.9.1 Background

During the 90s several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 were developed for the treatment of bone pain secondary to metastasis from PCa [1268]. 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 6.5.7.4).

#### 6.5.9.2 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) [1269]. 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.

The PSMA therapeutic radiopharmaceutical supported with the most robust data is <sup>177</sup>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 [1270]. The early data were based on single-centre experience [1271]. Data from uncontrolled prospective phase II trials reported high response rates with low toxic effects [1272, 1273]. Positive signals are also coming from a randomised trial [1248].

In TheraP, a randomised phase II trial, patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by <sup>68</sup>Ga-PSMA-11 and <sup>18</sup>F-FDG PET-CT scans, were randomised to receive <sup>177</sup>Lu-PSMA-617 (6.0–8.5 GBq intravenously every 6 weeks for up to 6 cycles) or cabazitaxel (20 mg/m<sup>2</sup> for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for <sup>177</sup>Lu-PSMA-617 vs. cabazitaxel, respectively, by ITT; difference 29% (95% CI: 16–42;  $p < 0.0001$ ; and 66% vs. 44% by treatment received; difference 23% [9–37];  $p = 0.0016$ ). Secondary endpoints included ORR, rPFS and PSA FSF as well as QoL [1248].

Finally, an open-label phase III trial (VISION) compared <sup>177</sup>Lu-PSMA-617 radioligand therapy with protocol-permitted SOC in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARTA and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. Eligible patients had to present with at least one PSMA-positive metastatic lesion exceeding the uptake of the liver parenchyma on a <sup>68</sup>Ga-PSMA-11 PET-CT and without PSMA-negative lesions in any LN with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis.

More than 800 patients were randomised. <sup>177</sup>Lu-PSMA-617 plus SOC significantly prolonged both imaging-based PFS and OS as compared with SOC alone (see Table 6.5.3). Grade 3 or above AEs were higher with <sup>177</sup>Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. <sup>177</sup>Lu-PSMA-617 has shown to be a valuable additional treatment option in this mCRPC population [1267].

#### 6.5.10 **Immunotherapy for mCRPC**

The immune checkpoint inhibitor pembrolizumab was approved by the FDA for all *MMR*-deficient cancers or in those with instable microsatellite status (MSI-high) [1196]. This also applies to PCa but it is a very rare finding in this tumour entity [1197]. In all other PCa patients pembrolizumab monotherapy is still experimental. It shows limited anti-tumour activity with an acceptable safety profile, again in a small subset of patients. A phase II trial enrolled 258 patients treated with pembrolizumab [1274]. The objective response rate was around 4%, but those responses were durable. Combination immunotherapy is under investigation.

The CTLA-4 inhibitor ipilimumab was evaluated in docetaxel pre-treated mCRPC patients after RT to bone metastases in a placebo-controlled phase III RCT. Although the trial's primary endpoint OS was not improved significantly, a pre-planned long-term analysis showed that OS rates at 3, 4, and 5 years were approximately two to three times higher in the ipilimumab arm (2 years [25.2% vs. 16.6%], 3 years [15.3% vs. 7.9%], 4 years [10.1% vs. 3.3%], and 5 years [7.9% vs. 2.7%]). These data support the hypothesis that a subset of mCRPC patients might derive a long-term benefit from CTLA-4 inhibition. Further prospective data are needed to support the routine use of ipilimumab [1275]. It has not been approved for the use in PCa management.

#### 6.5.11 **Platinum chemotherapy**

Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1276]. More recently, the combination of cabazitaxel and carboplatin was evaluated in pre-treated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5–5.7) to 7.3 months (95% CI: 5.5–8.2; HR: 0.69, 95% CI: 0.50–0.95,  $p = 0.018$ ) and the combination was well tolerated [1277]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including *TP53*, *RB1*, and *PTEN* [1278].

Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [1279], also after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients as well as patients without DDR gene alterations also showed a

50% PSA decline in up to 36% of patients [1280]. In view of the excellent tolerability of e.g. carboplatin monotherapy, platinum could be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Prospective controlled trials are ongoing.

#### 6.5.12 **Monitoring of treatment**

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, total testosterone level, full blood count, renal function, baseline liver function tests, alkaline phosphatase), bone scan and CT of chest, abdomen and pelvis [1281, 1282]. 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 [1283]. Prostate-specific antigen alone is not reliable enough [1284] for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA [1285]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [1220]. 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 [1281]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost and patients with no objective benefit should have their treatment modified. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of no longer 'clinically benefiting' to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [1286]. These recommendations also seem valid for clinical practice outside trials.

#### 6.5.13 **When to change treatment**

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Preferably, any treatment change should precede development of *de novo* symptoms or worsening of existing symptoms. Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore it is not clear how to select the most appropriate 'second-line' treatment, in particular in patients without HRR alterations or other biomarkers. A positive example, however, is the CARD trial which clearly established cabazitaxel as the better third-line treatment in docetaxel pre-treated patients after one ARTA compared to the use of a second ARTA [1198].

The ECOG PS has been used to stratify patients. Generally men with a PS of 0–1 are likely to tolerate treatments and those with a PS of  $\geq 2$  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 a given treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in a summary paper published following the 2019 APCCC Conference [1287].

#### 6.5.14 **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 [1287, 1288]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

##### 6.5.14.1 *Common complications due to bone metastases*

Most patients with CRPC have painful bone metastases. External beam RT is highly effective, even as a single fraction [1289, 1290]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [1291]. 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 [1292]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1293, 1294]. 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 [1295]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

#### 6.5.14.2 Preventing skeletal-related events

##### 6.5.14.2.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anti-cancer treatments, but for docetaxel, were available. Six hundred and forty three patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for 15 consecutive months, or placebo [1296]. 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.

##### 6.5.14.2.2 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,  $p = 0.028$ ) [1289]. 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 [1297].

The efficacy and safety of denosumab ( $n = 950$ ) compared with zoledronic acid ( $n = 951$ ) in patients with mCRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR: 0.82,  $p = 0.008$ ). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm ( $p < 0.0001$  for both). However, these findings were not associated with any survival benefit and in a *post-hoc* re-evaluation of endpoints, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1298].

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) [1298-1300]. 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 [1301]. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial [1302] (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1297]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy [1303]. 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) [1300]. 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 [1300, 1304, 1305].

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

Summary of evidence	LE
First-line treatment for mCRPC will be influenced by which treatments were used when metastatic cancer was first discovered.	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e., hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist.	3

Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be $< 50$ ng/dL before diagnosing castrate-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents.	Strong
Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong

6.5.16 **Guidelines for systematic treatments of castrate-resistant disease**

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive 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, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
<b>Novel agents</b>	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer <sup>177</sup> Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

6.5.17 **Guidelines for supportive care of castrate-resistant disease**

These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy/volumetric arc radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

6.5.18 **Guideline for non-metastatic castrate-resistant disease**

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong



## 6.6 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 treatment of prostate cancer

Recommendations	Strength rating
Inform patients that based on robust current data with up to 12 years of follow-up, no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all active local 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, magnetic resonance imaging, or with this information combined into a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
<b>Radiotherapeutic treatment</b>	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease.	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
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or intermediate-risk disease with ISUP grade 2 and ≤ 33% of biopsy cores involved.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10–20 ng/mL.	Weak
Offer LDR or HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak
<b>Active therapeutic options outside surgery or radiotherapy</b>	
Offer whole-gland cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
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>	<b>Selection of patients</b>	
	Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
	Patients with intraductal and cribriform histology on biopsy should be excluded from AS.	Strong
	Perform MRI before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
	If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
	If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
	<b>Follow-up strategy</b>	
	Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
In case of PSA progression or change in DRE or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong	
<b>Active treatment</b>	Offer surgery or 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.	Strong
<b>Radiotherapeutic treatment</b>	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa and good urinary function.	Strong
	Use intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) 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 therapeutic options</b>	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Strong
	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 with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
	Patients with ISUP grade group 3 disease must be excluded from AS protocols.	Strong
	Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
<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 based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2).	Strong
<b>Radiotherapeutic treatment</b>	Offer LDR brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
	For IMRT/VMAT plus image-guided radiotherapy (IGRT), 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 ADT (4–6 months).	Strong
	Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Weak
	Offer HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
	In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	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 IMRT/VMAT plus IGRT with 76–78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
<b>Therapeutic options outside surgery or radiotherapy</b>	Do not offer either whole gland nor focal therapy to patients with high-risk localised disease.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong
<b>Locally-advanced disease</b>		
<b>Radical prostatectomy</b>	Offer RP to selected patients with locally-advanced PCa as part of multi-modal therapy.	Strong
<b>Extended pelvic lymph node dissection</b>	Perform an ePLND prior to RP in locally-advanced PCa.	Strong
<b>Radiotherapeutic treatments</b>	Offer patients with locally-advanced disease IMRT/VMAT plus IGRT in combination with long-term ADT.	Strong
	Offer patients with locally advanced disease and good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT.	Weak
	Offer long-term ADT for at least two years.	Weak
	Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or ≥ 2 high-risk factors (cT3–4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong

<b>Therapeutic options outside surgery or radiotherapy</b>	Do not offer whole gland treatment or focal treatment to patients with locally-advanced PCa.	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 IMRT/VMAT plus IGRT) plus long-term ADT.	Weak
<b>Adjuvant treatment after radical prostatectomy</b>		
<b>pN0 &amp; pN1 disease</b>	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Only offer adjuvant IMRT/VMAT plus IGRT to high-risk patients (pN0) with adverse pathology (ISUP grade group 4–5 and pT3 with or without positive margins).	Strong
	Discuss three management options with patients with pN1 disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak
<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 positron-emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak
	Treat men with no evidence of metastatic disease with salvage RT and additional hormonal therapy.	Weak

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

Recommendations		Strength rating
<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 or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
	Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
	Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
	Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
	Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy ( $\geq 1$ year) and are willing to accept the increased risk of side effects.	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 (RT) (using the doses and template from the STAMPEDE study) 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 (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
	Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
	Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong
<b>Biochemical recurrence after treatment with curative intent</b>		
<b>Biochemical Recurrence (BCR) after radical prostatectomy (RP)</b>	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Offer early salvage IMRT/VMAT plus IGRT to men with two consecutive PSA rises.	Strong
	A negative PET/CT scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
	Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with BCR.	Weak
<b>BCR after RT</b>	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Only offer salvage RP, brachytherapy, HIFU, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
<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.	Strong
	Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong
<b>Systemic treatments of castrate-resistant disease</b>		
	Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
	Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m <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, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
	Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
	Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
	Avoid sequencing of androgen receptor targeted agents.	Weak
	Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
<b>Novel agents</b>		
	Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
	Offer <sup>177</sup> Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong
<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 IMRT/VMAT plus IGRT and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong
<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 and overall survival.	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 IMRT plus IGRT or LDR- or HDR-brachytherapy, or any combination of these, including neoadjuvant and adjuvant therapy. Unestablished alternative treatments such as HIFU, cryosurgery and focal therapy options do not have a well-defined, validated, PSA cut-off to define BCR but follow the general principles as presented in this section. In general, a confirmed rising PSA is considered a sign of disease recurrence.

#### 7.1.2 Why follow-up?

The first post-treatment clinic visit focuses on detecting treatment-related complications and assist patients in coping with their new situation apart from providing information on the pathological analysis. Men with PCa are at increased risk of depression and attention for mental health status is required [1306, 1307]. Tumour or patient characteristics may prompt changing the follow-up schedule. Follow-up of men diagnosed with PCa may allow early treatment of disease and treatment-related problems. The use of salvage treatment should be considered in light of the expected life-expectancy, especially when below 10 years in asymptomatic patients.

#### 7.1.3 How to follow-up?

The procedures indicated at follow-up visits vary according to the clinical situation. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications in the post-treatment period is highlighted in Sections 6.1.2.4, 6.1.2.4.3, 6.3.9.2, 6.3.10.2.2, 6.3.11.2 and 8.2. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

##### 7.1.3.1 Prostate-specific antigen monitoring

Measurement of PSA is the cornerstone of follow-up after local treatment. While PSA thresholds depend on the local treatment used, PSA recurrence almost always precedes clinical recurrence [1003, 1308]. The key question is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value (see Section 6.3) [1005]. No prospective studies are available on the optimal timing for PSA testing.

##### 7.1.3.1.1 Active surveillance follow-up

Patients included in an AS programme should be monitored according to the recommendations presented in Section 6.2.2.

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

Following RP, the PSA level is expected to be undetectable. Biochemical recurrence is any rising PSA after prostatectomy as defined in Chapter 6. Prostate-specific antigen level is expected to be undetectable 2 months after a successful RP [1309]. Prostate-specific antigen is generally determined every 6 months until 3 years and yearly thereafter but the evidence for a specific interval is low [516] and mainly based on the observation that early recurrences are more likely to be associated with more rapid progression [1005, 1310, 1311]. A rising PSA may occur after longer intervals up to 20 years after treatment and depends on the initial risk group [932]. A yearly PSA after 3 years is considered adequate considering the fact that a longer interval to BCR is correlated with a lower EAU-BCR risk score but around 50% of recurrence should be expected beyond 3 years. As mentioned in Section 6.3.2 no definitive threshold can be given for relapse after RP. Persistently measurable PSA in patients treated with RP is discussed in Section 6.2.6.

Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with a PSA nadir < 0.01 ng/mL have a high (96%) likelihood of remaining relapse-free within 2 years [1312]. In addition, post-RP PSA levels > 0.01 ng/mL in combination with clinical characteristics such as ISUP grade and surgical margin status may predict PSA progression and can be useful to establish follow-up intervals [1311]. However, up to 86% of men were reported to have PSA values below 0.2 ng/mL at 5 years after an initial PSA nadir below 0.1 ng/mL within 6 months after surgery [1313]. Lastly, PSA and associated PSA-DT [1314] calculated prior to 0.2 ng/mL may help identify suitable candidates for early intervention [1315]. Prostate-specific antigen monitoring after salvage

RT to the prostatic fossa is done at similar intervals and an early and rapid PSA rise predicts more rapid progression [1310] and is correlated to metastases-free and PCa-specific survival [1316].

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

Following RT, PSA drops more slowly as compared to post RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT although the optimal cut-off value remains controversial [1317]. The interval before reaching the nadir can be up to 3 years, or more. At the 2006 RTOG-ASTRO Consensus Conference the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome (mainly metastases), namely, an increase of 2 ng/mL above the post-treatment PSA nadir [1004]. This definition also applies to patients who received HT [1004].

#### 7.1.3.1.4 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level although rarely [1318]. However, this has only been proven in patients with unfavourable 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 [1319]. 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 [1320, 1321].

#### 7.1.3.1.5 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).

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

Most patients who fail treatment for PCa do so within 7 years after local therapy [534]. Patients should be followed more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE (if considered) are recommended every 6 months until 3 years and then annually. Whether follow-up should be stopped if PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question.

Risk assessment to predict metastases-free and PCa-specific survival after recurrence after primary treatment may guide individual decisions on a need for longer follow-up [937, 1005, 1322]. Even in men with a PSA-DT less than 10 months after RP who choose to defer treatment, a median metastasis-free survival of 192 months and OS of 204 months from RP was observed, indicating the relatively long disease-free intervals observed in men with a rising PSA after local treatment [1323].

Symptomatic recurrence without a PSA rise is extremely rare, however, the symptoms typical for recurrent disease may vary and are poorly defined by published data. In case of the following symptoms PSA testing should be performed to exclude a possible cancer recurrence in particular in men not followed up by regular testing of their PSA levels: skeletal pain, haematuria, progressive voiding complaints, progressive lower body oedema, progressive bowel complaints or complaints of fatigue, sarcopenia or unexplained weight loss [1324].

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

Summary of evidence	LE
A rising PSA must be differentiated from a clinically meaningful relapse. The PSA threshold that best predicts further metastases after RP is > 0.4 ng/mL and > NADIR + 2 after IMRT/VMAT plus IGRT (± ADT).	3
Palpable nodules combined with increasing serum PSA suggest at least local recurrence.	2a

Recommendations	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and PSA measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

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

### **7.2.1 Introduction**

Androgen deprivation therapy is used in various situations: combined with RT for localised or locally-advanced disease, as monotherapy for a relapse after a local treatment, or in the presence of metastatic disease often in combination with other treatments. All these situations are based on the benefits of testosterone suppression either by drugs (LHRH agonists or antagonists) or orchidectomy. Inevitably, the disease will become castrate-resistant, although ADT will be maintained.

This section addresses the general principles of follow-up of patients on ADT alone. As treatment of CRPC and follow-up are closely linked, Section 6.5.7 includes further information on other drug treatments. Furthermore the specific follow-up needed for every single drug is outside the scope of this text, as is follow-up after chemotherapy.

To detect disease- and treatment-related complaints, regular clinical follow-up is mandatory and cannot be replaced by imaging or laboratory tests alone. Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs.

### **7.2.2 Purpose of follow-up**

The main objectives of follow-up in patients receiving ADT are to ensure treatment compliance, to monitor treatment response, to detect side effects early, and to guide treatment at the time of CRPC. After the initiation of ADT, it is recommended that patients are evaluated every 3 to 6 months. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

### **7.2.3 General follow-up of men on ADT**

Patients under ADT require regular follow-up, including monitoring of serum testosterone, creatinine, liver function and metabolic parameters at 3 to 6 month intervals. Men on ADT can experience toxicity independent of their disease stage.

#### **7.2.3.1 Testosterone monitoring**

Testosterone monitoring should be considered standard clinical practice in men on ADT. Many men receiving medical castration will achieve a castrate testosterone level (< 20 ng/dL), and most a testosterone level < 50 ng/dL. However, approximately 13–38% of patients fail to achieve these levels and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [1309] referred to as 'acute on-chronic effect' or 'breakthrough response' [1325]. Breakthrough rates for the < 20 ng/dL threshold were found to be more frequent (41.3%) and an association with worse clinical outcomes was suggested [1325].

The timing of measurements is not clearly defined. A 3 to 6-month testosterone level assessment has been suggested to ensure castration is achieved (especially during medical castration) and maintained. In case a castrate testosterone level is not reached, switching to another agonist or antagonist or to an orchiectomy should be considered. In patients with a confirmed rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castration-resistant state. Ideally, suboptimal testosterone castrate levels should be confirmed with mass spectrometry or an immunoassay [1326, 1327]. After ADT cessation (intermittent treatment or temporary ADT use as with EBRT) testosterone recovery is dependent on patients age and the duration of ADT [1328, 1329].

#### **7.2.3.2 Liver function monitoring**

Liver function tests will detect treatment toxicity (especially applicable for NSAA), but rarely indicate disease progression. Men on combined ADT should have their transaminase levels checked at least yearly but in particular in the first 6 months of treatment initiation since liver function disorders were observed relatively early in the majority of patients in larger trials [1330]. In view of potential liver toxicity a more frequent check is needed with some drugs (like abiraterone acetate) [1331]. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis, therefore it may be helpful to determine bone-specific isoenzymes as none are directly influenced by ADT [1332].

#### **7.2.3.3 Serum creatinine and haematological parameters**

Estimated glomerular filtration rate monitoring is good clinical practice as an increase may be linked to ureteral obstruction or bladder retention. A decline in haemoglobin is a known side effect of ADT. A significant decline after 3 months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue although other causes should be considered [1333]. Anaemia is often multi-factorial and other possible aetiologies should be excluded. An early decrease in haemoglobin 3 months after ADT initiation predicted better survival whereas a decrease beyond 6 months was associated with poor outcome in the SPCG-5 population [1334]. Radiotherapy to more extensive bone metastases locations may result in myelosuppression and haematological toxicity [1335, 1336].

#### 7.2.3.4 *Monitoring of metabolic complications*

The most severe complications of androgen suppression are metabolic syndrome, cardiovascular morbidity, mental health problems, and bone resorption (see Section 8.2.4.5).

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and routinely) in addition to checking blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Prior to starting ADT a cardiology consultation should be considered in men with a history of cardiovascular disease and in men older than 65 years. Men on ADT are at increased risk of cardiovascular problems and hypertension and regular checks are required [1337]. More profound androgen ablation resulted in a higher cardiovascular toxicity [1338] and cardio-respiratory fitness decreased even after 6 months of ADT [1339]. Although LHRH antagonists have been suggested to provide a more favourable cardiovascular toxicity profile compared to LHRH agonists, the prematurely closed PRONOUNCE study found no difference at 12 months in major adverse cardiovascular events between men receiving degarelix or leuprolide [1340].

#### 7.2.3.5 *Monitoring bone problems*

Androgen deprivation therapy increases the risk of osteoporosis. Administration of ADT for more than a year, as compared to less than one year, showed a higher risk of osteoporosis (HR: 1.77 and 1.38, respectively) [1341]. Several scores (e.g., Fracture Risk Assessment Tool [FRAX score], Osteoporosis Self-Assessment Tool [OST], Osteoporosis Risk Assessment Instrument [ORAI], Osteoporosis Index of Risk [OSIRIS], Osteoporosis Risk Estimation [SCORE]) can help identify men at risk of osteoporotic complications but validation of these scores in the ADT setting is required (see Section 8.3.2.2) [1342-1344].

Routine bone monitoring for osteoporosis should be performed using dual emission X-ray absorptiometry (DEXA) scan [1345-1347]. Presence of osteoporosis should prompt the use of bone protective agents. The criteria for initiation of bone protective agents are mentioned in Section 8.3.2.2. If no bone protective agents are given, a DEXA scan should be done regularly, at least every 2 years [1348].

A review summarising the incidence of bone fractures showed an almost doubling of the risk of fractures when using ADT depending on patients' age and duration and type of ADT with the highest incidence in older men and men on additional novel ARTA medication across the entire spectrum of disease [1349]. In case of an osteoporotic fracture a bone protective agent is mandatory. Vitamin D and calcium levels should be regularly monitored when patients receive ADT and patients should be supplemented if needed. (see Section 8.3.2.2).

#### 7.2.3.6 *Monitoring lifestyle, cognition and fatigue*

Lifestyle (e.g., diet, exercise, smoking status, etc.) affects QoL and potentially outcome [1332, 1333]. During follow-up men should be counselled on the beneficial effects of exercise to avoid ADT-related toxicity [1350]. Androgen deprivation therapy may affect mental and cognitive health and men on ADT are three times more likely to report depression [1351]. Attention to mental health should therefore be an integral part of the follow-up scheme. Men on ADT may experience complaints of fatigue possibly related to systemic inflammation [1352]. Cognitive performance and fatigue may arise within 6 months after initiation of ADT but can increase over time [1353]. These aspects affect patients as well as their partners and couple counselling should be considered [1354].

### 7.2.4 **Methods of follow-up in men on ADT without metastases**

#### 7.2.4.1 *Prostate-specific antigen monitoring*

Prostate-specific antigen is a key marker for following the course of androgen-sensitive non-metastasised PCa. Imaging should be considered when PSA is rising > 2 ng/mL or in case of symptoms suggestive of metastasis.

#### 7.2.4.2 *Imaging*

In general, asymptomatic patients with a stable PSA level do not require further imaging, although care needs to be taken in patients with aggressive variants when PSA levels may not reflect tumour progression [1355]. New bone pain requires at least targeted imaging and potentially a bone scan. When PSA progression suggests CRPC status and treatment modification is considered, imaging, by means of a bone and CT scan, is recommended for restaging. Detection of metastases greatly depends on imaging (see Section 6.3.4).

#### 7.2.5 **Methods of follow-up in men under ADT for metastatic hormone-sensitive PCa**

In metastatic patients it is of the utmost importance to counsel about early signs of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk. The intervals for follow-up in M1 patients should be guided by patients' complaints and can vary. Since most men will receive another anti-cancer therapy combined with ADT such as ARTA, chemotherapy or local RT, follow-up frequency should also be dependent on the treatment modality.

### 7.2.5.1 PSA monitoring

In men on ADT alone, a PSA decline to < 4 ng/mL suggests a likely prolonged response and follow-up visits may be scheduled every 3 to 6 months provided the patient is asymptomatic or clinically improving. This applied to men on ADT monotherapy as well as after ADT plus docetaxel [1151]. Depending on symptoms and risk assessment, more frequent visits may be indicated. Treatment response may be evaluated based on a change in serum PSA level [1150, 1151] and bone- and CT scan although there is no consensus about how frequently these should be performed [1287]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. A rising PSA should prompt assessment of testosterone level, which is mandatory to define CRPC status, as well as restaging using imaging. However, it is now recognised that a stable PSA during ADT is not enough to characterise a non-progressive situation [1356].

### 7.2.5.2 Imaging as a marker of response in metastatic PCa

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [1357, 1358].

When bone scan is used to follow bone metastases, a quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1359]. Nonetheless, bone scan is limited by the so-called 'flare' phenomenon which is defined by the development of new images induced by treatment on a first follow-up scan which, after longer observation, actually represent a favourable response. Flare is observed within 8 to 12 weeks of treatment initiation and can lead to a false-positive diagnosis of disease progression. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. Magnetic resonance imaging can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available [1360]. The ability of PET/CT to assess response has been evaluated in a few studies. Until further data are available, MRI and PET/CT should not be used outside trials for treatment monitoring in metastatic patients [1361].

Men with metastasised PCa on ADT should also in the absence of a PSA rise be followed up with regular imaging since twenty-five percent of men with, or without, docetaxel in the CHAARTED trial developed clinical progression without a PSA rise [1356]. One in eight men with a PSA < 2 ng/mL showed clinical progression [1356]. The addition of docetaxel to ADT in the CHAARTED trial population did not reduce the incidence of clinical progression at low PSA values and this rate was similar for both low- and high-volume disease as per CHAARTED criteria [1356]. However, the optimal timing and image modality to be used remain unclear, as is the real clinical value of any findings.

### 7.2.6 Guidelines for follow-up during hormonal treatment

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3–6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong



## 8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (Section 8.2) will summarise long-term consequences ( $\geq 12$  months) of therapies for PCa. Based on two systematic reviews, the second (Section 8.3) provides evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and also supportive interventions aimed at improving disease-specific QoL across all stages of disease.

### 8.1 Introduction

Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as close relations and work or vocation. These multifaceted issues all have a bearing on an individual's perception of QoL [1362]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others including fellow patients. Attention to the psychosocial concerns of people with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1363]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Psychological distress can be caused by the cancer diagnosis itself, cancer symptoms and/or treatment side effects [1364]. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed. Cross-sectional patient-reported outcomes studies in general PCa populations show the impact of treatment on global and disease-specific QoL is greater than that described in clinical trial populations who often have less co-morbidity and belong to higher socio-economic groups. Individuals undergoing two or more treatments have more symptoms and greater impact on QoL [1365, 1366].

### 8.2 Adverse effects of PCa therapies

#### 8.2.1 Surgery

A lack of clear consensus in reporting surgical complications following RP, specifically urinary incontinence and stricture rates, and the introduction of different techniques has resulted in a wide variation in the types of complications reported, as well as variation in the overall incidence of complications [1367-1370]. The most common post-operative complication is ED but other related issues to consider include dry ejaculation, which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [1371]. The second most commonly occurring complication is long-term incontinence [1367-1370] but voiding difficulties may also occur associated with bladder neck contracture (e.g., 1.1% after RALP) [1372].

For those undergoing minimally invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar and can occur more rarely with 8 mm and 5 mm trocars [1373]. A key consideration is whether long-term consequences of surgery are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [555, 645-648], and can be compared with contemporaneous reports after RRP [649]. From these reports, the mean continence rates at 12 months were 89–100% for patients treated with RALP and 80–97% for patients treated with RRP. A prospective controlled non-randomised trial of patients undergoing RP in 14 centres using RALP or RRP demonstrated that at 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The unadjusted OR was 1.08 (95% CI: 0.87–1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The unadjusted OR was 0.81 (95% CI: 0.66–0.98) [650, 1374]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1374, 1375]. A single-centre randomised phase III study comparing RALP and RRP ( $n = 326$ ) also demonstrates similar functional outcomes with both techniques at 24 months [550]. Prostatectomy was found to increase the risk of complaints from an inguinal hernia, in particular after an open procedure when compared to minimal invasive approaches [1376, 1377].

#### 8.2.2 Radiotherapy

##### 8.2.2.1 Side-effects of external beam radiotherapy

Analysis of the toxicity outcomes of the ProtecT trial shows that patients treated with EBRT and 6 months of ADT report bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding (described in detail in Section 8.3.1.1 below) [1378]. 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 [1379].

A systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrates an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62) with similar risks over lag times of



5 and 10 years. Absolute excess risks over 10 years are small (1–4%) but should be discussed with younger patients in particular [1380].

#### 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%) [1381]. Chronic urinary morbidity is more common with combined EBRT and BT and can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Urethral strictures account for at least 50% of urinary complications and can be resolved with dilation in the majority [763, 769]. Prevention of morbidity depends on careful patient selection and IPSS score, backed up by urodynamic studies.

### 8.2.3 **Local primary whole-gland treatments other than surgery or radiotherapy**

#### 8.2.3.1 *Cryosurgery*

In 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 [827]. There was no significant difference between cryotherapy vs. EBRT in terms of urinary incontinence at one year (< 1%); cryotherapy had a similar ED rate (range 0–40%) to RP at one year. There were insufficient data to compare cryotherapy vs. EBRT in terms of ED.

#### 8.2.3.2 *High-intensity focused ultrasound*

In terms of toxicity there are insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at one year HIFU had lower incontinence rates than RP (OR: 0.06, 95% CI: 0.01–0.48) [827].

### 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 partners can be found in two clinical reviews [1382, 1383].

A small RCT evaluated the QoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. Patients treated by ADT reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue and irritability during treatment [1384]. 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 [1385]. A prospective observational study of non-metastatic PCa found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [1386]. Another retrospective non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than patients undergoing orchiectomy. The stage at diagnosis had no effect on health outcomes [1387].

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 [1388]. 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 [1389], preserved libido and erectile function [1390]. 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 people undergoing ADT, affecting up to 93% [1391]. Androgen deprivation therapy reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1392].

#### 8.2.4.2 *Hot flushes*

Hot flushes are a common side-effect of ADT (prevalence estimated between 44–80% of men on ADT) [1391]. They appear 3 months after starting ADT, usually persist long-term and have a significant impact on QoL.

Serotonin re-uptake inhibitors (e.g., venlafaxine or sertraline) also appear to be effective in men but less than hormone therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [1393]. After 6 months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, venlafaxine was inferior -47.2% (interquartile range -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group.

With a placebo effect influencing up to 30% of patients [1394], the efficacy of clonidine, veralipride,

gabapentine [1395] and acupuncture [1396] 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) [1397]. Severe fractures in men are associated with a significant risk of death [1398]. A precise evaluation of BMD should be performed by DEXA, ideally before or shortly after starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture and causes should be investigated. Other risk factors include increasing age, body mass index of 19 or less, history of previous fracture or parent with fractured hip, current smoking, use of glucocorticoids, rheumatoid arthritis, alcohol consumption > 2 units per day, history of falls and a number of other chronic medical conditions [1399]. Fracture risk algorithms which combine BMD and clinical risk factors such as FRAX score can be used to guide treatment decisions but uncertainty exists regarding the optimal intervention threshold, therefore no specific risk algorithm can be recommended for men on ADT for PCa. Obesity (increase in body fat mass by up to 10% and/or body mass index > 30) and sarcopenia (decrease in lean tissue mass by up to 3%) as well as weight loss are common and occur during the first year of ADT [1400]. These changes increase the fracture risk [1401].

Bicalutamide monotherapy may have less impact on BMD but is limited by its suboptimal efficacy [1402, 1403] (see Section 6.1.4.1.5.2.3). The intermittent LHRH-agonist modality might be associated with less bone impact [1404].

#### 8.2.4.4 *Metabolic effects*

Lipid alterations are common and may occur as early as the first 3 months of treatment [1400]. Androgen deprivation therapy also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [1405], 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 [1406]:

- 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 [1407]. Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [1408]. 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 [1409].

#### 8.2.4.5 *Cardiovascular morbidity*

Cardiovascular mortality is a common cause of death in PCa patients [1140, 1410, 1411]. Several studies showed that ADT after only 6 months was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1412]. The RTOG 92-02 [1413] and 94-08 [1414] 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 and EORTC 22863 [1415]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [1416, 1417]. A meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease patients treated for PCa, e.g. the associations between 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 [1418]. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1419] or presenting with a metabolic syndrome [1420]. It has been suggested that antagonists might be associated with less cardiovascular morbidity compared to agonists, but, as yet, there is no definite evidence [1340]. In a phase III RCT the use of relugolix, an oral LHRH antagonist, was associated with a reduced risk of major adverse cardiovascular events when compared to leuprolide, an injectable LHRH agonists, at 2.9% vs.

6.2%, respectively, over a follow-up time of 48 weeks (HR 0.46, 95% CI: 0.24–0.88 [795]).

These concerns about LHRH agonists resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [1139]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, minimising alcohol intake, improved nutrition and smoking cessation [71, 1421].

#### 8.2.4.6 *Fatigue*

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure. Reporting clinically significant fatigue is associated with severe psychological distress and should prompt screening for anxiety and/or depression [1422]. Anaemia may be a cause of fatigue [1391, 1423]. 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 may be required in patients with severe anaemia. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [1424].

#### 8.2.4.7 *Neurological side effects*

Castration seems also to be associated with an increased risk of stroke [1425], and is suspected to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1426].

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

Living longer with PCa does not necessarily equate to living well [1362, 1363]. There is clear evidence of unmet needs and ongoing support requirements for some individuals after diagnosis and treatment for PCa [1427]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety and stress in caregivers [1428]. 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 [1382, 1429]. Direct symptoms from advanced or metastatic cancer, e.g., pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1430, 1431]. Patients' QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1432, 1433].

The concept of 'quality of life' is subjective and can mean different things to different people, 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 after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated systematic reviews around cancer-specific QoL outcomes in patients with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

The tools with the best evidence for psychometric properties and feasibility for use in routine practice and research settings to assess PROMs in patients with localised PCa were EORTC QLQ-C30 and QLQ-PR25. Since EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25 module [1434].

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

Questionnaire	Domains/items
Functional Assessment of Cancer Therapy-General (FACT-G) [1435]	Physical well-being, social/family well-being, emotional well-being, and functional well-being.
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1436]	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) [1437]	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) [1438]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Expanded prostate cancer index composite (EPIC) [1439]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [1440]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1441]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [1442]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [1443]	Urinary, bowel, and sexual domains.

### 8.3.1 **Long-term (> 12 months) quality of life outcomes in men with localised disease**

#### 8.3.1.1 *Men undergoing local treatments*

The results of the ProtecT trial (n = 1,643 men) reported no difference in EORTC QLQ-C30 assessed global QoL, up to 5 years of follow-up in men aged 50–69 years with T1–T2 disease randomised for treatment with AM, RP or RT with 6 months of ADT [1378]. 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 [1370, 1444]. The Prostate Cancer Outcomes Study (PCOS) studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT [1370]. 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 [1379]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side effects is reduced with IMRT compared to older 3D-CRT techniques. This is supported by a contemporary 5-year prospective, population-based cohort study where PROMs were compared in men with favourable- and unfavourable-risk localised disease [1444]. 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 compared to pre-treatment values [1445]. 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 [1446]. 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 [1447].

### 8.3.1.2 Guidelines for quality of life in men undergoing local treatments

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

### 8.3.2 Improving quality of life in men who have been diagnosed with PCa

#### 8.3.2.1 Men undergoing local treatments

In men with localised disease, nurse-led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, relationship issues, depression, managing bowel and urinary function problems) provided positive short-term effects (4 months) on sexual function (effect size 0.45) and long-term (12 months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [1448].

Exercise programs during RT combined with ADT result in consistent benefits for cardiovascular fitness (standardised mean difference [SMD], 0.83; 95% CI: 0.31–1.36;  $p < 0.01$ ) and muscle function (SMD, 1.30; 95% CI: 0.53–2.07;  $p < 0.01$ ) with a reduction in urinary toxicity (SMD, -0.71; 95% CI: -1.25 to -0.18;  $p < 0.01$ ) [1449].

Evidence of moderate quality shows that supervised exercise therapy probably is superior to no exercise therapy in improving ‘disease-specific quality of life’ and ‘walking performance’ in patients with PCa undergoing ADT. The results apply to all patients receiving ADT regardless of cancer stage [1450].

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 [1451]. 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% [1452].

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 [1453]. However, a multi-centre double blind RCT ( $n = 423$ ) in men aged  $< 68$  years, with normal pre-treatment erectile function undergoing either open, conventional or robot-assisted laparoscopic nerve-sparing RP, tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6, 95% CI: 3.1–16.0) when compared to 20 mg ‘on demand’ or placebo at 9 months of follow-up [678]. 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 [1454]. A detailed discussion can be found in the EAU Sexual and Reproductive Health Guidelines [1455].

#### 8.3.2.2 Men undergoing systemic treatments

Similar to men treated with a radical approach (see above), in men with T1-T3 disease undergoing RT and ADT, a combined nurse-led psychological support and physiotherapist-led multi-disciplinary rehabilitation has reported improvements in QoL. Specifically this intervention involved action planning around patients’ needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5, 95% CI: 0.6–8.4), irritative (adjusted mean 5.8, 95% CI: 1.4–10.3) and hormonal (adjusted mean 4.8, 95% CI: 0.8–8.8) EPIC domains were found up to 22 weeks of follow-up [1456]. In a 3-year follow-up with 92% response rate from the initial study, fewer participants had moderate-severe bowel problems in the intervention ( $n = 2$ ; 3%) vs. control group ( $n = 10$ ; 14%) ( $p = 0.016$ ) but the benefits in terms of urinary function were maintained only in those participants with moderate-severe urinary problems at baseline [1457].

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 [1458]. 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 [1459, 1460]. 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) [1423]. Supervised exercise interventions delivered over 12 months are effective in reducing psychological distress; particularly in those men with highest levels of baseline anxiety and depression [1461]. In untrained older men, systematic review suggests lower volume exercise programs at moderate-to-high intensity are as effective as higher volume resistance training for enhancing body composition, functional capacity and muscle strength and may reduce barriers to exercise and enhance adherence [1462].

If dietary intake is not adequate, vitamin D and calcium supplementation should be offered, as there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [1463]. Online tools are available to calculate daily calcium intake for individual patients. For vitamin D deficiency a dose of at least 800 IU/day colecalciferol can be recommended. Use of a 25(OH) assay may be helpful to measure vitamin D levels [1464, 1465].

Anti-resorptive therapy is recommended for men on ADT for > 6 months with either a BMD T score of < -2.5 or with an additional risk factor for osteoporosis or annual bone loss confirmed to exceed 5%, or in cases of severe fracture. Referral to a bone specialist should be considered in complex cases with severe fracture and/or multiple risk factors. Alendronate, risedronate, zoledronate and denosumab have all been shown to prevent bone loss in men with hormone-sensitive locally-advanced and metastatic PCa on ADT [1466-1469]. Patients should be warned about the < 5% risk of osteonecrosis of the jaw and/or atypical femoral fractures associated with these drugs. Bisphosphonates increase BMD in the hip and spine by up to 7% in one year [1468, 1470]. The optimal regimen for zoledronic acid for men on ADT with hormone-sensitive locally-advanced and metastatic PCa remains unclear: quarterly [1471] or yearly [1472] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1473]. A quarterly regimen should be considered for a BMD  $\leq$  2.5 as a yearly injection is unlikely to provide sufficient protection [1474, 1475]. Care should be taken when discontinuing treatment as rebound increased bone resorption can occur.

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after 2 years, using a 60 mg subcutaneous regimen every 6 months [1476]. 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 [1298] without any impact on OS, but with an increase in side effects. Therefore, this later regimen cannot be recommended.

### 8.3.2.3 Decision regret

Several treatments with curative intent for localised PCa are available all with comparable 10-year OS [516]. They vary in terms of the incidence of major side effects, including urinary symptoms, bowel symptoms and compromised sexual functioning [1378, 1379, 1477]. For this reason, patients' treatment preferences, in which they weigh expected benefits against likely side effects, are a central consideration in shared decision-making and in making informed treatment decisions [1478-1480].

It remains challenging, however, to evaluate whether the decision-making process can be viewed as successful; that is, whether the choice of treatment best reflects the patient's preferences and expectations [1481, 1482]. According to Decision Justification Theory (DJT), it is the more specific information on which treatment experiences lead to regret that decision regret needs to be better understood and to minimise it in future patients [1483]. Maguire *et al.*, found that about 25% of men with PCa undergoing either single or combined modality treatments report experiencing worse side effects than expected [1484]. Schroeck *et al.*, found urinary incontinence most strongly correlated with regret after prostatectomy [1485].

Unmet expectations are comparable among the treatment groups, except for fatigue. Fatigue is less frequently reported as worse than expected by patients who received BT when compared to patients who received RP or EBRT. This could be explained by the less invasive treatment course of BT in comparison to EBRT with or without ADT and RP [1486]. Unmet expectations were more frequently reported by patients with positive surgical margins following surgery; having had a passive role in the decision-making process; and who had higher scores on the decisional conflict scale (i.e. more uncertainty about the treatment decision). Interestingly, positive surgical margins are not directly associated with an increased risk of PC-related mortality [1064]. Active participation and support in the process of forming a preference increases the chance of choosing a treatment that is in line with patients' expectations [1480, 1487-1489].

While it may seem desirable to tailor the patients' role in decision-making to their initial preference, and particularly to a preference for deferring to the advice of the clinician, this does not result in less decisional conflict or regret. Increasing patients knowledge regardless of initial preference may actually be preferable [1485].



### 8.3.2.4 Decision aids in prostate cancer

Shared decision-making can increase patients' comfort when confronted with management decisions but has been shown to improve health outcome [1490] and more training seems needed for health care professionals guiding patients [1491]. Patient education decreased PSA testing [1492] and increased adherence to active surveillance protocols [1493, 1494]. Autonomous active decision-making by patients was associated with less regret after prostatectomy regardless of the method chosen and decision aids reduce decisional conflict [1495]. Still, guidance is needed to optimise patients' understanding of the options [1496]. Patients prioritised effectiveness and pain control over mode of administration and risk of fatigue when confronted with treatment choice in metastasised PCa [1497]. When implementing decision aids clinical validity and utility should be carefully evaluated and distinguished [1498]. A decision aid should educate as well as promote shared decision-making to optimise efficacy [1499] and pay attention to communicative aspects [1500].

### 8.3.2.5 Guidelines for quality of life in men undergoing systemic treatments

Recommendations	Strength rating
Offer men on androgen deprivation therapy (ADT), 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise men on ADT to maintain a healthy weight and diet, to stop smoking, reduce alcohol to $\leq 2$ units daily and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men with T1–T3 disease specialist nurse-led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	Strong
Offer men starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Offer anti-resorptive therapy to men on long term ADT with either a BMD T-score of $< -2.5$ or with an additional clinical risk factor for fracture or annual bone loss on ADT is confirmed to exceed 5%.	Strong

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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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