EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer

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9. REFERENCES

10. CONFLICT OF INTEREST
1. INTRODUCTION

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

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

Guidelines are not mandates and do not purport to be a legal standard of care.

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

All imaging sections in the text have been developed, jointly with the European Society of Urogenital Radiology (ESUR). Representatives of ESUR in the PCa Guidelines Panel are (in alphabetical order): Prof. Dr. O Rouvière and Dr. I.G. Schoots.

Section 6.3: Treatment - Definitive Radiotherapy, has 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. M. Bolla, Prof. Dr. A.M. Henry, Prof. Dr. M.D. Mason and Prof. Dr. T. Wiegel.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/prostatecancer/?type=panel.

1.2.1 Acknowledgement
The PCa Guidelines Panel are most grateful for the support and considerable expertise provided by Prof. Dr. J-P. Droz, Emeritus Professor of Medical Oncology (Lyon, France) on the topic of ‘Management of PCa in senior adults’. As a leading expert in this field, and prominent member of the International Society of Geriatric Oncology, his contribution has been invaluable.

1.3 Available publications
A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile 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 2017 document presents a full update of the 2016 full text document.

1.4.2 Summary of changes
New and relevant evidence has been identified, collated and appraised through a structured assessment of the literature and incorporated in all chapters of the 2017 EAU PCa Guidelines.

Key changes for the 2017 print:
• Chapter 3 - Epidemiology and aetiology. This section has been completely renewed.
• Chapter 4 - Classification and staging systems. This chapter has been expanded with a new section (4.3 Prognostic relevance of stratification). Additional information on the International Society of Urological Pathology Gleason grading has been included in Table 4.2.2 (EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer).
• Section 6.6.8 - Imaging as marker of response in metastatic prostate cancer. This is a new section.
• Chapter 6.7 - Management of PCa in older men. Two new figures have been included.
• Chapter 8 - Quality of life outcomes in prostate cancer. This chapter is partly based on the findings of a new systematic review (SR) (see below). A second review is ongoing, the findings of which will be incorporated in the 2018 print of these Guidelines.
Changes in the summaries of evidence and recommendations can be found in sections:

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

#### Summary of evidence

- Prostate cancer is a major health issue in men, the incidence mainly dependent on age.
- Genetic factors are associated with risk of (aggressive) PCa but ongoing trials will need to define the clinical applicability of screening for genetic susceptibility of PCa.
- A variety of exogenous/environmental factors may have an impact on the risk of progression.
- 5-ARIs are not EMA-approved for PCa prevention.
- Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.
- In hypogonadal men, testosterone supplementation does not increase the risk of PCa.

#### Recommendation

- No definitive recommendation can be provided for specific preventive or dietary measures to reduce the risk of developing prostate cancer.

### Table 4.2.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

<table>
<thead>
<tr>
<th>Definition</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSA &lt; 10 ng/mL and GS &lt; 7 (ISUP Grade 1) or cT1-2a</td>
<td>PSA 10-20 ng/mL or GS 7 (ISUP Grade 2/3) or cT2b</td>
<td>PSA &gt; 20 ng/mL or GS &gt; 7 (ISUP Grade 4/5) or cT2c</td>
</tr>
<tr>
<td>Locality</td>
<td>Localised</td>
<td>Locally advanced</td>
<td></td>
</tr>
</tbody>
</table>
|            | GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

### 6.1.5 Guidelines for active surveillance and watchful waiting

#### Recommendations - active surveillance

- Perform multiparametric magnetic resonance imaging before a confirmatory biopsy. **LE 2b**
- During confirmatory biopsy include systematic and targeted biopsies. **LE 2a**

### 6.2.7.5 Guidelines for eLND in prostate cancer and pN+ patients

- **Recommendation**: Do not perform a frozen section of nodes during radical prostatectomy to decide whether to proceed with, or abandon, the procedure.

### 6.2.10 Guidelines for radical prostatectomy

- **Recommendations**: Offer both radical prostatectomy and radiotherapy in patients with low- and intermediate-risk disease and a life expectancy > 10 years. **LE 1b**
- **Recommendations**: Offer active surveillance as an alternative to surgery in patients with low-risk disease and a life expectancy of > 10 years. **LE 1b**
6.3.8 Summary of evidence and guidelines for definitive radiotherapy

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The optimum duration of androgen deprivation therapy (ADT) with external beam radiation therapy (EBRT) is well established in the literature. There is no evidence that these durations should change when using brachytherapy boost with EBRT.</td>
<td>1b</td>
</tr>
<tr>
<td>Limited data, from experienced centres only, are available for the use of fractionated high-dose-rate brachytherapy as monotherapy in patients with low and intermediate-risk PCa.</td>
<td>2a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate hypofractionation (HFX) with IMRT including image-guided radiation therapy (IGRT) to the prostate only can be offered to carefully selected patients with localised disease (as discussed in the text).</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Moderate HFX should adhere to radiotherapy-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

6.9.4.6 Guidelines for imaging in patients with biochemical recurrence

<table>
<thead>
<tr>
<th>Prostate-specific antigen (PSA) recurrence after radical prostatectomy</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ≥1 ng/mL: position emission tomography (PET)/computed tomography (CT) imaging is recommended using choline or prostate-specific membrane antigen (PMSA).</td>
<td>2b</td>
<td>A</td>
</tr>
</tbody>
</table>

8.3.1.1 Guidelines for long term quality of life in men with localised disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advise eligible patients for active surveillance, that global quality of life is equivalent for up to five years compared to radical prostatectomy or radiotherapy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.</td>
<td>1b</td>
<td>C</td>
</tr>
</tbody>
</table>

8.3.2.1 Guidelines on improving quality of life in men who have been diagnosed with prostate cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer men on androgen deprivation therapy, twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>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.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

2. METHODS

2.1 Data identification

For the 2017 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 Guidelines was performed. The search was limited to studies representing only high levels of evidence (i.e. SRs with meta-analysis, randomised controlled trials (RCTs), and prospective comparative studies) published in the English language. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time
frame between June 1st 2015 to June 23rd, 2016. A total of 1,914 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/prostatecancer?type=appendices-publications.

Specific sections of the text have been updated based on a SR questions prioritised by the Guidelines Panel. These reviews were performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html:

- What is the negative predictive value of multiparametric MRI in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the EAU Prostate Cancer Guidelines Panel [prior to print] [3].
- The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A systematic review [4].
- Systematic review of quality of life outcomes as assessed by PROMS following primary treatment of clinically localised prostate cancer.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/.

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) and the European Society for Urogenital Radiology (ESUR) have endorsed the PCa Guidelines.

2.2 Review
Publications ensuing from the systematic reviews have all been peer-reviewed. The following sections were subjected to peer review prior to publication:

All Imaging sections:
- Section 5.2.3 - The role of imaging in PCa diagnosis;
- Section 5.3 - The role of imaging in clinical staging;
- Section 6.1.2.1 - The role of multiparametric magnetic resonance imaging in active surveillance
- Section 6.6.8 (new section) - Imaging as a marker of response in metastatic PCa,
- Sections 6.10.4 and 6.10.5 - The role of imaging in PSA-only recurrence after treatment with curative intent.
- Section 6.10 – Treatment - Management of PSA-only recurrence after treatment with curative intent.
- Section 6.10 – Treatment – Castration-resistant PCa

2.3 Future goals
The results of ongoing and new SRs will be included in the 2017 update of the PCa Guidelines.

Ongoing SRs:
- How does biochemical recurrence following curative treatment for prostate cancer impact on overall survival, cancer-specific survival and development of metastatic disease? [6].
- What evidence based supportive interventions improve disease-specific quality of life in men with prostate cancer?

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology
Prostate cancer remains the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [7]. The frequency of autopsy-detected PCa is roughly the same worldwide [8]. A SR of autopsy studies showed a prevalence of PCa at age < 30 years of 5% (95% CI: 3-8%), increasing by an odds ratio of 1.7 (1.6-1.8) per decade, to a prevalence of 59% (48-71%) by age > 79 years [9].

The incidence of PCa diagnosis, however, varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] of 111.6 and 97.2 per 100,000, respectively), and in Western and Northern Europe (ASR 94.9 and 85), 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 (ASR 10.5 and 4.5), whilst rates in Eastern and Southern Europe, which were low, have showed a steady increase [7, 8].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (Caribbean, 29 per 100,000 and Sub-Saharan Africa, ASRs 19-24 per 100,000), intermediate in the USA and very low in Asia (2.9 per 100,000 in South-Central Asia) [7].

3.2 Aetiology
3.2.1 Family history/genetics
Family history and racial/ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [10, 11]. However, only a small subpopulation of men with PCa (~9%) have true hereditary disease. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset PCa (< 55 years) [11]. Patients with hereditary PCa usually have a disease onset six-seven years earlier than average, but their clinical course does not seem to differ in other ways, e.g. for disease aggressiveness [11, 12]. Men with African ethnicity origin show a higher incidence of PCa and generally have a more lethal course of disease [13].

Of the underlying determinants of genomic diversity and mechanisms between genetic and environmental factors, much remains unknown. Genome-wide association studies have identified 100 common susceptibility loci contributing to the risk for PCa, explaining ~38.9% of the familial risk for this disease [14, 15]. Furthermore, an incidence was found of 11.8% of germline mutations in genes mediating DNA-repair processes among men with metastatic PCa [16]. Germline mutations in genes such as HOXB13 and BRCA1/2 have been associated with an increased risk of PCa, targeted genomic analysis of these genes could offer options to identify families at high risk [17, 18]. Trials of screening for PCa-targeting BRCA mutation carriers are ongoing [19].

3.2.2 Risk factors
As Japanese men move from Japan to California, their risk of PCa increases, approaching that of American men [20]. A wide variety of exogenous/environmental factors have been discussed as being aetiologically important for the risk of progression from latent to clinical PCa [21]. However, currently there are no effective preventative dietary or pharmacological interventions.

3.2.2.1 Metabolic syndrome (MetS)
The single components hypertension (p = 0.035) and waist circumference > 102 cm (p = 0.007) of MetS have been associated with a significantly greater risk of PCa, but conversely, having > 3 components of MetS is associated with a reduced risk (odds ratio [OR]: 0.70 95%; CI: 0.60-0.82) [22, 23].

3.2.2.1.1 Diabetes/metformin
On a population level, metformin users (but not other oral hypoglycaemics) 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) [24]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with PCa (OR: 1.19; p = 0.50) [25].

3.2.2.1.2 Cholesterol/statins
A meta-analysis of fourteen large prospective studies did not show an association between blood total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) levels and the risk of either overall PCa or high-grade PCa [26]. Results of the REDUCE study also did not show a preventive effect of statins on PCa risk [25].

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) [27]. This effect seems mainly explained by environmental determinants of height/BMI rather than genetically elevated height or BMI [28].

3.2.2.2 Dietary factors
The association between a wide variety of dietary factors and PCa have been studied (Table 3.1).
Table 3.1: Dietary factors that have been associated with prostate cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>High alcohol intake, but also total abstention from alcohol have been associated with a higher risk of PCa and PCa-specific mortality [29].</td>
</tr>
<tr>
<td>Dairy</td>
<td>A weak correlation between insulin-like growth factor-I (IGF-1) levels and high intake of protein from dairy products and the risk of PCa was found [30].</td>
</tr>
<tr>
<td>Fat</td>
<td>No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCas was found [31]. A relation between intake of fried foods and risk of PCa may exist [32].</td>
</tr>
<tr>
<td>Lycopene (carotenes)</td>
<td>A trend towards a favourable effect of lycopene on PCa incidence has been identified in meta-analyses [33], RCTs comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [34].</td>
</tr>
<tr>
<td>Meat</td>
<td>A meta-analysis did not show an association between red meat or processed meat consumption and PCa [35].</td>
</tr>
<tr>
<td>Vitamin D (25(OH)D)</td>
<td>An 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 [36, 37].</td>
</tr>
<tr>
<td>Selenium/Vitamin E</td>
<td>Selenium and Vitamin E were found not to affect PCa incidence [38].</td>
</tr>
</tbody>
</table>

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 Gleason 6 cancer only), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade PCa [39-41]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for this indication.

3.2.2.3.2 Testosterone
Hypogonadal men receiving testosterone supplementation did not have an increased risk of PCa [42].

3.2.2.4 Other risk factors
Balding was associated with a higher risk of PCa death [43]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR:1.31; 95% CI: 1.14-1.52) [44]. Occupational exposure may also play a role, based on a meta-analysis, night-shift work is associated with an increased risk (2.8%; p = 0.030) of PCa [45]. Pilots also have been found to have an increased risk of PCa diagnosis (RR 2.0) [46]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24; 95% CI: 1.18-1.31) [47].

In contradiction, vasectomy was not associated with an increased risk of PCa [48]. No association between self-reported acne and risk of (aggressive) PCa was found [49]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa [50, 51]. Ultraviolet radiation exposure decreased the risk of PCa (hazard ratio [HR]: 0.91; 95% CI: 0.88-0.95) [52]. A protective effect for PCa of circumcision was found [53]. Higher ejaculation frequency (~ 21 times per month versus 4-7 times) has been associated with a 20% lower risk of PCa [54].

3.2.3 Summary of evidence and guidelines for epidemiology and aetiology

Summary of evidence
Prostate cancer is a major health issue in men, the incidence mainly dependent on age.

Genetic factors are associated with risk of (aggressive) PCa but ongoing trials will need to define the clinical applicability of screening for genetic susceptibility of PCa.

A variety of exogenous/environmental factors may have an impact on the risk of progression.

5-ARIs are not EMA-approved for PCa prevention.

Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.

In hypogonadal men, testosterone supplementation does not increase the risk of PCa.

Recommendation
No definitive recommendation can be provided for specific preventive or dietary measures to reduce the risk of developing prostate cancer.
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 formulation of recommendations for the treatment of these patient populations. Throughout these Guidelines the 2017 Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1.1) [55] and the EAU risk group classification, which is essentially based on D’Amico’s classification system for PCa, are used (Table 4.2.2) [56]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after surgery or external beam radiotherapy (EBRT).

Table 4.1.1: Tumour Node Metastasis (TNM) classification of PCa [55]

<table>
<thead>
<tr>
<th>T - Primary Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
</tr>
<tr>
<td>T1 Clinically inapparent tumour that is not palpable</td>
</tr>
<tr>
<td>T1a Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)</td>
</tr>
<tr>
<td>T2 Tumour that is palpable and confined within the prostate</td>
</tr>
<tr>
<td>T2a Tumour involves one half of one lobe or less</td>
</tr>
<tr>
<td>T2b Tumour involves more than half of one lobe, but not both lobes</td>
</tr>
<tr>
<td>T2c Tumour involves both lobes</td>
</tr>
<tr>
<td>T3 Tumour extends through the prostatic capsule¹</td>
</tr>
<tr>
<td>T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement</td>
</tr>
<tr>
<td>T3b Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional Lymph Nodes²</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1 Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant Metastasis³</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>M1a Non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b Bone(s)</td>
</tr>
<tr>
<td>M1c Other site(s)</td>
</tr>
</tbody>
</table>

¹ Invasion into the prostate apex or into (but not beyond) the prostate capsule is not classified as T3, but as T2.
² Metastasis no larger than 0.2 cm can be designated pNmi.
³ T2a to c only exist for clinical T2 (cT2). For pathological T2 they are no longer present in the 2017 TNM. Only pT2 exists.

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

The 2005 International Society of Urological Pathology (ISUP) modified Gleason score of biopsy-detected PCa comprises the Gleason grade or the most extensive (primary pattern) pattern, plus the second most common pattern (secondary pattern), if two are present. If one pattern is present, it needs to be doubled to yield the Gleason score. For three grades, the Gleason score comprises the most common grade plus the highest grade, irrespective of its extent. When a carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the Gleason score. A Gleason score ≤ 4 should not be given based on prostate biopsies [57]. In addition to reporting of the carcinoma features for each biopsy, an overall (or global) Gleason score based on the carcinoma-positive biopsies can be provided. The 2014 ISUP Gleason grading conference of prostatic carcinoma [58, 59] limits the number of PCa grades, ranging them from 1 to 5 (see table 4.2.1), in order to:

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

The ISUP 2014 Gleason grading represents a compression of Gleason scores ≤ 6 to ISUP grade 1, and Gleason scores 9-10 to ISUP grade 5, whereas Gleason score 7 is expanded to ISUP grade 2, i.e. 7 (3 + 4) and ISUP grade 3, i.e. 7 (4 + 3).

Table 4.2.1: International Society of Urological Pathology 2014 grades

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>ISUP grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>1</td>
</tr>
<tr>
<td>7 (3 + 4)</td>
<td>2</td>
</tr>
<tr>
<td>7 (4 + 3)</td>
<td>3</td>
</tr>
<tr>
<td>8 (4 + 4 or 3 + 5 or 5 + 3)</td>
<td>4</td>
</tr>
<tr>
<td>9-10</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4.2.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

<table>
<thead>
<tr>
<th>Definition</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td>PSA &lt; 10 ng/mL and GS &lt; 7 (ISUP grade 1) and cT1-2a</td>
<td>PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) and cT2b</td>
<td>PSA &gt; 20 ng/mL or GS &gt; 7 (ISUP grade 4/5) or cT2c</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>any PSA or GS cT3-4 or cN+</td>
<td>Any ISUP grade</td>
<td></td>
</tr>
</tbody>
</table>

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

4.3 Prognostic relevance of stratification
A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management. The adoption of the current ISUP grading system, defining the split-up of Gleason score 7 cancers into ISUP grade 2 (primary Gleason grade 3) and ISUP 3 (primary Gleason grade 4) because of their distinct prognostic impact [59] strengthens such a separation of the intermediate-risk group into a low-intermediate (ISUP grade 2) and high intermediate-risk (ISUP grade 3) group. Emerging clinical data support this distinction between favourable- and unfavourable-risk patient categories within the intermediate-risk group [60].

5. DIAGNOSTIC EVALUATION

5.1 Screening and early detection
Population or mass screening is defined as the ‘systematic examination of asymptomatic men (at risk)’ and is usually initiated by health authorities. In contrast, early detection or opportunistic (ad-hoc) testing consists of individual case findings, which are initiated by the man being tested (patient) and/or his physician. The co-primary objectives of both strategies are:

- reduction in mortality due to PCa;
- at least, a maintained quality of life (QoL) as expressed by QoL-adjusted gain in life years (QUALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world [61]. Mortality due to PCa has decreased in most Western countries but the magnitude of the reduction varies between countries. The reduced mortality rate seen recently in the USA is considered to be partly due to a widely adopted aggressive PCa screening policy [62]. However, there is still no level 1 evidence that PSA mass screening is cost-effective in reducing PCa mortality [63].

Currently, screening for PCa is one of the most controversial topics in the urological literature [64]. Three large
prospective RCTs published data on screening in 2009 [65-67]. Heated discussions and debates resulted in many conflicting positions and policy papers. Some authors argue that following the current American Urological Association (AUA) guidelines [68] or the US Preventive Services Task Force recommendations for screening [69] may lead to a substantial number of men with aggressive disease being missed [70, 71]. 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 [72]. The potential impact of this topic would necessitate the highest level of evidence produced through a systematic literature search of all published trials or cohorts summarised in a meta-analysis. Subgroup analyses of cohorts that are part of large trials, or mathematical projections alone, cannot provide the quality of evidence needed to appropriately address this clinical question.

A Cochrane review published in 2013 [63], which has been updated since [73] presents the main overview of the date. The findings of the updated publication (based on a literature search until April 3, 2013) are almost identical to the 2013 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 five 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).

Moreover, screening was associated with minor and major harms such as over-diagnosis and over-treatment. Surprisingly, the diagnostic tool (i.e. biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [40, 41].

The impact on the patient’s overall QoL is still unclear [74-76], but screening has never been shown to be detrimental at population level. All these findings have led to strong advice against systematic population-based screening in all countries, including Europe.

Since 2013, the European Randomized Study of Screening for Prostate Cancer (ERSPC) data have been updated with 13 years of follow up (see Table 5.1.1) [77]. 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 and to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials [78].

<table>
<thead>
<tr>
<th>Table 5.1.1: Follow-up data from the ERSPC study [77]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of follow-up</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>13</td>
</tr>
</tbody>
</table>

An individualised risk-adapted strategy for early detection might be offered to a well-informed man with at least ten-fifteen years of life expectancy. However, this approach may still be associated with a substantial risk of over-diagnosis. It is therefore important to carefully identify the patient cohorts likely to benefit most from individual early diagnosis, taking into account the potential balances and harms involved.

Men at elevated risk of having PCa are those > 50 years, or at age > 45 years with a family history of PCa (both paternal or maternal [79]), or African-Americans [80]. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [81, 82] are also at increased risk of PCa metastasis or death from PCa several decades later. The long-term survival and QoL benefits of such an approach remains to be proven at a population level. In 2014, as for breast cancer, a genetic abnormality associated with an increased risk has been shown prospectively i.e. BRCA2 [19, 83]. Several new biological markers such as TMPRSS2-Erg fusion, PCA3 [84, 85] or kallikreines as incorporated in the Phi or 4Kscore tests [86, 87] have been shown to add sensitivity and specificity on top of PSA, potentially avoiding unnecessary biopsies and lowering over-diagnosis. At this time there is too limited data to base a recommendation on.

Risk calculators may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available:
Informed men requesting an early diagnosis should be given a PSA test and undergo a digital rectal examination (DRE) [89]. 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 considered based on the initial PSA level. This could be every two years for those initially at risk, or postponed up to eight to ten years in those not at risk [90].

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 fifteen-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 6.7 on senior adults and in the recently updated SIOG Guidelines [91].

Based on the tools currently available, an individualised strategy will diagnose many insignificant lesions (over 50% in some trials), most of which will not require any form of active treatment (see Section 6.1 - Deferred treatment). It is important to realise 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.

5.1.1 **Guidelines for screening and early detection**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life-expectancy of at least ten to fifteen years.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Offer early PSA testing in well-informed men at elevated risk of having PCa:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• men &gt; 50 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• men &gt; 45 years of age and a family history of PCa;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• African-Americans &gt; 45 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• men with a PSA level of &gt; 1 ng/mL at 40 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• men with a PSA level of &gt; 2 ng/mL at 60 years of age.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• men with a PSA level of &gt; 1 ng/mL at 40 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• men with a PSA level of &gt; 2 ng/mL at 60 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpone follow-up to eight years in those not at risk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decide on the age at which early diagnosis of PCa should be stopped based on life expectancy and performance status; men who have a life-expectancy of &lt; 15-years are unlikely to benefit.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 or specimens from transurethral resection of the prostate (TURP) or prostatectomy for benign prostatic enlargement (BPE).

5.2.1 **Digital rectal examination**

Most PCas are located in the peripheral zone and may be detected by DRE when the volume is ≥ 0.2 mL. In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [92]. Suspect DRE in patients with PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [93]. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy [94, 95].

5.2.2 **Prostate-specific antigen**

The use of PSA as a serum marker has revolutionised PCa diagnosis [96]. Prostate-specific antigen is organ- but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and
other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS) [97].

There are no agreed standards defined for measuring PSA [98]. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [99]. Table 5.2.1 demonstrates the occurrence of Gleason ≥ 7 (or ISUP grade 2) PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant PCa. The use of nomograms may help in predicting indolent PCa [100].

Table 5.2.1: Risk of PCa in relation to low PSA values

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>Risk of PCa (%)</th>
<th>Risk of Gleason &gt; 7 PCa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-0.5</td>
<td>6.6</td>
<td>0.8</td>
</tr>
<tr>
<td>0.6-1.0</td>
<td>10.1</td>
<td>1.0</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>17.0</td>
<td>2.0</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>23.9</td>
<td>4.6</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>26.9</td>
<td>6.7</td>
</tr>
</tbody>
</table>

5.2.2.1 PSA density
Prostate specific antigen density is the level of serum PSA divided by the TRUS-determined prostate volume. The higher the PSA density, the more likely it is that the PCa is clinically significant (see Section 6.1.3).

5.2.2.2 PSA velocity and doubling time
There are two methods of measuring PSA kinetics:
- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [101];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [102].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treating PCa [103], but 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. These measurements do not provide additional information compared with PSA alone [104-107].

5.2.2.3 Free/total PSA ratio
Free/total (f/t) PSA ratio can be used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. Prostate cancer was detected by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 ng/mL [108]. Free/total PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow up of known PCa.

Free/total 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) [109].

5.2.2.4 Additional serum testing
A few assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the 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]). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multicentre studies demonstrated that both the PHI and 4K test out-performed f/t PSA PCa detection, with an improved prediction of clinically significant PCa in men with a PSA between 2-10 ng/mL [87, 110] [111]. In a head to head comparison both tests performed equally [112].

5.2.2.5 PCA3 marker
Prostate cancer gene 3 (PCA3) is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available Progensa urine test for PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies [113-116].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts Gleason score, and its use for monitoring in active surveillance (AS) is, as yet, not confirmed [117]. 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 [118].
5.2.2.6 **Guidelines for risk-assessment of asymptomatic men**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In order to avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a prostate specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools:</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>• risk-calculator;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• an additional serum or urine-based test (e.g. Prostate Health Index test [PHI], four kallikrein [4K]score or Prostate cancer gene 3 [PCA3]) or imaging.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2.3 **Prostate biopsy**

5.2.3.1 **Baseline biopsy**

The need for prostate biopsy is based on PSA level and/or suspicious DRE. Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [119]. Risk stratification is a potential tool for reducing unnecessary biopsies [119].

Limited PSA elevation alone should not prompt immediate biopsy. Prostate specific antigen level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections [UTIs]) in the same laboratory [120, 121]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [122].

Ultrasound (US)-guided biopsy is now the standard of care. A transrectal approach is used for most prostate biopsies, although some urologists prefer a perineal approach. Cancer detection rates are comparable with both approaches [123, 124].

5.2.3.2 **Repeat biopsy after previously negative biopsy**

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2.1 for risk estimates);
- suspicious DRE, 5-30% cancer risk [92, 93];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 40% risk [125];
- extensive (multiple biopsy sites, i.e., > 3) high-grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [125, 126];
- a few atypical glands immediately adjacent to high-grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [127];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade prostate carcinoma [128];
- positive multiparametric magnetic resonance imaging (mpMRI) findings (see Section 5.2.4).

Additional information may be gained by the Progensa DRE urine test for PCA3, the serum 4Kscore and PHI tests or a tissue-based epigenetic test (ConfirmMDx). The role of PHI and Progensa PCA3 in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective [118]. The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCA focus shows distinct epigenetic alterations. If, due to sampling bias, the PCA is missed at biopsy, demonstration of epigenetic changes in the adjacent benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes (RASSF1, GSTP1 and APC) in benign prostatic tissue. A multicentre study found a negative predictive value of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men [129]. Given the limited available data, no recommendation can be made regarding its routine application.

**Table 5.2.2: Description of additional investigational tests after a negative prostate biopsy***

<table>
<thead>
<tr>
<th>Name of test</th>
<th>Test substrate</th>
<th>Molecular</th>
<th>FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progensa</td>
<td>DRE urine</td>
<td>IncRNA PCA3</td>
<td>yes</td>
</tr>
<tr>
<td>PHI</td>
<td>Serum</td>
<td>Total, free and p2PSA</td>
<td>yes</td>
</tr>
<tr>
<td>4Kscore Test</td>
<td>Serum/plasma</td>
<td>Total, free, intact PSA, hK2</td>
<td>no</td>
</tr>
<tr>
<td>ConfirmMDX</td>
<td>Benign prostate biopsy</td>
<td>Methylated APC, RASSF1 and GSTP1</td>
<td>no</td>
</tr>
</tbody>
</table>

*Isolated high-grade PIN in one or two biopsy sites is no longer an indication for repeat biopsy [130].
5.2.3.3 **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 [131]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback [132].

5.2.3.4 **Sampling sites and number of cores**

On baseline biopsies, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS. Sextant biopsy is no longer considered adequate. For a prostate volume of 30-40 mL, ≥ 8 cores should be sampled. Ten to twelve core biopsies are recommended [133], with > 12 cores not being significantly more conclusive [134, 135].

5.2.3.5 **Diagnostic transurethral resection of the prostate**

Transurethral resection of the prostate should not be used as a tool for cancer detection [136].

5.2.3.6 **Seminal vesicle biopsy**

Indications for seminal vesicle (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20-25% [137]. A seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent radiotherapy. Its added value compared with mpMRI is questionable.

5.2.3.7 **Transition zone biopsy**

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to repeat biopsies [138].

5.2.3.8 **Antibiotics prior to biopsy**

Oral or intravenous antibiotics are recommended. Quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin [139]. Increased quinolone resistance [140] is associated with a rise in severe post-biopsy infection [141].

5.2.3.9 **Local anaesthesia prior to biopsy**

Ultrasound-guided periprostatic block is recommended [142]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [143].

5.2.3.10 **Fine-needle aspiration biopsy**

Fine-needle aspiration biopsy is no longer recommended.

5.2.3.11 **Complications**

Biopsy complications are listed in Table 5.2.3 [144]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [145]. Low-dose aspirin is no longer an absolute contraindication [146]. A SR found favourable infections rates for transperineal compared to transrectal biopsies with similar rates of haematuria, haematospermia and urinary retention [147].

<table>
<thead>
<tr>
<th>Complications</th>
<th>Percentage of patients affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematospermia</td>
<td>37.4</td>
</tr>
<tr>
<td>Haematuria &gt; 1 day</td>
<td>14.5</td>
</tr>
<tr>
<td>Rectal bleeding &lt; 2 days</td>
<td>2.2</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever &gt; 38.5°C</td>
<td>0.8</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>0.7</td>
</tr>
<tr>
<td>Rectal bleeding &gt; 2 days +/- surgical intervention</td>
<td>0.7</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0.2</td>
</tr>
<tr>
<td>Other complications requiring hospitalisation</td>
<td>0.3</td>
</tr>
</tbody>
</table>
5.2.4 The role of imaging

5.2.4.1 Transrectal ultrasound (TRUS) and ultrasound-based techniques

Grey-scale TRUS is not reliable at detecting PCa [148]. Thus, there is no evidence that US-targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography and contrast-enhanced US are still under investigation. Currently there is not enough evidence for their routine use.

5.2.4.2 Multiparametric magnetic resonance imaging

Correlation with radical prostatectomy (RP) shows that mpMRI, associating T2-weighted imaging with diffusion-weighted imaging, dynamic contrast-enhanced imaging, and/or H1-spectroscopy, has good sensitivity for the detection and localisation of Gleason score > 7 cancers (see Table 5.2.4) [149-152].

Table 5.2.4: PCa detection rates (%) by mpMRI for tumour volume and Gleason score in radical prostatectomy specimen [151]

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Tumour volume (mL)</th>
<th>0.5-2</th>
<th>&gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS6</td>
<td>&lt; 0.5</td>
<td>21-29%</td>
<td>43-54%</td>
</tr>
<tr>
<td>GS7</td>
<td>63%</td>
<td>82-88%</td>
<td>97%</td>
</tr>
<tr>
<td>GS &gt;7</td>
<td>80%</td>
<td>93%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Multiparametric magnetic resonance imaging can reliably detect aggressive tumours in candidates for prostate biopsy with a negative (NPV) and positive predictive value (PPV) ranging from 63 to 98% and from 34 to 68%, respectively [153]. As a result, mpMRI is increasingly performed before prostate biopsy.

Theoretically, pre-biopsy mpMRI could be used in two different ways. The first strategy uses mpMRI to improve the detection of clinically significant prostate cancer (csPCa). In this diagnostic pathway, MRI-targeted biopsy (TBx) would be added to systematic biopsies in case of positive mpMRI, and systematic biopsies would be performed in all patients with negative mpMRI. The second strategy uses mpMRI as a triage test before biopsy. In this diagnostic pathway, only MRI-TBx would be performed in case of a positive mpMRI. Patients with negative mpMRI results would not undergo a prostate biopsy at all.

A large body of evidence suggests that MRI-TBx has a higher detection rate of detecting csPCa as compared to systematic biopsy [154-158]. However, sub-groups analysis showed that the impact of mpMRI was most marked in the repeat-biopsy setting, but not in biopsy-naive men [154, 155]. Single centre RCTs performed in biopsy-naive men provided contradictory findings as to whether or not the combination of systematic biopsies and MRI-TBx had a higher detection rate for PCa and csPCa than systematic biopsies alone [159-161]. Two large multicentre studies (MRI-FIRST and PRECISION) are currently ongoing to define the added value of pre-biopsy MRI in biopsy-naive patients. It is therefore too early to make recommendations on the routine use of pre-biopsy mpMRI in biopsy-naive patients.

Magnetic resonance imaging-targeted biopsies can be obtained through cognitive guidance, Ultrasound/mpMRI fusion software or direct in-bore guidance. Controlled studies and a SR did not show a clear superiority of one technique over the others [158, 162-164].

Whether systematic biopsies can be omitted in patients (or prostate lobes) with negative mpMRI depends on the NPV of mpMRI. A SR performed under the auspices of the EAU-ESTRO-ESUR-SIOG PCa Guidelines Panel showed a highly variable prevalence of overall PCa (13.0-74.7%) and csPCa (13.7-50.9%) in patients undergoing pre-biopsy mpMRI (unpublished results). Due to the fact that the NPV decreases when prevalence increases, it is necessary to risk-stratify patients before defining the patients that could safely omit biopsy in case of a negative mpMRI. Prostate-specific antigen density [165] or risk calculators [88] can be used to identify groups of patients with low risk of PCa in whom mpMRI would have a high NPV. The impact of these risk-stratification tools on the NPV of pre-biopsy mpMRI needs to be carefully evaluated, both in the biopsy-naive and in the repeat-biopsy setting.

Despite the use of the new PIRADS v2 scoring system [166], mpMRI has a low specificity, with high rates of false positives, especially among lesions scored 3/5 and 4/5 [167]. Multiparametric magnetic resonance imaging inter-reader reproducibility is also moderate [168-171], which currently limits its broad use outside expert centres. At this moment it is too soon to define if quantitative approaches and computer-aided diagnosis systems will improve the characterisation of lesions seen at mpMRI in the future [172-174].
5.2.4.3 **Guidelines for imaging**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before repeat biopsy, perform multiparametric magnetic resonance imaging (mpMRI) when clinical suspicion of PCa persists in spite of negative biopsies.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>During repeat biopsy, include systematic biopsies and targeting of any mpMRI lesions seen.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

5.2.5 **Pathology of prostate needle biopsies**

5.2.5.1 **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 [175]. 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 [176, 177]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [138] and intervening unstained sections are kept for immunohistochemistry.

5.2.5.2 **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 [178-180]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [178]. Table 5.2.5 lists the recommended terminology for reporting prostate biopsies [176].

**Table 5.2.5: Recommended terminology for reporting prostate biopsies [176]**

<table>
<thead>
<tr>
<th>Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign/negative for malignancy; if appropriate, include a description</td>
</tr>
<tr>
<td>Active inflammation</td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
</tr>
<tr>
<td>High-grade prostatic intraepithelial neoplasia (PIN)</td>
</tr>
<tr>
<td>High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)</td>
</tr>
<tr>
<td>Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation,</td>
</tr>
<tr>
<td>suspicious for cancer</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
</tr>
</tbody>
</table>

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 Gleason grading system [181]. A global Gleason score comprising all biopsies is also reported according to the ISUP 2014 grade (see Section 4.2). Intraductal carcinoma, lymphovascular invasion (LVI) and extra-prostatic extension (EPE) must each be reported, if identified. More recently, expansile cribriform pattern of PCa as well as intraductal carcinoma in biopsies were identified as independent prognosticators of metastatic disease [182].

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the Gleason score, tumour volume, surgical margins and pathologic stage in RP specimens and predicts BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [183-185]. 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 [186]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [187] triggering immediate treatment vs. AS in patients with Gleason score 6.

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

- type of carcinoma;
- primary and secondary/worst Gleason grade (per biopsy site and global);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (at least per biopsy site);
- if present: EPE, seminal vesicle invasion, LVI, intraductal carcinoma/cribriform pattern, peri-neural invasion;
- ISUP 2014 grade (global).
5.2.5.3 Tissue-based prognostic biomarker testing

The Prolaris test (Myriad Genetics) measures the expression of 31 cell-cycle associated genes in biopsy-derived PCa tissue and may be of clinical use to determine whether a patient needs curative treatment or may have his treatment deferred [188]. Similarly, Oncotype Dx is a RNA-based test based on 12 carcinoma-associated genes and 5 reference genes which can be applied to carcinoma tissue in prostate biopsies to determine the aggressiveness of the carcinoma. Both tests were shown in prospective studies to provide prognostic information in men with clinically localised PCa, additional to conventional clinico-pathological parameters, including Gleason score and PSA level. The results of prospective multicentre studies are awaited before a recommendation can be made regarding their routine application.

5.2.6 Histopathology of radical prostatectomy specimens

5.2.6.1 Processing of radical prostatectomy specimens

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded, to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most widely accepted method includes complete embedding of the posterior prostate, and a single mid-anterior left and right section. Compared with total embedding, partial embedding detected 98% of PCa with a Gleason score > 7 and accurate staging in 96% of cases [189].

Ink the entire RP specimen upon receipt in the laboratory, to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin, which provides more homogeneous fixation and sectioning after 24 hours [190]. 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 [57]. 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.

5.2.6.1.1 Guidelines for processing prostatectomy specimens

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure total embedding, by conventional (quadrant) or whole-mount sectioning.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Ink the entire surface before cutting, to evaluate the surgical margin.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Examine the apex and base separately, using the cone method with sagittal or radial sectioning.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

5.2.6.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.6). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.7). Synoptic reporting results in more transparent and complete pathology reporting [191].

Table 5.2.6: Mandatory elements provided by the pathology report

<table>
<thead>
<tr>
<th>Mandatory elements provided by the pathology report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathological type: &gt; 95% of PCa represents conventional (acinar) adenocarcinoma.</td>
</tr>
<tr>
<td>Grading according to Gleason score (or therapy-related changes) and ISUP 2014 grade group.</td>
</tr>
<tr>
<td>Tumour (sub)staging and surgical margin status: location and extent of extraprostatic extension (EPE), presence of bladder neck invasion, laterality of EPE or seminal vesicle invasion, location and extent of positive surgical margins.</td>
</tr>
<tr>
<td>Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.</td>
</tr>
</tbody>
</table>
Table 5.2.7: Example checklist: reporting of prostatectomy specimens

<table>
<thead>
<tr>
<th>Histopathological type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of carcinoma, e.g. conventional acinar, or ductal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (predominant) Gleason grade</td>
<td></td>
</tr>
<tr>
<td>Secondary Gleason grade</td>
<td></td>
</tr>
<tr>
<td>Tertiary Gleason grade (if applicable)</td>
<td></td>
</tr>
<tr>
<td>Global Gleason score/ISUP 2014 grade</td>
<td></td>
</tr>
<tr>
<td>Approximate percentage of Gleason grade 4 or 5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour quantitation (optional)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of prostate involved</td>
<td></td>
</tr>
<tr>
<td>Size/volume of dominant tumour nodule</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological staging (pTNM)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>If extraprostatic extension is present:</em></td>
<td></td>
</tr>
<tr>
<td>indicate whether it is focal or extensive;</td>
<td></td>
</tr>
<tr>
<td>specify sites;</td>
<td></td>
</tr>
<tr>
<td>indicate whether there is seminal vesicle invasion.</td>
<td></td>
</tr>
<tr>
<td><em>If applicable, regional lymph nodes:</em></td>
<td></td>
</tr>
<tr>
<td>location;</td>
<td></td>
</tr>
<tr>
<td>number of nodes retrieved;</td>
<td></td>
</tr>
<tr>
<td>number of nodes involved.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical margins</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>If carcinoma is present at the margin:</em></td>
<td></td>
</tr>
<tr>
<td>specify sites.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of lymphovascular/angio-invasion</td>
<td></td>
</tr>
<tr>
<td>Location of dominant tumour</td>
<td></td>
</tr>
<tr>
<td>Presence of intraductal carcinoma/cribriform architecture</td>
<td></td>
</tr>
</tbody>
</table>

5.2.6.2.1 Gleason score in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system [181] is the strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [192].

The Gleason score is the sum of the most and second-most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises ≤ 5% of the cancer volume, it is not incorporated in the Gleason score (5% rule). The primary and secondary grades are reported in addition to the Gleason score. A global Gleason score is given for multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. Tertiary Gleason grade 4 or 5, particularly if > 5% of the PCa volume, is an unfavourable prognostic indicator for BCR. The tertiary grade and its approximate proportion of the cancer volume should also be reported [193] in addition to the global Gleason score as well as the ISUP 2014 grade group (see Section 4.2).

5.2.6.2.2 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with periprostatic 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 [194].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [195] or extension as < 1 high-power field (HPF) [196], whereas others measure the depth of extent in millimetres [197].

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 [198, 199] and should be recorded as EPE (pT3a). A positive margin at the bladder neck should be reported as EPE (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [200].
5.2.6.3 PCa volume
The independent prognostic value of PCa volume in RP specimens has not been established [196, 201-204]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [201]. 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 [205].

5.2.6.4 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 [202] 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 [206].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [207]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [196]. However, some indication must be given of the multifocality extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [208], or number of blocks with positive margin involvement.

5.2.7 Guidelines for the clinical diagnosis of prostate cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use transurethral resection of the prostate as a tool for cancer detection.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Use the International Society of Urological Pathology (ISUP) 2014 Gleason grading system for grading of PCa.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>In symptomatic men, base the initial decision to perform a biopsy on prostate-specific antigen (PSA) testing and digital rectal examination (DRE).</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Use the additional diagnostic options in asymptomatic men with a normal DRE and a PSA between 2.0 and 10 ng/mL, (risk calculator, or an additional serum or urine-based test [e.g. Prostate Health Index, 4Kscore or prostate cancer gene 3] or imaging).</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Do not initially offer transition zone biopsies due to low detection rates.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>For initial diagnosis, perform a core biopsy of ten to twelve systematic transrectal or transperineal peripheral zone biopsies under ultrasound guidance.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Perform transrectal prostate needle biopsies under antibiotic protection.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Use a local anaesthetic by periprostatic infiltration for transrectal prostate needle biopsies.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Adhere to the 2010 ISUP consensus meeting Guidelines for processing and reporting of prostatectomy specimens.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Perform one set of repeat biopsies for persistent indications for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at initial biopsy).</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

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

5.3.1 T-staging
5.3.1.1 Definitions
Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland (e.g., neurovascular bundle, anterior prostate, or bladder neck) and corresponds to stage T3a. It is to be distinguished from seminal vesicle invasion (SVI) which corresponds to stage T3b (see Section 5.2 for details).

5.3.1.2 DRE, PSA level and biopsy findings
The first level of assessment is local tumour stage because the distinction between organ-confined (T1/T2) and extraprostatic (T3/T4) disease affects treatment decisions. Digital rectal examination is positively correlated with tumour stage in < 50% of cases [209], although it often underestimates tumour extension. More extensive T-staging is only recommended if it directly affects treatment decisions.

Serum PSA levels increase with tumour stage, although they are limited for accurate prediction of final
pathological stage [210]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [211]. An increase in tumour-positive biopsies is an independent predictor of EPE, margin involvement, and lymph node (LN) invasion [212]. Serum PSA, Gleason score, and T-stage are more useful together than alone in predicting final pathological stage [192, 213]. Models may help to select candidates for nerve-sparing surgery and lymphadenectomy (LND) (see Section 6.2.5).

Seminal vesicle invasion is predictive of local relapse and distant metastatic failure. Seminal vesicle biopsies can improve pre-operative staging accuracy [214]. This is not recommended for first-line examination, but should be reserved for patients with high risk of SVI in whom a positive biopsy would modify treatment. Patients with T-stage > 2a and serum PSA > 10 ng/mL are candidates for SV biopsy [215, 216]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [217].

Transperineal 3D prostate mapping biopsy (PMB) is an alternative to transrectal biopsies because it provides more accurate tumour localisation, extent and Gleason grading [218], and has acceptable morbidity [147].

5.3.1.3 Transrectal ultrasound
Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [219]. Transrectal ultrasound-derived techniques (e.g. 3D-TRUS, colour Doppler) [220, 221] cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine staging.

5.3.1.4 Multiparametric magnetic resonance imaging
T2-weighted imaging remains the most useful method for local staging on mpMRI. At 1.5T (Tesla), mpMRI has good specificity but low sensitivity for detecting T3 stages. Pooled data from a meta-analysis for EPE, SVI, and overall stage T3 showed a sensitivity and specificity of 0.57 (95% CI: 0.49-0.64) and 0.91 (95% CI: 0.88-0.93), 0.58 (95% CI: 0.47-0.68) and 0.96 (95% CI: 0.95-0.97), and 0.61 (95% CI: 0.54-0.67) and 0.88 (95% CI: 0.85-0.91), respectively [222]. Multiparametric magnetic resonance imaging cannot detect microscopic EPE. Its sensitivity increases with the radius of extension within peri-prostatic fat. In one study, the EPE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [223]. In another study, mpMRI sensitivity, specificity and accuracy for detecting pT3 stage was, 40%, 95% and 76%, respectively, for focal (i.e. microscopic) EPE, and 62%, 95% and 88% for extensive EPE [224].

The use of high field (3T) or functional imaging in addition to T2-weighted imaging improves sensitivity for EPE or SVI detection [222], but the experience of the reader remains of paramount importance [225] and the inter-reader agreement remains moderate with kappa values ranging from 0.41 to 0.68 [226]. Multiparametric magnetic resonance imaging, although not perfect for local staging, may improve prediction of the pathological stage when combined with clinical data [227, 228]. Other MRI-derived parameters such as the tumour volume or the contact length of the tumour with the capsule [229-231], or the Gleason score obtained through MRI-TBx [232] could further improve the local staging.

Given its low sensitivity for focal (microscopic) EPE, mpMRI is not recommended for local staging in low-risk patients [227, 233, 234]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [235].

5.3.2 N-staging
N-staging should be performed only when it might directly influence treatment decisions. High PSA values, T2b-T3 stage, poor tumour differentiation and perineural invasion are associated with high risk of nodal metastases [236, 237]. Measurement of PSA alone is unhelpful in predicting LN metastases. Nomograms can define patients at low risk (< 10%) of nodal metastasis, although nomograms may be more accurate in establishing the extent of nodal involvement [213, 238]. The simple Roach formula can also be used [239]. Patients with low- and intermediate-risk PCa may be spared N-staging before potentially curative treatment.

Gleason 4 pattern in sextant biopsies can define the risk of N1 disease. Risk of nodal metastases was 20-45% if any core had a predominant Gleason 4 pattern, or > 3 cores had any Gleason 4 pattern. For the remaining patients, the risk was 2.5%, suggesting that nodal staging is unnecessary in selected patients [240].

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 with the size of LN metastases, since microscopic invasion does not enlarge LNs. The normal range for non-metastatic LNs also varies with different anatomical regions. As a result, the ideal size threshold remains uncertain [241, 242]. Computed tomography and MRI sensitivity is less than 40% [243, 244]. Among 4,264 patients 654 (15.3%) of
whom had positive LNs at LND, CT was positive in only 105 (2.5%) patients [241]. Detection of microscopic LN invasion by CT is < 1% in patients with a Gleason score < 8, PSA < 20 ng/mL, or localised disease [245-247].

Diffusion-weighted MRI may detect metastases in normal-sized nodes, but a negative diffusion-weighted MRI cannot rule out the presence of LN metastases [242, 248]. Moreover, this scan is technically challenging to perform in the pelvis where artifacts due to bowel gas can interfere with the quality of the imaging.

Because of their low sensitivity, CT or MRI should not be used for nodal staging in low-risk patients and be reserved for high-risk cancer patients.

5.3.2.2 Choline PET/CT

$^{11}$C- or $^{18}$F-choline positron emission tomography (PET)/CT have good specificity for LN metastases, but a sensitivity of 10-73% [249, 250].

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 [251]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10-35%), the sensitivity was only 8.2% in a region based and 18.9% at a patient-based analysis, which is too low to be of clinical interest [252].

In intermediate/high-risk patients, comparisons between choline PET/CT and diffusion-weighted MRI gave contradictory results, with PET/CT sensitivity found to be superior [253], similar [254, 255] or inferior [252] than that of diffusion-weighted MRI.

Because of its insufficient sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases.

5.3.2.3 New methods

$^{68}$Ga-labelled prostate-specific membrane antigen-PET CT ($^{68}$Ga-PSMA PET/CT) seems to exhibit promising sensitivity for LN involvement. A recent meta-analysis of five retrospective studies, performed in an initial staging and/or recurrence setting, reported combined sensitivities and specificities of 86% (95% CI: 37-98%) and 86% (95% CI: 3-100%) at patient level, and 80% (95% CI: 66-89%) and 97% (95% CI: 92-99%) at lesion level [256]. Similarly, $^{18}$F-labelled PSMA targeting compounds are being developed commercially. However, these results must be interpreted with care, as careful validation studies have not been performed.

5.3.3 M-staging

5.3.3.1 Bone scan

$^{99m}$Tc-Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. A 2014 meta-analysis showed a combined sensitivity and specificity of 79% (95% CI: 73-83%) and 82% (95% CI: 78-85%) at patient level and 59% (95% CI: 55-63%) and 75% (95% CI: 71-79%) at lesion level [257]. Adding single-photon emission computed tomography (SPECT) to plain BS has been shown to reduce the number of equivocal lesions [258]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score and these three factors were the only independent predictors of BS positivity in a study of 853 patients [259]. The mean BS positivity rate in 23 different series was 2.3% in patients with PSA levels < 10 ng/mL, 5.3% in patients with PSA level between 10.1 and 19.9 ng/mL, and 16.2% in patients with PSA levels of 20.0-49.9 ng/mL. It was 6.4% in men with organ-confined cancer and 49.5% in men with locally advanced cancers. Detection rates were 5.6% and 29.9% for Gleason scores of 7 and ≥ 8 respectively [241]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive BS [260, 261].

Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score or clinical stage [241].

5.3.3.2 Other modalities

$^{18}$F-sodium fluoride ($^{18}$F-NaF) PET or PET/CT shows similar specificity and superior sensitivity to BS. It may even have the highest sensitivity for bone metastases, as compared to all other imaging techniques [262, 263]. However, unlike choline PET/CT, it does not detect LN metastases, and it is less cost-effective compared to BS [262].

It remains unclear whether choline PET/CT is more sensitive than conventional BS, but it has higher specificity, with fewer indeterminate bone lesions [249, 251, 264].

Diffusion-weighted whole-body and axial MRI are more sensitive than BS and targeted conventional radiography in detecting bone metastases in high-risk PCa [265, 266]. Whole-body MRI is also more sensitive and specific than combined BS, targeted radiography and abdominopelvic CT [267]. A meta-analysis found that MRI is more sensitive than choline PET/CT and BS for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity (Table 5.3.1) [257].
Only limited evidence is available on the performance of $^{68}$Ga-PSMA PET/CT in initial staging. A meta-analysis reported a combined positivity rate of 40% (95% CI: 19-64%) in patients undergoing primary staging. However, the positivity rate fell to 27% (95% CI: 15-42%) when studies with a sample size < 10 were excluded [256].

Table 5.3.1: Sensitivity and specificity for detecting bone metastases on a per-patient basis [257]

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone scan</td>
<td>78</td>
<td>85</td>
<td>95% (0.73-0.83)</td>
</tr>
<tr>
<td>Choline PET/CT</td>
<td>91</td>
<td>99</td>
<td>95% (0.83-0.96)</td>
</tr>
<tr>
<td>MRI</td>
<td>97</td>
<td>95</td>
<td>95% (0.91-0.99)</td>
</tr>
</tbody>
</table>

CI = confidence interval; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

Although evidence shows that choline PET/CT and mpMRI are more accurate than BS, the clinical benefit of detecting bone metastases at an earlier time-point using more sensitive techniques remains unclear in the initial staging setting [268]. Bone scan is therefore usually preferred in most centres.

5.4 Guidelines for staging of prostate cancer

<table>
<thead>
<tr>
<th>Any risk group staging</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use computed tomography and transrectal ultrasound for local staging.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-risk localised PCa</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use additional imaging for staging purposes.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate-risk PCa</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In predominantly Gleason pattern 4 (ISUP grade 3), include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.</td>
<td>2a</td>
<td>A*</td>
</tr>
<tr>
<td>In predominantly Gleason pattern 4 (ISUP grade 3), use prostate multiparametric magnetic resonance imaging (mpMRI) for local staging.</td>
<td>2b</td>
<td>A</td>
</tr>
</tbody>
</table>

*Upgraded following panel consensus.

<table>
<thead>
<tr>
<th>High-risk localised PCa/High-risk locally advanced PCa</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use prostate mpMRI for local staging.</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>

6. DISEASE MANAGEMENT

6.1 Treatment: Deferred treatment (active surveillance/watchful waiting)

6.1.1 Introduction

Many men with screening-detected localised PCa will not benefit from definitive treatment [269] and 45% of them are candidates for deferred management. There are two distinct strategies for conservative management that aim to reduce over-treatment: active surveillance (AS) and watchful waiting (WW) (Table 6.1.1).

6.1.1.1 Definition

6.1.1.1.1 Active surveillance

Active surveillance aims to achieve correct timing for curative treatment in patients with clinically localised PCa, rather than delay palliative treatment [270]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, still potentially curable, while considering individual life expectancy.
6.1.1.2 Watchful waiting
Watchful waiting (WW) is also known as deferred or symptom-guided treatment. It refers to conservative management, until the development of local or systemic progression with (imminent) disease-related complaints. Patients are then treated according to their symptoms, in order to maintain QoL.

Table 6.1.1: Definitions of active surveillance and watchful waiting [269]

<table>
<thead>
<tr>
<th>Treatment intent</th>
<th>Active surveillance</th>
<th>Watchful waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Curative</td>
<td>Palliative</td>
</tr>
<tr>
<td>Assessment/markers used</td>
<td>Predefined schedule</td>
<td>Patient-specific</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>DRE, PSA, re-biopsy, mpMRI</td>
<td>Not predefined</td>
</tr>
<tr>
<td>Aim</td>
<td>&gt; 10 years</td>
<td>&lt; 10 years</td>
</tr>
<tr>
<td>Comments</td>
<td>Low-risk patients</td>
<td>Can apply to patients with all stages</td>
</tr>
</tbody>
</table>

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

6.1.2 Deferred treatment of localised PCa (stage T1/T2, Nx/N0, M0)
Mortality from untreated screen-detected PCa in patients with Gleason scores 5-7 might be as low as 7% at fifteen years follow-up [269].

6.1.2.1 Active surveillance
Active surveillance is currently reserved for selected low-risk patients. Current data are from ongoing prospective or retrospective cohorts; no formal RCT is available comparing this modality to standard treatment. The ProtecT trial [271] is discussed later as it is not a formal AS strategy.

One of the largest published cohorts with the longest follow-up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [272]. These men presented with stage T1c or T2a and PSA ≤ 10 ng/mL, age ≤ 70 years and a Gleason score ≤ 6 or age > 70 years with a Gleason score of ≤ 7. After a median follow-up of 6.4 years the ten- and fifteen-year OS were 80% and 62%, respectively, and DSS rates were 98.1% and 94.3%, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years (43.5%), a Gleason score progression on repeat biopsies (35%) and patient preference (6%). Thirty men (3%) developed metastases during follow-up: 2% of those initially classified as Gleason 6 compared to 9.7% if initially Gleason 7, and fifteen men died [273].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a SR including > 3,900 patients [274]. There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated.

**Selection criteria** for AS are limited by a lack of prospective RCTs, or findings from a formal consensus meeting. The criteria most often published include: Gleason 6, when specified < 2-3 positive cores with < 50% cancer involvement in every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc [274, 275]. The latter threshold remains controversial [275, 276]. A pathology consensus group suggested excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [277] and perineal invasion [278]. A Canadian consensus group pose that AS is the treatment of choice for low-risk disease, without stratifying for biopsy results, although they clearly recommend that men < 55 years should be closely scrutinised for high-volume Gleason 6 cancer. The same authors pose that low volume Gleason 7 (3 + 4) (< 10% pattern 4) may also be considered for AS. However, recent findings suggest that any grade 4 pattern is associated with a three-fold increased risk of metastases compared to Gleason 6, while a PSA up to 20 ng/mL might be an acceptable threshold [279-281].

In this setting, re-biopsy within six to twelve months to exclude sampling error is mandatory [275, 281] even if this could be modified in the future [282].

**Biological markers**, including urine PCA3, transmembrane protease, serine 2-TMPRSS2-ERG fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself [283-285]. However, further data will be needed before such markers can be used in standard clinical practice.
**Imaging** with mpMRI is of particular interest due to its high NPV value for lesion upgrading and for staging anterior prostate lesions [286, 287]. A formal SR is available [287]. The added value of mpMRI and targeted biopsies could be promising in:

1. reducing misclassifications at initial diagnosis and follow-up;
2. reducing unnecessary (targeted or systematic) biopsies at follow-up, and;
3. aiding in monitoring patients on surveillance.

The added value may differ at different time points in an AS setting. At confirmatory biopsy in men who did not have an mpMRI before, the reclassification rate due to targeted biopsies can be estimated to be 2-22% (absolute numbers) [287-291]. The added value of mpMRI for surveillance/repeat biopsies (hence more than one year following the confirmatory biopsy assessment) has not been evaluated yet. However, combined data of confirmatory and surveillance repeat biopsies show a reclassification rate due to targeted biopsies of 2-14% (absolute numbers) [292-294]. These numbers are directly related to the eligibility criteria for AS, and the reclassification criteria used within these populations.

The concordance of systematic and targeted biopsies at confirmatory biopsies is approximately 80%. However omitting systematic biopsies may induce a misclassification rate of 3-13% [287-290, 292-294], therefore systematic biopsy should be systematically performed, even facing a normal mpMRI.

Targeted biopsies of suspicious lesions on mpMRI are mainly performed for Likert/PIRADS (Prostate Image Reporting and Data System) > 3 lesions. Although increased rates of reclassification occur in PIRADS 4 and 5 lesions, a substantial proportion of PIRADS 3 lesions show reclassification following targeted biopsies [288, 289], thereby confirming the significance to biopsy Likert/PIRADS ≥ 3 lesions within AS management.

The follow up strategy is based on serial DRE (at least once/year), PSA (at least once, every six months) and repeated biopsy (at a minimum interval of three to five years). Based on two small single centre studies [295, 296], not all patients with progression/reclassification at biopsy had radiological progression and vice versa. Therefore, mpMRI cannot be used as a stand-alone tool to trigger follow-up biopsies, but efforts are being made to define and standardise radiological progression during AS [297].

Risk prediction in men on AS is under investigation to further reduce unnecessary biopsies and misclassification [298]. In an AS cohort of 259 men with Gleason 6 and Gleason 7 (3 + 4) cancers detected by MRI-targeted and systematic biopsies, independent predictors of upgrading at 3 years were Gleason 7 (3 + 4), PSA density ≥ 0.15 ng/mL/cm³ and a score 5 lesion on MRI [299]. Thus, the role of mpMRI in risk prediction should be further investigated.

**Switching to active treatment**

The decision to start active treatment should be based on a change in the biopsy results (Gleason score, number of positive cores, length in the core involvement), or T-stage progression. These criteria are recognised in all published cohorts. A PSA change (especially a PSA-DT < 3 years) is a less powerful indicator to change management based on its weak link with grade progression [300, 301]. Active treatment may also be instigated upon a patient’s request. This occurs in around 10% of patients on AS [302]. Overall, no major perturbation of health-related QoL (HRQoL) and psychological well-being was apparent in the first years [303].

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

<table>
<thead>
<tr>
<th>Studies</th>
<th>n</th>
<th>Median follow-up (mo)</th>
<th>pT3 in RP patients*</th>
<th>OS</th>
<th>CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van As et al., 2008 [304]</td>
<td>326</td>
<td>22</td>
<td>8/18 (44%)</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Carter et al., 2007 [305]</td>
<td>407</td>
<td>41</td>
<td>10/49 (20%)</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Adamy et al., 2011 [306]</td>
<td>533-1,000</td>
<td>48</td>
<td>4/24 (17%)</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>Soloway et al., 2010 [307]</td>
<td>99</td>
<td>45</td>
<td>0/2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Roemeling et al., 2007 [308]</td>
<td>278</td>
<td>41</td>
<td></td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Khatami et al., 2007 [309]</td>
<td>270</td>
<td>63</td>
<td>n.r.</td>
<td>85</td>
<td>98.1</td>
</tr>
<tr>
<td>Klotz et al., 2015 [272]</td>
<td>993</td>
<td>77</td>
<td></td>
<td>90</td>
<td>99.7</td>
</tr>
<tr>
<td>Total</td>
<td>2,130-3,000</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients receiving active therapy following initial active surveillance.

CSS = cancer-specific survival; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.
6.1.2.2  Watchful waiting
The rationale behind WW is that PCa often progresses slowly, and is predominantly diagnosed in older men with a high incidence of comorbidity and other causes of mortality [310]. Watchful waiting is possible in patients with localised PCa and a limited life expectancy.

6.1.2.2.1  Patient selection for watchful waiting
Studies on WW have included patients 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 ten years [311-316], and 80-95% for T1/T2 and Gleason score ≤ 7 [317]. In three studies with data beyond fifteen years, the DSS was 80%, 79% and 58% [313, 315, 316], and two reported twenty-year CSS rates of 57% and 32%, respectively [313, 315]. Many patients classified as Gleason 6 would now be classified as Gleason 7 based on the revised Gleason classification, suggesting that the above-mentioned results should be considered as minimal. Patients with well-, moderately- and poorly-differentiated tumours had ten-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [317]. Observation was most effective in men aged 65-75 years with low-risk PCa [318].

Gleason 6-10 tumours carry a continuously increasing mortality risk up to fifteen years follow-up after WW [319]. Others have shown that the mortality risk of PCa was high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 tumours (Table 6.1.3) [320, 321].

In an analysis at ten years follow up in 19,639 patients aged > 65 years who were not given curative treatment, most men with a Charlson comorbidity index (CCI) score ≥ 2 died from competing causes at ten years whatever their initial age. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at ten years, especially for well- or moderately-differentiated lesions [322]. This highlights the importance of checking the CCI before considering a biopsy.

Table 6.1.3: Fifteen-year mortality risk for localised PCa in relation to Gleason score in patients aged 55-74 years [320, 321, 323]

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Cancer mortality risk* (%)</th>
<th>Cancer-specific mortality† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>4-7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>6-11</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>18-30</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>42-70</td>
<td>76</td>
</tr>
<tr>
<td>8-10</td>
<td>60-87</td>
<td>93</td>
</tr>
</tbody>
</table>

* Figures differ among age groups and represent the true risk in the study population (considering actual competing mortality from other causes).
† Figures compensate for differences in competing mortality and indicate outcome if the patient lives for fifteen years.

6.1.2.2.2  Outcome of watchful waiting compared to active treatment
The SPCG-4 randomised study compared WW to RP (Table 6.1.4) [323] before the PSA era and found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 12.8 years. The PIVOT trial made a similar comparison in 731 randomised men (50% with non-palpable disease) [324] and found no benefit of treatment within ten years. Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a relative-risk reduction in mortality of 33% and 31%, respectively. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%). Overall, no major perturbation of HRQoL and psychological well-being was apparent in the first years [325].
### Table 6.1.4: Outcome of SPCG-4 at fifteen years follow-up [323]

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

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

The data on deferred and conservative management of low-risk disease contrasts with the recent increase in the incidence of local treatment from 25 to 34% in the USA in men with a life expectancy < 10 years [326]. Swedish data show a higher prevalence of deferred treatment in low-risk disease of 46% [327].

#### 6.1.2.3 The ProtecT study

The ProtecT trial randomised 1,643 patients between active treatment (RP or EBRT) and active monitoring (AM) [271]. In this AM schedule, patients with a PSA rise of more than 50% in twelve months underwent a repeat biopsy, but none had systematic repeat biopsies (which presents an intermediary approach, between AS and WW). Most patients had low-risk disease with 90% PSA < 10 ng/mL, 77% Gleason 6 (20% Gleason 7), 76% T1c. After ten years of follow up, the CSS was the same between those actively treated and those on AM (99% and 98.8% respectively), as was the OS. Only metastatic progression differed (6% in the AM group as compared to 2.6% in the treated group). The key finding is that AM is as effective as active treatment at ten years, at a cost of increased progression and a double metastatic risk. Metastases remain quite rare (6%), but more frequent compared to results from AS protocols based on patient selection. This confirms that for low-risk patients, some form of initial AM is safe. Beyond ten years, no data is available yet and AS is possibly safer, especially in younger men, based on initial patient selection. Individual life expectancy must be evaluated before considering any active treatment in low-risk situations, and for those with up to ten years individual life expectancy, AM or WW are probably very good options.

#### 6.1.3 Deferred treatment for locally advanced PCa (stage T3-T4, Nx-N0, M0)

The final analysis of the largest RCT focusing on this specific question was published in 2013 [328]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa were treated with androgen-deprivation therapy (ADT), either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS HR was 1.21 (95% CI: 1.05-1.39), favouring immediate treatment but showing no significant difference in PCa mortality or symptom-free survival which raises the question of its clinical value. Patients with a baseline PSA > 50 ng/mL had a > 3.5-fold higher mortality risk than those with a PSA baseline of ≤ 8 ng/mL. If baseline PSA was 8-50 ng/mL, the mortality risk was ~7.5-fold higher in patients with a PSA-DT of < 12 months compared with > 12 months. The median time to start deferred treatment was seven years. In the deferred arm, 25.6% died without needing treatment (44%).

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

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. Median survival is 42 months, therefore, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even death from PCa, without receiving any benefit from hormone treatment has been highlighted [329, 330]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.
Guidelines for active surveillance and watchful waiting

### Recommendations - active surveillance

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss surgery and radiotherapy as treatment options with patients suitable for such treatments.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Offer active surveillance to patients with the lowest risk of cancer progression: &gt; ten years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Counsel patients about the possibility of needing further treatment in the future.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>During confirmatory biopsy include systematic and targeted biopsies.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Base follow up on digital rectal examination, prostate-specific antigen (PSA) and repeated biopsies.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>

### Recommendations - watchful waiting for localised prostate cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>While on watchful waiting, base the decision to start non-curative treatment on symptoms and disease progression (see Section 6.1.2.2).</td>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>

### Recommendations - watchful waiting for locally advanced prostate cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In locally advanced M0 patients unwilling or able to receive any form of local treatment, offer a deferred treatment policy using androgen-deprivation therapy as monotherapy to asymptomatic patients with a PSA doubling time &gt; 12 months and a PSA &lt; 50 ng/mL and non-poorly differentiated tumour.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

### 6.2 Treatment: Radical prostatectomy

#### 6.2.1 Introduction

The goal of RP by any approach must be eradication of disease, while preserving continence and, whenever possible, potency [331]. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [322]. An estimation of life expectancy is paramount in counselling a patient about surgery [332] (see also Section 6.7). Currently, three large prospective RCTs have reported the benefit of RP over WW [324, 333] and over AM [271] in men with low- and intermediate-risk PCa.

Radical prostatectomy can be performed by open, laparoscopic or robot-assisted (RARP) approach. In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss but not early (twelve weeks) functional or oncological outcomes [334, 335]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can improve cancer control with RP [336-338].

Management decisions should be made after all treatments have been discussed in a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after balancing benefits and side effects of each therapy modality, together with the patient.

#### 6.2.2 Low-risk PCa

At ten years’ follow-up, a benefit for metastases-free and PFS but not CSS or OS for RP compared to AM was seen in the ProtecT study where the majority of men had early, localised disease (i.e. > 75% had either clinical T1 or Gleason sum score 6 disease) [271]. In the SPCG-4 study [333], death from any cause and distant metastases was significantly reduced in low-risk PCa at eighteen years of follow up for RP compared with WW, although this finding was based on a sub-group analysis as the majority of men in the trial (i.e. 62%) did not have low-risk disease. However, death from PCa was not reduced. In the PIVOT trial, a pre-planned subgroup analysis of men with low-risk PCa showed that RP did not significantly reduce all-cause mortality or death from PCa at ten years compared with WW.

The decision to offer RP in cases of low-risk cancer should be based on the probability of clinical progression, side-effects and potential benefit to survival [339]. The results of the ProtecT trial suggest that AM and surgery are alternatives to EBRT in patients whose tumours are most likely to be clinically insignificant (this is covered in more detail in Sections 6.1 and 6.3). Apart from disease characteristics, age and comorbidities also impact
on decision-making regarding treatment choices. Individual patient preferences should always be considered in shared decision-making.

If RP is performed in low-risk PCa, pelvic LND is not necessary as the risk for pN+ does not exceed 5% [340].

### 6.2.3 Intermediate-risk, localised PCa

Patients with intermediate-risk PCa should be informed about the results of two RCTs [324, 333] comparing RP 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 eighteen 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 ten years.

When managed with non-curative intent, intermediate-risk PCa is associated with ten- and fifteen-year PCa-specific mortality (PCSM) rates of 13% and 19.6%, respectively [341].

The risk of having positive LNs in intermediate-risk PCa is between 3.7% and 20.1% [340]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [340]. In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes. Table 6.2.1 presents data from three RCTs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial</th>
<th>Population</th>
<th>Year of treatment</th>
<th>Median follow-up (mo)</th>
<th>Risk category</th>
<th>12-year CSS (%)</th>
<th>18-year CSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilt, et al. 2012 [324]</td>
<td>PIVOT</td>
<td>Early years of PSA testing</td>
<td>1994-2002</td>
<td>120</td>
<td>Low-risk</td>
<td>100**</td>
<td>n.a</td>
</tr>
</tbody>
</table>

*10-year CSS
** Based on sub-group analysis of risk groups

CSS = cancer-specific survival; n = number of patients; n.r. = not reported; PSA = prostate-specific antigen; RP = radical prostatectomy.

### 6.2.4 High-risk and locally advanced PCa

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 [342]. When managed with non-curative intent, high-risk PCa is associated with ten- and fifteen-year PCSM rates of 28.8% and 35.5%, respectively [341].

There is no consensus regarding the optimal treatment of men with high-risk PCa. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Extended LND should be performed in all high-risk PCa cases, as the estimated risk for positive LNs is 15-40% [340].

#### 6.2.4.1 High-risk PCa

##### 6.2.4.1.1 Gleason score 8-10

The incidence of organ-confined disease is 26-31% in men with a Gleason 8-10 on biopsy. A high rate of downgrading exists between the biopsy Gleason score and the Gleason score of the resected specimen [343]. Several retrospective case series have demonstrated CSS rates over 60% at fifteen years after RP in the context of a multimodal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy GS > 8 [343-346] [347].

##### 6.2.4.1.2 Prostate-specific antigen > 20 ng/mL

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a CSS at fifteen years of over 70% [345, 346, 348-351].
6.2.4.2 Locally advanced PCa
Surgery for locally advanced disease as part of a multimodal therapy has been reported [352-354]. Retrospective case series demonstrated over 60% CSS at fifteen years and over 75% OS at ten years [352-359].

For cT3b-T4 disease, PCa cohort studies showed a ten-year CSS of over 87% and an OS of 65% [360-362].

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Only limited evidence exists supporting RP of cN+ patients. In a recent study, the outcomes of 50 patients with cN+ were compared with those of 252 patients with pN1, but cN0 at pre-operative staging, and cN+ was not a significant predictor of CSS [363].

6.2.5 Indication and extent of pelvic lymph node dissection
A recent SR did not show any benefit of performing any PLND during RP for any oncological outcome, including survival [4]. However, it is generally accepted that eLND provides important information for staging and prognosis which cannot be matched by any other currently available procedure [255]. The individual risk of identifying positive LNs can be estimated using pre-operative nomograms. Only a few of these nomograms are based on eLND templates. A risk of nodal metastases over 5% (Briganti nomogram, MSKCC, or Roach formula) is an indication to perform nodal sampling by an eLND [340, 364, 365].

6.2.5.1 Technique of lymph node dissection
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 [366].

6.2.5.1.1 Sentinel node biopsy analysis
Sentinel node biopsy (SNB) was shown to have a sensitivity of 95.2% for detecting metastases at eLND in a SR [367]. Due to lack of any reliable evidence regarding oncological effectiveness, SNB is still an experimental nodal staging procedure (see Section 5.3.2.3). In addition, controversy regarding definitions and thresholds has limited its application in clinical practice, although efforts to standardise definitions based on consensus have recently been attempted [368].

6.2.6 Radical prostatectomy in cN0 patients who are found to have pathologically confirmed lymph node invasion (pN1)
At fifteen years of follow up, cN0 patients who were treated with RP but were found to have pN1 at the time of surgery, were reported to have a CSS and OS of 45% and 42%, respectively [369-375].

In terms of performing frozen section of nodes during RP, two retrospective observational studies have shown a better CSS and OS in favour of a completed RP vs. an abandoned RP in patients who were found to be pN+ at the time of surgery [372, 373, 376]. This highlights the fact that frozen section should no longer be performed and supports the role of RP as an important component of multimodal strategies of pN+ PCAs.

6.2.6.1 Outcome of pN1 disease
6.2.6.1.1 Prognostic indicators
The number of positive LNs [377], the number of removed LNs [369, 374, 377-382], tumour volume within the LN, and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [383]. A LN density (defined as the percentage of positive LNs in relation to the total number of analysed/removed LNs) over 20% was found to be associated with poor prognosis [384].

6.2.7 Adjuvant treatment
6.2.7.1 Adjuvant treatment after RP
For patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, both adjuvant or salvage radiotherapy to the prostatic fossa can be offered. (see Section 6.3.6). Adjuvant androgen ablation with bicalutamide did not improve PFS in localised disease after RP [385]. A SR showed a possible benefit for PFS but not OS for adjuvant androgen ablation therapy [386].

6.2.7.2 Adjuvant androgen ablation in men with pN1 disease
The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a ten-year CSS rate of 80% [370, 371]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective RCT [371]. However, this trial included mostly patients with high-volume
nodal disease and multiple adverse tumour characteristics and the findings may not apply to men with less extensive nodal metastases.

6.2.7.3 Adjuvant radiotherapy in men with pN1 disease
In a retrospective multicentre cohort study, maximal local control with RT of the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated adjuvantly with continuous ADT [375]. However, 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) and GS 7-10 and pT3-4 or R1, as well as men with three to four positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [375]. In a Surveillance, Epidemiology and End Results (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 [376]. No recommendation can be made for the extent of adjuvant RT in pN1 disease although whole pelvis RT was given in more than 70% of men in a large retrospective series which identified a benefit for adding RT to androgen ablation in pN1 patients [375]. However the optimal field (prostatic fossa only or whole pelvis) remains unclear.

6.2.7.4 Adjuvant chemotherapy
The TAX3501 trial, compared the role of leuprolide (eighteen months) with, and without, docetaxel (six cycles) closed prematurely due to poor accrual [387]. Adjuvant chemotherapy after RP should only be considered within a clinical trial.

6.2.7.5 Guidelines for extended lymph node dissection in prostate cancer and pN+ patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not perform a lymph node dissection (LND) in low-risk PCa.</td>
<td>2b A</td>
<td></td>
</tr>
<tr>
<td>Perform an extended(e)LND in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%.</td>
<td>2b B</td>
<td></td>
</tr>
<tr>
<td>Perform an eLND in high-risk PCa.</td>
<td>2a A</td>
<td></td>
</tr>
<tr>
<td>Do not perform a frozen section of nodes during radical prostatectomy (RP) to decide whether to proceed with, or abandon, the procedure.</td>
<td>2a A</td>
<td></td>
</tr>
<tr>
<td>Do not perform a limited LND.</td>
<td>2a A</td>
<td></td>
</tr>
<tr>
<td>Upon detection of nodal involvement during RP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• offer adjuvant androgen deprivation therapy (ADT);</td>
<td>1b A</td>
<td></td>
</tr>
<tr>
<td>• discuss adjuvant ADT with additional radiotherapy (see Section 6.2.6.3);</td>
<td>2b A</td>
<td></td>
</tr>
<tr>
<td>• offer observation (expectant management) to a patient after eLND with &lt; 2 nodes with microscopic involvement, and a PSA &lt; 0.1 ng/mL and absence of extranodal extension.</td>
<td>2b B</td>
<td></td>
</tr>
</tbody>
</table>

6.2.8 Comparing RP surgical approaches
A previous SR 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 [388]. There was no evidence of differences in urinary incontinence (UI) rates at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [388-394]. Another SR and meta-analysis [335] included two small RCTs comparing RARP vs. LRP. The results suggested higher rates of erectile function recovery (RR 1.51; 95% CI: 1.19-1.92) and restoring early continence (RR 1.14; 95% CI: 1.04-1.24) in the RARP group. Increased surgical experience has lowered the complication rates of RP and improved cancer cure [395-398]. Consequently, there is emerging data to suggest some benefits of the robotic approach over the laparoscopic and open approaches, in terms of perioperative, recovery and short-term functional outcomes; however, there is uncertainty over oncological outcomes, longer-term functional and QoL outcomes [334].

6.2.9 Indications for nerve-sparing surgery
Nerve-sparing RP can be performed safely in most men with localised PCa [399, 400]. Clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa, and any GS > 7 on biopsy. An externally validated nomogram predicting side-specific extracapsular extension can help guide decision making [401, 402]. Multiparametric MRI might be helpful in selecting a nerve-sparing approach (see Section 5.3.1.4).

If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle (NVB). Alternatively, the use of intra-operative frozen-section analysis can help guide these decisions [403].
There is conflicting data on the early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation post-surgery [404, 405]. However, a large multicentre RCT including men < 68 years old with normal pre-operative erectile function, showed benefit from daily dosing of 5 mg tadalafil, after nerve-sparing RP for organ-confined non-metastatic PCa [406].

6.2.10 Guidelines for radical prostatectomy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer both radical prostatectomy (RP) and RT in patients with low- and intermediate-risk disease and a life expectancy &gt; 10 years.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Offer AS as an alternative to surgery or RT in patients with low-risk disease and a life expectancy of &gt; 10 years.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Offer nerve-sparing surgery in patients with a low risk of extracapsular disease (refer to Partin tables/nomograms).</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Offer RP in patients with high-risk localised PCa and a life expectancy of &gt; 10 years only as part of multi-modal therapy.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Offer RP in selected patients with locally advanced (cT3a) disease and a life expectancy &gt; 10 years only as part of multi-modal therapy.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Offer RP in highly selected patients with locally advanced disease (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Do not offer neoadjuvant hormonal therapy before RP.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Do not offer adjuvant hormonal therapy after RP for pN0 disease.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

6.3 Treatment: definitive radiotherapy

6.3.1 Introduction

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the accepted best standard for EBRT. Regardless of the technique used, the choice of treatment is multidisciplinary. After the extent of the tumour has been properly assessed, the following are taken into account [407]:

- 2017 TNM classification;
- Gleason score, defined using an adequate number of core biopsies (at least 10);
- Baseline PSA;
- Age of the patient;
- Patient’s comorbidity, life expectancy, and QoL;
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings (max urinary peak flow > 15 mL/s when considering brachytherapy [408]);
- And the EAU prognostic factors classification.

6.3.2 Technical aspects: three-dimensional conformal radiotherapy and intensity-modulated external-beam radiotherapy

Anatomical data are acquired by scanning the patient in the treatment position. The data are transferred to the three-dimensional (3D) treatment planning system, which visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field using portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm.

It is possible to use IMRT with linear accelerators, equipped with the latest multileaf collimators and specific software. At the time of irradiation, a multileaf collimator automatically (and in the case of IMRT continuously) adapts to the contours of the target volume seen by each beam. This allows for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves, which are particularly useful as a means of sparing the rectum. To date, no RCT have been published comparing dose escalation using IMRT and 3D-CRT.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [409]. Tomotherapy is another evolving technique for the delivery of IMRT, which uses a linear accelerator mounted on a gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of RT, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists and computer scientists.
6.3.3 Radiotherapy for localised PCa

6.3.3.1 Dose escalation

Several RCTs have shown that dose escalation (range 74-80 Gy) has a significant impact on five-year survival without biochemical relapse [410-419]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant HT has varied. The best evidence of an OS benefit for patients with intermediate- or high-risk PCa, but not with low-risk PCa, comes from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database (NCDB) covering a total of 42,481 patients [420].

In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT + HT. Currently, it is not possible to make different recommendations according to the patient’s risk group.

If IMRT and IGRT are used for dose escalation, severe late side effects ≥ Grade 3 for the rectum is about 2-3% and for the genito-urinary tract is 2-5% [412, 419, 421-434] (see also Chapter 8).

Table 6.3.1: Randomised trials on dose escalation in localised PCa

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>PCa condition</th>
<th>Radiotherapy Dose</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson 2011 [410]</td>
<td>301</td>
<td>T1-T3, N0, M0, PSA 10 ng/mL vs. PSA &gt; 10 ng/mL</td>
<td>70 vs.78 Gy</td>
<td>Median 9 yr</td>
<td>Disease specific mortality (DSM) vs. other cause of death</td>
<td>High risk/PSA &gt; 10 % DSM @ 70 Gy 4% DSM @ 78 Gy (p = 0.05) Higher risk 15 % DSM @ 70 Gy 2% DSM @ 78 Gy (p = 0.03)</td>
</tr>
<tr>
<td>PROG 95-09 2010 [411]</td>
<td>393</td>
<td>T1b-T2b PSA 15 ng/mL 75% GS &lt; 6</td>
<td>70.2 vs.79.2 Gy</td>
<td>Median 8.9 yr for survivors</td>
<td>10-year ASTRO BCF</td>
<td>All patients: 32% BF @ 70.2 Gy 17% BF @ 79.2 Gy (p &lt; 0.0001) Low-risk patients: 28% BF @ 70.2 Gy 7% BF @ 79.2 Gy (p &lt; 0.0001)</td>
</tr>
<tr>
<td>MRC RT01 2014 [407]</td>
<td>843</td>
<td>T1b-T3a, N0, M0 PSA &lt; 50 ng/mL neoadjuvant HT</td>
<td>64 vs. 74 Gy</td>
<td>Median 10 yr</td>
<td>BFS; OS</td>
<td>43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)</td>
</tr>
<tr>
<td>Dutch RCT 2014 [419]</td>
<td>664</td>
<td>T1b-T4 143 pts. with (neo)adjuvant HT</td>
<td>68 vs. 78 Gy</td>
<td>Median 110 mo</td>
<td>Freedom biochemical (Phoenix) and/or clinical failure (FFF) @ 10 yr.</td>
<td>43% FFF @ 68 Gy 49% FFF @ 78 Gy (p = 0.045)</td>
</tr>
<tr>
<td>French GETUG 06 2011 [414]</td>
<td>306</td>
<td>T1b-T3a, N0, M0 PSA &lt; 50 ng/mL</td>
<td>70 vs. 80 Gy</td>
<td>Median 61 mo</td>
<td>BCF (ASTRO)</td>
<td>39% BF @ 70 Gy 28% BF @ 80 Gy</td>
</tr>
<tr>
<td>Retrospective NCDB study 2015 [420]</td>
<td>16,714</td>
<td>intermediate risk 73% T ≤ 2a 76% GS ≤ 7a</td>
<td>&lt; 75.6 Gy vs. ≥ 75.6 Gy 49% HT</td>
<td>Median 85-86 mo</td>
<td>OS</td>
<td>Propensity adjusted HR: 0.84 favouring dose escalation (p &lt; 0.001)</td>
</tr>
<tr>
<td>Retrospective NCDB study 2015 [420]</td>
<td>13,538</td>
<td>high risk 40% T ≥ 2b 67% GS ≥ 7b</td>
<td>&lt; 75.6 Gy vs. ≥ 75.6 Gy 77% HT</td>
<td>Propensity adjusted HR: 0.82 favouring dose escalation (p &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCF = biochemical failure; BFS = biochemical progression-free survival; GS = Gleason score; HR = hazard ratio; HT = hormone therapy; OS = overall survival; PSA = prostate-specific antigen.
6.3.3.2 Hypofractionation

In radiobiology, the linear quadratic model uses two coefficients, alpha ($\alpha$) and beta ($\beta$) to describe the dose-response relationship. In clinical practice, these coefficients are used to calculate the effect of different fractionation schemes. Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue. In fast growing tissue including many tumours, cells have little time to repair photon-induced DNA damage. The $\alpha/\beta$ ratio is then typically around 10 Gy. In contrast, tissue with a low cell renewal has a good opportunity for repair between fractions of irradiation. In such tissue, the $\alpha/\beta$ ratio is 3 Gy or lower. Slowly proliferating cells with low $\alpha/\beta$ ratios are very sensitive to an increased dose per fraction [417].

While the correct $\alpha/\beta$ ratio is still controversial, a meta-analysis of 25 studies with > 14,000 patients concludes that PCa, due to its slow growth, has an $\alpha/\beta$ ratio of approximately 1.5 Gy. Assuming this value, hypofractionated RT could be more effective than conventional fractions of 1.8-2 Gy [418]. Beyond the radiobiological aspects, hypofractionation (HFX) can increase the convenience for the patient and lower costs for the health care system.

Several studies report on HFX applied in various techniques and in part also including HT [435-444]. A SR concludes that studies on moderate HFX (2.5-4 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 [445]. Extreme HFX (5-10 Gy/fx) typically requires IGRT and stereotactic body radiotherapy (SBRT). Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade genitourinary and rectal toxicity, and long-term side effects may not all be known yet [445-447].

On behalf of the German Society of Radiation Oncology, an international expert panel has released a comprehensive overview on HFX for clinical routine [448]. Taking into account the published results and the uncertainties of the correct $\alpha/\beta$ ratio, moderate HFX (Table 6.3.2) plus dose escalation should be done by experienced teams, accompanied by meticulous RT quality assessment and close attention to organ-at-risk dose-constraints until long-term data are available. It should be restricted to high-quality EBRT using IGRT and IMRT in carefully selected patients and adhere to published phase 3 protocols with documented safety and efficacy. The Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP)-regimen with 60 Gy in 20 fractions over four weeks or the RTOG regimen with 70 Gy in 28 fractions over six weeks at present seem to be the first choices. Meticulous follow-up and documentation of outcome and late toxicity are mandatory. Hypofractionation to the pelvic LNs and post-operative HFX in the adjuvant or salvage setting are experimental and should be reserved for clinical trials.
Table 6.3.2: Major phase 3 randomised trials of moderate hypofractionation for localised PCa

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Risk, GS, or NCCN</th>
<th>Regimen</th>
<th>BED, Gy</th>
<th>Median FU, mo</th>
<th>Outcome</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 2016 [439]</td>
<td>550</td>
<td>low risk</td>
<td>70 Gy/28 fx</td>
<td>80</td>
<td>69.6</td>
<td>5 yr. DFS</td>
<td>Gr 2 GI 18.3% (p = 0.005)</td>
</tr>
<tr>
<td></td>
<td>542</td>
<td></td>
<td>73.8 Gy/41 fx</td>
<td></td>
<td></td>
<td></td>
<td>Gr 2 GU 26.2% (p = 0.009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80 Gy/35 fx</td>
<td></td>
<td></td>
<td></td>
<td>Gr 2 GI 11.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80 Gy/28 fx</td>
<td></td>
<td></td>
<td></td>
<td>Gr 2 GU 20.5%</td>
</tr>
<tr>
<td>Dearmaley et al. 2012</td>
<td>1077/19 fx</td>
<td>15% low 73% intermediate 12% high</td>
<td>57 Gy/19 fx</td>
<td>73.3</td>
<td>77.1 74</td>
<td>5 yr. BCDF 85.9% (19 fx)</td>
<td>acute Gr ≥ 2 GI 38% (19 fx) 38% (20 fx) 25% (37 fx) 5 yr. Gr ≥ 2 GI 11.3% (19 fx) 11.9% (20 fx) 13.7 (37 fx) 5 yr. Gr ≥ 2 GU 6.6% (19 fx) 11.7% (20 fx) 9.1% (37 fx)</td>
</tr>
<tr>
<td>2016 [435, 440]</td>
<td></td>
<td></td>
<td>60 Gy/20 fx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1074/20 fx</td>
<td></td>
<td>74 Gy/37 fx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1065/37 fx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluwini et al. 2015, 2016 [438, 443, 444]</td>
<td>403</td>
<td>30% GS &lt; 6 45% GS &gt; 7 25% GS 8-10</td>
<td>64.6 Gy/19 fx</td>
<td>90.4 78</td>
<td>78 Gy/39 fx</td>
<td>5 yr. RFS 80.5% (NS)</td>
<td>3 yr. Gr ≥ 2 GU 41.3% Gr ≥ 3 GU 19.0% (p = 0.02)</td>
</tr>
<tr>
<td></td>
<td>392</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gr ≥ 2 GI 21.9% 3 yr. Gr ≥ 2 GU 39.0%</td>
</tr>
</tbody>
</table>

BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/β of 1.5 Gy; DFS = disease-free survival; FU = follow-up; fx = fractions; GI = gastrointestinal; Gr = Grade; GS = Gleason score; GU = genitourinary; NCCN = National Comprehensive Cancer Network; NS = not significant; n.s. = not stated.

Radiotherapy with > 3.4 Gy has been suggested to define extreme HFX [448]. Respective studies largely include low- to intermediate-risk patients and obtain very favourable results. Table 6.3.3 gives an overview on selected studies. It seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.3.3: Selected trials on extreme hypofractionation for localised PCa

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>med FU (mo.)</th>
<th>Risk-Group</th>
<th>Techniques</th>
<th>Regimen (TD/fx)</th>
<th>Outcome</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al. 2014 [449]</td>
<td>1,743</td>
<td>n.s.</td>
<td>41% low 42% intermediate 10% high 7% data missing</td>
<td>mainly robotic IGRT</td>
<td>35–40 Gy/4–5 fx (8% SBRT-boost 19.5–21.8 Gy/3 fx after 45–50 Gy EBRT)</td>
<td>FFBF 92% @ 2 yr. 99% low risk 97–85% intern. risk 87% high risk</td>
<td>G3 GU 0% G3 GI 0%</td>
</tr>
<tr>
<td>Katz et al. 2014 [450]</td>
<td>515</td>
<td>72</td>
<td>63% low 30% intermediate 7% high</td>
<td>robotic IGRT</td>
<td>35–36.25 Gy/5 fx</td>
<td>FFBF @ 7yr. 96% low risk 89% intern.risk 69% high risk</td>
<td>G ≥ 2 GU 9% G ≥ 2 GI 4%</td>
</tr>
</tbody>
</table>

FFBF = freedom from biochemical failure; FU = follow-up; TD = total dose; fx = number fractions; GI = gastrointestinal; G = grade; GU = genitourinary; IGRT = image-guided radiation therapy; n.s. = not stated; EBRT external beam radiotherapy in standard fractionation.
6.3.3.3  Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with luteinising-hormone-releasing hormone (LHRH) ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [451-455] (Table 6.3.3). These trials included high-risk PCa patients, mostly by virtue of locally advanced (T3-T4 N0-X) disease, though with a wide range of clinical risk factors, such as PSA level or Gleason grade (high-risk localised, T1-2, N0-X PCa). The most powerful conclusion from these studies comes from the EORTC 22863 trial, which is the basis for the combination of RT and ADT in patients with locally advanced PCa as standard practice today.

In daily practice, ADT starts either at the onset of RT (for adjuvant ADT) or two or three months before (for neoadjuvant), but the concurrent component is crucial to potentiate RT. Long-term ADT, ranging from two to three years is recommended for locally advanced disease [416, 456] rather than short term (six months) [455]. Dose escalation phase III RCTs are on-going to assess its impact on DFS. Cardiovascular mortality may be related to ADT, not RT, as addressed in Section 8.2.

Whether these results should be applied to patients with intermediate- or high-risk localised PCa is unclear. The Boston trial has shown an improved eight-year OS rate for patients without moderate or severe comorbidity assigned to six months of complete ADT (p = 0.01) [454], and the RTOG 94-08 study showed an increased ten-year OS rate for intermediate risk only with four months of complete ADT (p = 0.003) [415].

The EORTC trial 22961, an equivalence trial with 970 patients (78% T3-4, 92% N0) combined RT (70 Gy) with either six months or with three years of LHRH analogue treatment. With a median follow-up of 6.4 years, both CSS and overall mortality were significantly lower with long-term androgen suppression [416].

In the RTOG 9910 trial, 1,579 intermediate-risk PCa patients were randomised to LHRH antagonist therapy for eight weeks before RT (70.2 Gy in 2-D or 3-D techniques) followed by either another eight or 28 weeks of anti-hormonal treatment. Extended androgen suppression did not significantly improve ten-year rates of distant (both arms 6%), loco-regional (6% vs. 4%) or biochemical progression (both arms 27%), or DSS (96% vs. 95%) or OS (66% vs. 67%). The 8 + 8 week scheme was confirmed as a standard procedure [457].

Table 6.3.3: Studies of use and duration of androgen deprivation therapy in combination with radiotherapy for prostate cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>TNM stage</th>
<th>n</th>
<th>Trial</th>
<th>ADT</th>
<th>RT</th>
<th>Effect on OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22863, 2010</td>
<td>T1-2 poorly differentiated M0, or T3-4 N0-1 M0</td>
<td>415</td>
<td>EBRT ± ADT</td>
<td>LHRH agonist for 3 yr.</td>
<td>70 Gy RT</td>
<td>Significant benefit at ten yr. for combined treatment (HR: 0.60, 95%, CI: 0.45-0.80, p = 0.0004).</td>
</tr>
<tr>
<td>RTOG 85-31, 2005</td>
<td>T3 or N1 M0</td>
<td>977</td>
<td>EBRT ± ADT</td>
<td>Orchiectomy or LHRH agonist 15% RP</td>
<td>65-70 Gy RT</td>
<td>Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with GS 7-10</td>
</tr>
<tr>
<td>Granfors, et al. 2006</td>
<td>T3 N0-1 M0</td>
<td>91</td>
<td>EBRT ± ADT</td>
<td>Orchiectomy</td>
<td>65 Gy RT</td>
<td>Significant benefit (p = 0.02 p = 0.03), mainly caused by LN-positive tumours</td>
</tr>
<tr>
<td>D’Amico, et al. 2008</td>
<td>T2 N0 M0 (localised unfavourable risk)</td>
<td>206</td>
<td>EBRT ± ADT</td>
<td>LHRH agonist plus flutamide for 6 mo.</td>
<td>70 Gy 3D-CRT</td>
<td>Significant benefit (HR: 0.55, 95% CI: 0.34-0.90, p = 0.01) that may pertain only to men with no, or minimal, comorbidity TROG 96-01</td>
</tr>
<tr>
<td>Study</td>
<td>T stage</td>
<td>N stage</td>
<td>M stage</td>
<td>ADT duration</td>
<td>Radiotherapy</td>
<td>Results</td>
</tr>
<tr>
<td>-------</td>
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<td>---------</td>
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<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Denham, et al. 2011 [455]</td>
<td>T2b-4 N0 M0</td>
<td>802</td>
<td>Neoadjuvant ADT duration</td>
<td>Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression</td>
<td>66 Gy 3D-CRT</td>
<td>No significant difference in OS reported; benefit in PCa-specific survival (HR: 0.56; 95% CI: 0.32-0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65-1.08; p = 0.18)</td>
</tr>
<tr>
<td>RTOG 94-13, 2007 [459]</td>
<td>T1c-4 N0-1 M0</td>
<td>1292</td>
<td>ADT timing comparison</td>
<td>Goserelin plus flutamide 2 mo. before, plus concomitant suppression</td>
<td>Whole pelvic RT vs. prostate only; 70.2 Gy</td>
<td>No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression groups (interaction suspected)</td>
</tr>
<tr>
<td>RTOG 86-10, 2008 [453]</td>
<td>T2-4 N0-1</td>
<td>456</td>
<td>EBRT ± ADT</td>
<td>Goserelin plus flutamide 2 mo. before, plus concomitant therapy</td>
<td>65-70 Gy RT</td>
<td>No significant difference at 10 yr.</td>
</tr>
<tr>
<td>RTOG 92-02, 2008 [456]</td>
<td>T2c-4 N0-1 M0</td>
<td>1554</td>
<td>Short vs. prolonged ADT</td>
<td>LHRH agonist given for 2 years as adjuvant after 4 mo. as neoadjuvant</td>
<td>65-70 Gy RT</td>
<td>No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)</td>
</tr>
<tr>
<td>EORTC 22961, 2009 [416]</td>
<td>T1c-2ab N1 M0, T2c-4 N0-1 M0</td>
<td>970</td>
<td>Intermediate risk (94% T1-T2, 6% T3-4)</td>
<td>LHRH agonist for 6 mo. vs. 3 yr.</td>
<td>70 Gy 3D-CRT</td>
<td>Better result with 3-year treatment than with 6 mo. (3.8% improvement in survival at 5 yr.)</td>
</tr>
<tr>
<td>Pisansky, et al. 2014 [457]</td>
<td>T1b-2 Grade 2-3, T3 N0 M0</td>
<td>875</td>
<td>Short vs. prolonged ADT</td>
<td>LHRH antagonist 8 + 8 vs. 8 + 28 wk</td>
<td>70 Gy 3D-CRT vs. no RT</td>
<td>18.9% (30.7%) vs. 8.3% (12.4%) cancer specific mortality at 10 (15) yr. favouring combined treatment (HR: 0.35; p &lt; 0.0001 for 15 yr. results) NCIC CTG PR.3/MRC</td>
</tr>
<tr>
<td>SPCG-7/ SFUO-3, 2014 [460]</td>
<td>T3-4 (88%), PSA &gt; 20 ng/ml (64%), GLS 8-10 (36%) N0 M0</td>
<td>1205</td>
<td>ADT ± EBRT</td>
<td>LHRH agonist for 3 mo plus continuous flutamide</td>
<td>65-70 Gy 3D-CRT vs. no RT</td>
<td>10 yr. OS = 49% vs. 55% favouring combined treatment (HR: 0.7, p &lt; 0.001)</td>
</tr>
<tr>
<td>Mottet, et al. 2012 [463]</td>
<td>T3-4 N0 M0</td>
<td>273</td>
<td>ADT ± EBRT</td>
<td>LHRH agonist for 3 yr.</td>
<td>70 Gy 3D-CRT vs. no RT</td>
<td>Significant reduction of clinical progression; 5 yr. OS 71.4% vs. 71.5%</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; GS = Gleason score; LHRH = luteinising-hormone-releasing hormone; OS = overall survival; RT = radiotherapy; HR = hazard ratio; 3D-CRT = three-dimensional conformal radiotherapy.
6.3.3.4 Neoadjuvant chemotherapy plus radiotherapy
The GETUG 12 trial investigated the impact of neoadjuvant chemotherapy with docetaxel on the PFS in a cohort of 413 high-risk patients. Patients were randomly assigned to either goserelin 10.8 mg every three months for three years, plus four cycles of docetaxel and estramustine or to goserelin alone (arm 2). Local therapy was administered at three months and consisted of RT in 358 patients (87%). Toxicity included Grade 3-4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death. A PSA response (PSA < 0.2 ng/mL after three months of treatment) was obtained in 34% in the ADT + docetaxel arm and 15% in the ADT arm. With a median follow-up period of 4.6 years, the four-year PFS was 85% in arm 1 vs. 81% in arm 2 (p = 0.26), but the data need to mature [464].

6.3.3.5 Combined dose-escalated radiotherapy and androgen-deprivation therapy
Zelefsky et al. [465] reported a retrospective analysis comprising 571 patients with low-risk PCa (22.4%), 1,074 with intermediate-risk PCa (42.1%), and 906 with high-risk PCa (35.5%). Three-dimensional-conformal RT or IMRT were administered. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last ten years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was three months for low-risk patients and six months for intermediate-risk and high-risk patients, starting three months before RT. The ten-year biochemical disease-free rate (BDFR) was significantly improved by dose escalation: 84% (> 75.6 Gy) vs. 70% for low-risk PCa (p = 0.04), 76% (> 81 Gy) vs. 57% for intermediate-risk PCa (p = 0.0001), and 55% (> 81 Gy) vs. 41% for high-risk patients (p = 0.0001). The six-month ADT also influenced the BDFR in intermediate- and high-risk patients, with 55% for intermediate-risk vs. 36% for high-risk patients (p < 0.0001). In the multivariate analysis, a dose > 81 Gy (p = 0.027) and ADT (p = 0.052) were found to be predictive factors for distant metastasis-free survival, but none of these parameters influenced OS.

6.3.3.6 Recommended external beam radiation therapy treatment policy for localised PCa
6.3.3.6.1 Low-risk PCa
Intensity-modulated RT with escalated dose without ADT is an alternative to brachytherapy (see below).

6.3.3.6.2 Intermediate-risk PCa
Patients suitable for ADT can be given combined IMRT with short-term ADT (four to six months) [415, 466, 467]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT at an escalated dose (76-80 Gy) or a combination of IMRT and brachytherapy.

6.3.3.6.3 Localised high-risk PCa
The high risk of relapse outside the irradiated volume makes it mandatory to use a combined modality approach, consisting of dose-escalated IMRT, possibly including the pelvic lymphatics + long-term ADT. The duration of ADT has to take into account WHO PS, comorbidities, and the number of poor prognostic factors. It is important to recognise that EBRT + short-term ADT did not improve OS in high-risk localised PCa, in the Boston and RTOG 94-13 and 86-10 trials [453, 454, 459], and long-term ADT is currently recommended for these patients.

6.3.3.6.4 Locally advanced PCa: T3-4 N0, M0
In locally advanced disease, RCTs have clearly established that the additional use of long-term ADT combined with RT produces better OS. Whilst RT is effective in this patient group, combined RT + ADT is clearly superior to ADT alone.

6.3.3.6.5 MRC PR3/PR07 study - The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study
This study comprised 1,205 patients, consisting of T3-4 (n = 1,057), or T2, PSA > 40 ng/mL (n = 119), or T2, PSA > 20 ng/mL and Gleason score > 8 (n = 25), who were randomly assigned to lifelong ADT (bilateral orchidectomy or LHRH agonist), with or without RT (65-70 Gy to the prostate, with or without 45 Gy to the pelvic LNs). With a median follow-up of eight years, OS was significantly improved in the patients allocated to ADT + RT (HR: 0.70; 95% CI: 0.57-0.85; p < 0.001). Deaths from PCa were significantly reduced by the addition of RT to ADT (HR: 46; 95% CI: 0.34-0.61; p < 0.001). Patients on ADT + RT reported a higher frequency of adverse events related to bowel toxicity, but only two of 589 patients had Grade 3 or greater diarrhoea at 24 months after RT [462].

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to three years
of ADT using an LHRH agonist (leuprorelin), with or without RT (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic LNs). After a median follow-up period of 67 months, there was a significant improvement in the five-year DFS (p < 0.001), metastatic DSS (p < 0.018), and loco-regional PFS (p < 0.0002), but the effect on OS was not reported [463].

Another study compared hormonal treatment alone (i.e. three months of continuous androgen blockade followed by continuous flutamide treatment (n = 439) with the same treatment combined with RT (n = 436) [460]. The ten (fifteen) year cumulative PCSM was 18.9% (30.7%) and 8.3% (12.4%) (HR: 0.35; [p < 4.1E-10 for fifteen year results]), and overall mortality was 35.3% (56.7%) and 26.4% (43.4%) (HR: 0.70; p = 0.0006 for fifteen-year results), respectively.

6.3.3.7 Lymph node irradiation

6.3.3.7.1 Prophylactic LN irradiation in clinically N0 prostate cancer (estimated cN0)

There is no level 1 evidence for prophylactic whole-pelvic irradiation, since RCTs have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic LNs in high-risk cases. Such studies include the RTOG 77-06 study (n = 484 with T1b-T2) [468], the Stanford study (n = 91) [469], and the GETUG 01 trial (n = 444 with T1b-T3 N0 pNx M0) [470]. In the RTOG 94-13 study [459], there were no differences in the PFS in patients treated with whole-pelvic or prostate-only RT, but interactions between whole-pelvic RT and the duration of ADT were reported following the subgroup analysis. Pelvic LND may be needed to improve the selection of patients who may be able to benefit from pelvic LN irradiation and to supplement the use of the Briganti tables [340] and/or the Roach formula [471]. The results of pelvic LND, especially in young patients, allows radiation oncologists to tailor both the planning target volume and the duration of ADT, particularly ensuring that there is no pelvic irradiation for pN0 patients, while it is possible to irradiate, in combination with long-term ADT. The real impact of such an approach remains, so far, hypothetical, since no randomised trials are available. The benefits of pelvic nodal irradiation at a high dosage using IMRT merit further investigation in a phase II trial. One such trial is currently recruiting through the RTOG, and PIVOTAL, a UK randomised phase II trial, has completed accrual.

6.3.3.7.2 Clinical, or pathological node positive, M0 disease

Outcomes in this group after RT as a sole modality are poor [416], and these patients should receive RT plus long-term ADT. The RTOG 85-31 randomised phase III trial, with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic RT with immediate HT had better five-year (54%) and nine-year (10%) PFS rates (PSA < 1.5 ng/mL) vs. 33% and 4%, respectively, for radiation alone (p < 0.0001). Multivariate analysis showed that this combination had a statistically significant impact on the OS [472]. Patients with pelvic LN involvement lower than the iliac regional nodes, < 80 years old, with a WHO PS 0-1 and no severe comorbidity, may be candidates for EBRT + immediate long-term HT. Recent data from the UK Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial suggests that pelvic RT could be beneficial for N1 disease, but this is not based on a randomised comparison [473] (see also Section 6.3.7).

6.3.4 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.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing [474]; the other study suggested a clearer advantage for protons [475].

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose, but it cannot be used as evidence for the superiority of proton therapy per se [411]. Thus, unequivocal information that shows an advantage of protons over IMRT photon therapy is still not available.

Studies from the SEER database, and from Harvard [476, 477], describing toxicity and patient reported outcomes do not point to an inherent superiority for protons. In terms of longer term gastrointestinal (GI) toxicity, proton therapy might even be inferior to IMRT [477].

A retrospective 2:1 matched-control analysis of 27,647 U.S. Medicare patients compared 314 men receiving proton therapy with 628 men who had IMRT. Despite the considerably higher costs for proton
therapy, there was some improvement in GU-tract toxicity after 6 months, but not after 12 months, and not at the GI tract [478].

A randomised trial comparing equivalent doses of proton-beam therapy with IMRT is needed to compare the efficacy of protons vs. photons; a study of this type is under consideration by the RTOG. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy.

6.3.5 Low-dose rate and high-dose rate brachytherapy

6.3.5.1 Low-dose rate (LDR) brachytherapy

There is a consensus on the following eligibility criteria for LDR monotherapy [479]:

- stage cT1b-T2a N0, M0;
- Gleason score 6 with \(\geq 50\%\) of biopsy cores involved with cancer or;
- Gleason score 3 + 4 with \(\leq 33\%\) of biopsy cores involved with cancer;
- an initial PSA level of \(\leq 10\) ng/mL;
- a prostate volume of \(< 50\) cm\(^3\);
- an International Prostatic Symptom Score (IPSS) \(< 12\) and maximal flow rate \(> 15\) mL/min on urinary flow tests [408].

Low-dose rate brachytherapy uses radioactive seeds permanently implanted into the prostate. Patients with low- and favourable intermediate-risk PCa are the most suitable candidates for LDR brachytherapy as monotherapy. The use of guidelines is strongly recommended [479-481]. There have been no RCTs comparing brachytherapy as monotherapy with other curative treatment modalities. Outcome data are available from a number of large population cohorts with mature follow-up [482-489]. The BDFS for Gleason 6 patients after five and ten years has been reported to range from 71\% to 93\% and 65\% to 85\%, respectively [482-489].

A significant correlation has been shown between the implanted dose and recurrence rates [490]. Patients receiving a D90 (dose covering 90\% of the prostate volume) of \(> 140\) Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after four years than patients who received less than 140 Gy (92 vs. 68\%).

In men with intermediate- or high-risk PCa, LDR brachytherapy boost with supplemental EBRT and hormonal treatment [491] may be considered. Dose-escalated EBRT has been compared with EBRT and LDR brachytherapy boost in intermediate-risk and high-risk patients in a RCT [492]. The ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) multi-centre Canadian trial compared EBRT (total dose of 78 Gy) to EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy). The use of LDR boost resulted in five- and seven-year PSA PFS rates of 89\% and 86\%, respectively compared to 84\% and 75\% in those treated with EBRT alone. This improvement in PSA control came with an increase in late urinary toxicity with 18\% experiencing G3+ toxicity in the LDR boost arm as compared to 8\% in the EBRT alone arm. Toxicity was mainly due to urethral strictures and incontinence and great care should be taken during treatment planning.

6.3.5.2 High-Dose Rate (HDR) brachytherapy

High-dose rate brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in the table below. The use of published guidelines is strongly recommended [493]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [494]. A single RCT of EBRT vs. EBRT and HDR brachytherapy boost has been reported [495]. A total of 218 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in twenty fractions, or EBRT with a dose of 35.75 Gy in thirteen fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the BDRF (p = 0.04) with five-, seven- and ten-year estimates of biochemical control of 75\%, 66\% and 46\% for combination treatment compared to 61\%, 48\% and 39\% for external beam alone. There were no differences in the rates of late bowel, urinary or sexual patient QoL over a ten-year follow-up period. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after two years, possibly due to a dose lower than the current standard used [495]. A SR of non-randomised trials has suggested the possibility that outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective RCT [496].

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 [497, 498]. Five year PSA control rates over 90\% are reported, with late G3+ genito-urinary toxicity rates < 5\% and no, or very minimal, G3+ gastro-intestinal toxicity rates [497, 498].
Differences in prostate brachytherapy techniques

<table>
<thead>
<tr>
<th>Low Dose Rate (LDR)</th>
<th>High Dose Rate (HDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Permanent seeds implanted</td>
<td>• Temporary implantation</td>
</tr>
<tr>
<td>• Uses I-125 (most common), Pd-103 or Cs-131 isotopes</td>
<td>• Ir-192 isotope introduced through implanted needles or catheters</td>
</tr>
<tr>
<td>• Radiation dose delivered over weeks and months</td>
<td>• Radiation dose delivered in minutes</td>
</tr>
<tr>
<td>• Acute side effects resolve over months</td>
<td>• Acute side effects resolve over weeks</td>
</tr>
<tr>
<td>• Radiation protection issues for patient and carers</td>
<td>• No radiation protection issues for patient or carers</td>
</tr>
</tbody>
</table>

A SR and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrate an increased risk of developing second cancers for bladder (OR 1.39), colorectal (OR 1.68) and rectum (OR 1.62) with similar risks over lag times of five and ten years. Absolute risks over ten years are small (1–4%) but should be discussed with younger men in particular [499].

6.3.6 Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0) (Table 6.3.5)
Extracapsular invasion (pT3), Gleason score ≥ 7 and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after five years [500]. Three prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]), as follows:

6.3.6.1 EORTC 22911
EORTC 22911 [501], with a target sample size of 1,005 patients, compared immediate post-operative RT (60 Gy) with RT delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after radical retropubic prostatectomy (RRP). Grade 4 toxicity was not observed (for criteria: see Tables 8.2.2 and 8.2.3). The rate of Grade 3 GU toxicity was 5.3% vs. 2.5% in the observation group after ten years. For patients younger than 70 years, the study concluded that immediate post-operative RT after surgery significantly improved the ten-year biological PFS to 60.6% vs. 41.1% in the observation group. Loco-regional control was better in the long-term follow-up at ten years after immediate irradiation (HR: 0.45; p < 0.0001). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after ten years (HR: 0.69; p = 0.008). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of ART was on biochemical progression (HR reduced to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after five years for pT3 with negative margins and other risk factors [501].

6.3.6.2 ARO trial
The conclusions of ARO trial 96-02 (n = 385) appear to support those of the EORTC study. After a median follow-up period of 112 months, the RT group (60 Gy) demonstrated a significant improvement in BDFR of 56% vs. 35%, respectively (p = 0.0001). However, unlike other studies, and of major interest, the randomisation of patients was carried out after they had achieved an undetectable PSA level following RP (< 0.1 ng/mL) and only pT3 tumours were included. This result indicates that ART is effective, even in the setting of an undetectable PSA after RP and additional risk factors [502].

6.3.6.3 SWOG 8794 trial
Conversely, the updated results, with a median follow-up of more than twelve years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a ten-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, p = 0.016) and a ten-year OS of 74% vs. 66% (median: 1.9 years prolongation; p = 0.023) [503, 504].

6.3.6.4 Conclusion
Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, two options can be offered in the framework of informed consent. These are:
• immediate ART to the surgical bed [501, 502, 504] after recovery of urinary function.
or
• clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [505, 506] (see Section 6.10.5.1).
Table 6.3.4: Overview of all three randomised trials for adjuvant radiation therapy after radical prostatectomy*

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Inclusion criteria</th>
<th>Randomisation</th>
<th>Definition of BCR PSA (ng/mL)</th>
<th>Median FU (mo)</th>
<th>Biochemical PFS survival</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 8794, 2009 [504]</td>
<td>431</td>
<td>pT3 cN0 ± involved SM</td>
<td>60-64 Gy vs. observation</td>
<td>&gt; 0.4</td>
<td>152</td>
<td>10 yr: 53% vs. 30% (p &lt; 0.05)</td>
<td>10 yr.: 74% vs. 66% Median time: 15.2 vs. 13.3 yr. p = 0.023</td>
</tr>
<tr>
<td>EORTC 22911, 2012 [501]</td>
<td>1,005</td>
<td>pT3 ± involved SM pN0 pt2 involved SM pN0</td>
<td>60 Gy vs. observation</td>
<td>&gt; 0.2</td>
<td>127</td>
<td>10 yr: 60.6% vs. 41% (p &lt; 0.001)</td>
<td>81% vs. 77% n.s.</td>
</tr>
<tr>
<td>ARO 96-02, 2014 [502]</td>
<td>388</td>
<td>pT3 (± involved SM) pN0 PSA post-RP undetectable</td>
<td>60 Gy vs. observation</td>
<td>&gt; 0.05 + confirmation</td>
<td>112</td>
<td>10 yr: 56% vs. 35% (p = 0.0001)</td>
<td>10 yr.: 82% vs. 86% n.s.</td>
</tr>
</tbody>
</table>

*See Section 6.10.5.1 for delayed (salvage) post-radical prostatectomy external irradiation. BCR = biochemical recurrence; n = number of patients; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

6.3.7 Summary of evidence and guidelines for definitive radiotherapy

**Summary of evidence**
- The highest effect of adjuvant radiotherapy is seen in patients with pT3R1 PCa. 1a
- The optimum duration of androgen deprivation therapy (ADT) with external beam radiation therapy (EBRT) is well established in the literature. There is no evidence that these durations should change when using brachytherapy boost with EBRT. 1b
- Limited data, from experienced centres only, are available for the use of fractionated high-dose-rate brachytherapy as monotherapy in patients with low and intermediate-risk PCa. 2a

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
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<tbody>
<tr>
<td>Offer external beam radiation therapy (EBRT) to all risk groups of non-metastatic PCa.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In low-risk PCa, use a total dose of 74 to 78 Gy.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>In patients with low-risk PCa, and selected intermediate-risk PCa, without a previous transurethral resection of the prostate (TURP) and with a good International Prostate Symptom Score and a prostate volume &lt; 50 mL, offer low-dose rate (LDR) brachytherapy.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>In patients with intermediate-risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (four to six months).</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In patients with high-risk localised PCa and locally advanced cN0 PCa, use EBRT to a dose of 76-78 Gy, or combined EBRT with brachytherapy boost (either high-dose rate [HDR] or LDR). Radiotherapy should be given in combination with long-term androgen deprivation therapy (two to three years).</td>
<td>1a</td>
<td>EBRT</td>
</tr>
<tr>
<td>Offer intensity-modulated radiotherapy (IMRT) for definitive treatment of PCa by EBRT.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Moderate hypofractionation (HFX) with IMRT including image-guided radiation therapy (IGRT) to the prostate only can be offered to carefully selected patients with localised disease (as discussed in the text).</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Moderate HFX should adhere to radiotherapy-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>
In patients with cN+ or pN+ PCa offer pelvic external irradiation in combination with immediate long-term ADT.

In patients with pT3, N0M0 PCa and an undetectable prostate-specific antigen (PSA) following radical prostatectomy, discuss adjuvant EBRT because it improves at least biochemical-free survival.

Inform patients with an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (see Section 6.9.5.1).

6.4 Treatment: Options other than surgery and radiotherapy for the primary treatment of localised prostate cancer

6.4.1 Background

Besides RP, EBRT and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa [507-510]. In this section, both whole gland and focal treatment will be considered, looking particularly at high-intensity focused US (HIFU) and cryosurgical ablation of the prostate (CSAP) as sufficient data are available to form the basis of some initial judgements on these latest additions to the management of PCa. Other options - such as photodynamic therapy, radiofrequency ablation and electroporation, among others - are considered to be in the early phases of evaluation and will therefore not be discussed in this edition of the Guidelines. Both HIFU and CSAP have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity and improved functional outcomes. In addition, a relatively newer development is focal ablative therapy, whereby lesion-targeted ablation is undertaken in a precise, organ-sparing manner.

6.4.2 Cryosurgery

Cryosurgery uses freezing techniques to induce cell death by:
- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [507-510].

Freezing of the prostate is ensured by the placement of 12-15 x 17 gauge cryoneedles under TRUS guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryosurgery devices are mainly used.

Potential candidates for CSAP are those who have organ-confined PCa and those identified as having minimal tumour extension beyond the prostate [507-509]. The PSA should be < 20 ng/mL, and the Gleason score should be < 7:
- patients with low-risk PCa, or intermediate-risk PCa whose condition prohibits RT or surgery;
- at the time of therapy, the size of the prostate should be < 40 mL; volume reduction may be achieved by androgen ablation to avoid any technical difficulty in placing cryoprobes under the pubic arch.

It is important that patients with a life expectancy > 10 years should be fully informed that there are limited data on the long-term outcome for cancer control > 10 years and that this treatment modality is still considered as experimental.

6.4.2.1 Results of cryosurgery for PCa

A comparative assessment of primary ablative therapies for localised PCa, including CSAP, was recently undertaken by Ramsay et al. [511]. The SR and network meta-analysis compared CSAP vs. RP and EBRT. Data from 3,995 patients across nineteen studies (including one RCT, four non-randomised comparative studies, and fourteen case series) were included. In the short-term, there was conflicting evidence relating to cancer-specific outcomes when CSAP was compared with either EBRT or RP. The only finding that reached statistical significance was one-year DFS, which was worse for cryotherapy than for either EBRT or RP. However, none of the other cancer-specific outcomes, such as BCF or OS, showed any significant differences. Overall, because of the high risk of bias across the studies, the findings for cancer-specific outcomes were considered inconclusive. The review noted significant inconsistencies in outcome definitions, measurement and reporting in the evidence base, in particular BCR.

6.4.3 High-intensity focused ultrasound of the prostate

High-intensity focused ultrasound consists of focused US waves, emitted from a transducer, that cause tissue
damage by mechanical and thermal effects as well as by cavitation [512]. The goal of HIFU is to heat malignant
tissues above 65°C so that it is destroyed by coagulative necrosis. High-intensity focused ultrasound
is performed under general or spinal anaesthesia, with the patient lying in the lateral position. Potential
candidates are patients with low-to-moderate risk as part of clinical trials. The patient should be informed
about the lack of long-term outcome data at > 10 years (see Section 7.4.4.2).

6.4.3.1 Results of high-intensity focused ultrasound in PCa
As with CSAP, various PSA thresholds are defined for biochemical cure, and no international consensus exists
on objective response criteria. The Stuttgart criteria (> PSA nadir + 1.2 ng/mL) have been proposed to define
BCR after HIFU treatment [513].

A recent SR and comparative assessment by network meta-analysis [511] compared HIFU vs. RP
and EBRT as primary treatment for localised PCa. Data from 4,000 patients across 21 studies (including one
non-randomised comparative study and 20 case series) were included. There was some evidence that BCF
rates were significantly higher at one year with HIFU than with EBRT. However, the difference was no longer
statistically significant at five years. Similar statistically significant findings were observed with regard to DFS
at one year, with worse outcomes for HIFU than for EBRT. The differences were no longer significant at three
years. At four years, in contrast to OS, the biochemical result was higher when using HIFU.

In an earlier SR and meta-analysis [514], 150 papers related to HIFU were identified and evaluated with regard
to various oncological and functional outcome parameters [514]. No RCT was available for analysis, and no
survival data were presented. No validated biochemical surrogate end-point was available for HIFU therapy.
The review found HIFU to be associated with a PFS (based on PSA ± biopsy data) of 63-87% (projected three-
to five-year data), but median follow up in the studies ranged from 12-24 months only.

6.4.4 Focal therapy of PCa
During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater
public and professional awareness, leading to the adoption of both formal and informal screening strategies.
The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10%
of the prostate volume, with a greater propensity for unifocal or unilateral disease [515-517]. 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 [518-520].

Ramsay et al.’s [502] SR and network meta-analysis of ablative therapy in men with localised PCa performed
a sub-group analysis of focal therapy vs. RP and EBRT. Nine case series reporting on focal therapy were
identified (five studies reporting on focal CSAP, three studies on focal HIFU, and one study reporting on both).
For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at three years.
For focal HIFU vs. RP or EBRT, there were no comparable data on oncological, continence nor potency
outcomes at one year or more. More recently, Valerio et al. [521] performed a SR to summarise the evidence
regarding the effectiveness of focal therapy in localised PCa. Data from 3,230 patients across 37 studies were
included, covering different energy sources including HIFU, CSAP, photodynamic therapy, laser interstitial
thermotherapy, focal brachytherapy, irreversible electroporation and radiofrequency ablation. The overall
quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and
retrospective in design, heterogeneity of definitions, approaches, follow-up strategies, outcomes, and duration
of follow-up. Although the review suggests that focal therapy has a favourable toxicity profile in the short to
medium-term, its oncological effectiveness remains unproven due to lack of reliable comparative data against
standard interventions such as RP and EBRT. Robust prospective trials reporting standardised outcomes [522]
are needed before recommendations in support of focal therapy for routine clinical practice can be made.
6.4.5  **Summary of evidence and guidelines for experimental therapeutic options to treat clinically localised prostate cancer**

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The available short-term data regarding cryosurgery and high-intensity focused ultrasound (HIFU) does not prove equivalence to standard interventions.</td>
<td>2b</td>
</tr>
<tr>
<td>There is no reliable long-term comparative data to indicate that cryosurgery or HIFU leads to equivalent oncological outcomes compared with radical prostatectomy or external beam radiation therapy.</td>
<td>3</td>
</tr>
<tr>
<td>Prostate specific antigen nadir values after ablative therapies may have prognostic value.</td>
<td>3</td>
</tr>
<tr>
<td>Focal therapy of any sort appears promising but remains investigational, with uncertainties surrounding outcome definitions, follow-up and re-treatment criteria.</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Only offer focal therapy within a clinical trial setting.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

6.5  **Treatment: Hormonal therapy - rationale and available drugs**

6.5.1  **Introduction**

6.5.1.1  **Different types of hormonal therapy**

Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor. These two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB) [523].

6.5.2  **Testosterone-lowering therapy (castration)**

6.5.2.1  **Castration level**

Surgical castration is still considered the primary treatment modality for ADT. It leads to a considerable decline in testosterone levels: the ‘castration level’.

The castrate level is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago, when testosterone testing was limited. Current methods have shown that the mean value after surgical castration is 15 ng/dL [524]. Therefore, a more appropriate level is defined as < 20 ng/dL (1 nmol/L). This new definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [525-527]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still < 50 ng/dL (1.7 mmol/L).

6.5.2.2  **Bilateral orchietomy**

Bilateral orchietomy, or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [528] and it is the quickest way to achieve a castration level, which is usually reached within less than twelve hours. It is irreversible and does not allow for intermittent treatment.

6.5.3  **Oestrogens**

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [529]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses [530, 531] these drugs are not considered as standard first-line treatment.

6.5.4  **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. After the first injection, they induce 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. 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.

6.5.4.1  **Achievement of castration levels**

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 two to four weeks [532]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [533] and comparable to orchietomy [533, 534].

6.5.4.2 ‘Flare-up’ phenomenon
The ‘flare-up’ phenomenon might 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 [535].

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.

6.5.5 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 only monthly formulations being available.

Degarelix
Degarelix is an 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 [536]. An extended follow-up has been published, suggesting a better PFS compared to monthly leuprorelin [536]. Its definitive superiority over the LHRH analogues remains to be proven.

6.5.6 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 is the sole action of non-steroidal anti-androgens and 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.

6.5.6.1 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 cyproterone acetate [CPA]) and hepatotoxicity.

6.5.6.1.1 Cyproterone acetate
Cyproterone acetate was the first licensed anti-androgen, but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31–41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT [537] CPA showed a poorer OS when compared with LHRH analogues. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in disease-specific and OS at a median follow-up of 8.6 years [538]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.5.6.2 Non-steroidal anti-androgens
Non-steroidal anti-androgen monotherapy does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [539]. Non-androgen pharmacological side effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profile than flutamide and nilutamide [540]. All three agents share a common potential liver toxicity (occasionally fatal), requiring regular monitoring of patients’ liver enzymes.

6.5.6.2.1 Nilutamide
Nilutamide monotherapy has not been compared to castration and is not licensed for monotherapy. Non-androgen pharmacological side effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, and specifically severe interstitial pneumonitis (potentially life-threatening).

6.5.6.2.2 Flutamide
Flutamide has been studied as monotherapy. Flutamide is a pro-drug, and the half-life of the active metabolite is five-six hours, allowing for a three times daily dose. The recommended total daily dosage is 750 mg. The
non-androgen pharmacological side-effect of flutamide is diarrhoea.

6.5.6.2.3 Bicalutamide
The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [539, 541].

6.5.7 New compounds (for castrate-resistant patients only)
During castration, the occurrence of castration-resistance (CRPC) is systemic. It is considered to be mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see Section 6.10 - 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 [542]. This has led to the development of two new compounds targeting the androgen axis: abiraterone acetate and enzalutamide. Both are currently approved for mCRPC only.

6.5.7.1 Abiraterone acetate
Abiraterone acetate (AA) is a CYP17 inhibitor (a combination of 17\(\alpha\)-hydrolase and 17,20-lyase inhibition). By blocking CYP17, AA 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 (2 x 5 mg) to prevent drug-induced hyperaldosteronism.

6.5.7.2 Enzalutamide
Enzalutamide is a novel anti-androgen with a higher affinity than bicalutamide for the AR receptor. While non-steroidal anti-androgens still allow transfer of ARs to the nucleus, enzalutamide also blocks AR transfer and therefore suppresses any possible agonist-like activity.

6.5.8 Cost-effectiveness of hormonal therapy options
A formal meta-analysis evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa. For men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT, providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits at relatively high costs. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred [543]. Finally, once ADT is started and if a major response is obtained, intermittent androgen deprivation (IAD) may be an effective option to lower treatment costs.

6.6 Treatment: Metastatic prostate cancer
6.6.1 Introduction
A SR of ADT in PCa has recently been published [523].

6.6.2 Prognostic factors
Median survival of patients with newly diagnosed metastases is at least 42 months [544] but the M1 population is very heterogeneous. Several prognostic factors for survival have been suggested including the number and location of bone metastases, visceral metastases, Gleason score, PS status and initial PSA [545], alkaline phosphatase [546], but none of these have been validated in a direct comparison. In clinical trials, the number and location of bone metastases and the presence of visceral lesion are the prognostic factors most often used [547].

Based on a large SWOG 9346 cohort, the PSA level after seven months of ADT was used to create three prognostic groups, group 1 with a PSA < 0.2 ng/mL and a median survival of 75 months, group 2 with a PSA < 4 ng/mL with a median survival of 44 months and group 3 with a PSA > 4 ng/mL and only thirteen months median survival [548]. This grouping, however, requires independent confirmation.

6.6.3 First-line hormonal treatment
Primary ADT has been the standard of care for over 50 years [523]. There is no level 1 evidence for, or against, a specific type of ADT, whether orchiectomy, an LHRH analogue or antagonist, except in patients with impending spinal cord compression for whom either a bilateral orchiectomy, or an LHRH antagonist are the preferred options.
6.6.3.1 Prevention of ‘flare-up’
The initial testosterone flare associated with LHRH agonists can be prevented by co-administration of an anti-androgen [549]. Prevention of ‘flare-up’ is important in symptomatic patients or when a clinical flare might lead to severe complications. Anti-androgen therapy is usually continued for four 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 [550].

6.6.4 Combination therapies
6.6.4.1 Complete androgen blockade
The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [551]. However, results with other anti-androgens or castration modalities have differed and SRs have shown that CAB using a non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [552, 553] beyond five years of survival [554] but this minimal advantage in a small subset of patients must be balanced against the increased side effects associated with long-term use of NSAAs.

6.6.4.2 Non-steroidal anti-androgen monotherapy
Based on a Cochrane SR [555] comparing NSAA monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events. The evidence quality of the studies included in this review was rated as moderate.

6.6.4.3 Intermittent versus continuous androgen deprivation therapy
Three independent reviews [556-558] and two meta-analyses [559, 560], looked at the clinical efficacy of IAD therapy. All of these reviews included eight RCTs of which only three were conducted in patients with exclusively M1 disease. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 [561] is the largest trial conducted in M1b patients. Out of 3,040 selected patients, only 1,535 were randomised based on the inclusion criteria set. This highlights that, at best, only 50% of M1b patients might be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2. The pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, inferior survival with IAD cannot be completely ruled out based on this study.

Other trials did not show any survival difference with a HR for OS of 1.04 (0.91-1.19). These reviews and the meta-analyses came to the conclusion that there was no difference in OS or CSS between IAD and continuous androgen deprivation. A recent review of the available phase III trials highlighted the limitations of most trials and suggests a cautious interpretation of the non-inferiority results [562]. None of the trials addressing M1 patients only showed a survival benefit, but there was a trend favouring continuous treatment for OS and PFS. Most of these trials, however, were non-inferiority trials. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side effects, such as hot flushes. In some cohorts the negative impact on sexual function was less pronounced with IAD. Two prospective trials came to the same conclusions [563, 564].

Other possible long-term benefits of IAD include bone protection [565] and a protective effect against metabolic syndrome. This possible protective effect has been challenged recently [566] with an increased risk for thrombotic and ischaemic events, while no benefit was observed for the endocrine, psychiatric, sexual and neurological side effects based on a detailed analysis from the SWOG 9346 trial. Testosterone recovery was observed in most studies [567] leading to intermittent castration. This, as well as the lack of any survival benefit in M1 patients, suggests that this modality must only be considered as an option in a well-informed patient bothered by significant side effects and willing to avoid them.

The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies [557, 567]. Nevertheless, there is consensus amongst authors on some statements:
- Intermittent androgen deprivation is based on intermittent castration; therefore, only drugs leading to castration are suitable.
- Luteinising-hormone releasing hormone antagonist might be a valid alternative to an agonist.
- The induction cycle cannot be longer than nine months, otherwise testosterone recovery is unlikely.
- Androgen deprivation therapy should be stopped only if patients have fulfilled all of the following criteria:
- well-informed and compliant patient;
- no clinical progression;
- a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.

- Strict follow-up is mandatory, with clinical examination every three to six months. The more advanced the disease, the closer the follow-up should be. The same laboratory should be used to assess the PSA level.
- Treatment is resumed when the patient progresses clinically, or has a PSA rising above a pre-determined (empirically set) threshold: usually 10-20 ng/mL in metastatic patients.
- The same treatment is used for at least three to six months.
- Subsequent cycles of treatment are based on the same principles until the first sign of castration resistance becomes apparent.
- The group of patients who will benefit most from IAD still has to be defined but the most important factor seems to be the patient’s response to the first cycle of IAD, e.g. the PSA level response [557].

6.6.4.4 Immediate versus deferred androgen deprivation therapy
In symptomatic patients, immediate treatment is mandatory. However, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies. A Cochrane review examined four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [555]. All of these studies were conducted in the pre-PSA era and included patients with advanced PCa, who had received early vs. deferred ADT, either as primary therapy or as adjuvant therapy after RP [568]. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications.

6.6.5 Hormonal treatment combined with chemotherapy
Three large RCT were conducted [473, 547, 569]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every three weeks) (within three months of ADT initiation). The primary objective in all three studies was OS. The key findings are summarised in Table 6.6.1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
<th>Med FU (mo)</th>
<th>Median OS (mo)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravis, et al. [569]</td>
<td>M1</td>
<td>385</td>
<td>50</td>
<td>58.9</td>
<td>54.2</td>
<td>1.01 (0.75-1.36)</td>
</tr>
<tr>
<td>ASCO GU 2015 [570]</td>
<td>HV : 47%</td>
<td></td>
<td>82.9</td>
<td>60.9</td>
<td>46.5</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Sweeney, et al. [547]</td>
<td>M1 HV: 65%</td>
<td>790</td>
<td>28.9</td>
<td>57.6</td>
<td>44</td>
<td>0.61 (0.47-0.8)</td>
</tr>
<tr>
<td>STAMPEDE [473]</td>
<td>M1 [61%]/N+ [15%]/relapse</td>
<td>1,184 /593 (D)</td>
<td>81</td>
<td>71</td>
<td>0.78 (0.66-0.93)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76</td>
<td>NR</td>
<td>0.82 (0.69-0.97)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>M1 only</td>
<td>725 + 362 (D)</td>
<td>60</td>
<td>45</td>
<td>0.76 (0.62-0.92)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

D = docetaxel; FU = follow-up; HR = hazard ratio; HV = high volume: either visceral metastases or more than four bone metastases, with at least one outside the spine and pelvis; n = number of patients; ZA = zoledronic acid.

In the GETUG 15 trial [569], all patients had newly diagnosed M1 PCa, either primary or after a primary treatment. They were stratified based on previous treatment, and Glaxo risk factors [545]. In the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial, the same inclusion criteria applied and patients were stratified according to disease volume; high volume being defined as either presence of visceral metastases or four, or more, bone metastases, with at least one outside the spine and pelvis [547].

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 patients), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1, or N1 or having two criteria out of three: T3/4, PSA ≥ 40 ng/mL, Gleason 8-10. 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, a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [473].

In the three trials toxicity was mainly haematological with around 12-15% Grade 3-4 neutropenia, and 6-12% Grade 3-4 febrile neutropenia. Determination of granulocyte colony-stimulating factor receptor (GCSF) was shown to be helpful and its use should be based on available guidelines [571, 572].
Based on these data, upfront docetaxel combined with ADT should be considered as a new standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [571]. Docetaxel is used at the standard regimen of 75 mg/sqm combined with steroids premedication, but without prolonged corticotherapy.

### 6.6.6 Prostate targeted therapy in newly diagnosed metastatic disease

Data from the retrospective SEER data-base [573] and the Munich cancer registry [574] suggest an OS and CSS benefit when RP or brachytherapy are added to ADT in newly diagnosed M1 patients. A small prospective experimental cohort of well selected patients responding to six months ADT and with ≤ 3 bone spots confirmed the feasibility and after a median 34 months follow up suggested a better CSS [575]. However, these results must be considered as experimental and deserve prospective trials (already underway) before being adopted in daily practice.

### 6.6.7 Metastasis-directed therapy

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. A recent SR clearly highlighted that at this time this approach must, as yet, be considered as experimental [576].

### 6.6.8 Imaging as marker of response in metastatic prostate cancer

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods (CT or MRI) using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [577, 578].

Quantitative estimation of tracer uptake at BS can be obtained through automated methods such as the Bone Scan Index [579]. Nonetheless, BS 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 that actually represent a favourable response on longer observation. Flare is observed within eight-twelve weeks of treatment initiation and can lead to false-positive diagnosis of disease progression. As a result, the Prostate Cancer Clinical Trials Working Group (PCWG) suggested that all patients with at least two new lesions on the first follow-up BS require a confirmatory BS at least six weeks later while the treatment is continued [580]. This means that a management change for primary therapy resistance cannot occur until after at least fourteen weeks of treatment. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. The ability of choline PET/CT to assess response has been assessed in a few studies that showed changes in disease extent and specific uptake values. It is noteworthy that the flare phenomenon can also be observed with choline PET/CT. Magnetic resonance imaging can directly assess the bone marrow and could assess progression based on morphologic criteria or changes in apparent diffusion coefficient. However, a large-scale validation of these criteria has not been performed [577, 578].

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

### 6.6.9 Guidelines for the first-line treatment of metastatic prostate cancer

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with chemotherapy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Use castration combined with any local treatment (radiotherapy/surgery) in an investigational setting only.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>
Guidelines for hormonal treatment of metastatic prostate cancer

6.6.10 | Recommendations | LE | GR
--- | --- | ---
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis). | 1b | A
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications. | 1b | A
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy. | 1a | A
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side effects, provided the patient is closely monitored. | 2b | B

Anti-androgens
In M1 patients treated with a luteinising-hormone releasing hormone (LHRH) agonist, offer short-term administration of anti-androgens to reduce the risk of the ‘flare-up’ phenomenon. | 2a | A
Start anti-androgens used for ‘flare-up’ prevention on the same day as an LHRH analogue is started or for up to seven days before the first LHRH analogue injection if the patient has symptoms. Treat for four weeks. | 3 | A
Do not offer anti-androgen monotherapy. | 1a | A

Intermittent treatment
In asymptomatic M1 patients, offer intermittent treatment to highly motivated men, with a major prostate-specific antigen (PSA) response after the induction period. | 1b | B
• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment.
• Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment.
• Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL).
In M1 patients, offer combined treatment with LHRH agonists and a non-steroidal anti-androgen. | 1b | A
Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction. | 2 | B

6.7 Management of prostate cancer in older men
6.7.1 Evaluating health status in senior adults
6.7.1.1 Introduction
With a median age at diagnosis of 68 years, PCa is common in men aged > 70 years. However, in the USA, the increase in men aged > 65 years being diagnosed will result in an estimated 70% increase in annual diagnosis of PCa by 2030 [581]. A similar increase is expected in Europe [582].
The SEER database shows that 71% of PCa-related deaths occur in men aged ≥ 75 years [583], probably due to the higher incidence of advanced/metastatic disease [584-586].

Despite the high incidence and mortality rates in senior adults, they may be under-treated [587, 588]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease receive curative treatment compared to 88% aged 65-74 [589].

6.7.1.2 Evaluation of life expectancy, comorbidity and health status
In localised disease, > 10 years life expectancy is considered mandatory for any benefit from local treatment. However, comorbidity is more important than age in predicting overall mortality in localised PCa [322]. Besides comorbidities, dependence in daily activities, malnutrition and cognitive impairment are associated with worse survival.

6.7.1.2.1 Comorbidity
Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP [590]. This can be explained by the observations from a study in which patients did not receive active local treatment for their PCa [322]. At ten years, most men with a CCI score > 2 had died from competing causes, irrespective of age or tumour aggressiveness.

Currently, the Cumulative Illness Score Rating-Geriatrics (CISR-G; Table 6.7.1) [591] is the best tool for assessing mortality risk unrelated to PCa [592].
Table 6.7.1: Cumulative Illness Score Rating-Geriatrics (CISR-G)

<table>
<thead>
<tr>
<th>Cumulative Illness Rating Scale</th>
<th>Rating strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild (or past significant problem)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (moderate disability or morbidity, requires first-line therapy)</td>
</tr>
<tr>
<td>3</td>
<td>Severe (constant significant disability/uncontrollable chronic problems)</td>
</tr>
<tr>
<td>4</td>
<td>Extremely severe (immediate treatment required/end organ failure/severe impairment in function)</td>
</tr>
</tbody>
</table>

Score

Heart
Vascular
Respiratory
Eyes, ears, nose, throat and larynx
Upper GI
Lower GI
Hepatic
Renal
Genitourinary
Musculoskeletal/integument
Neurological
Endocrine/metabolic
Psychiatric illness

Total score

Patients are considered fit if they have no Grade 3 score
Frail: one or two Grade 3 scores
Disabled: > 2 Grade 3, or any Grade 4 scores
Too sick: multiple Grade 4 scores

6.7.1.2.2 Dependence in daily activities
The level of dependence in daily activities influences survival in senior adults [593-595]. The Activities of Daily Living (ADL) scale rates accomplishment of basic activities of daily living, while the Instrumental Activities of Daily Living (IADL) scale rates activities requiring higher cognition and judgement.

6.7.1.2.3 Malnutrition
Malnutrition is associated with increased mortality in senior patients [596]. Nutritional status can be estimated from body weight during the previous three months:
- Good nutritional status < 5% weight loss;
- Risk of malnutrition: 5-10% weight loss;
- Severe malnutrition: > 10% weight loss.

6.7.1.2.4 Cognitive impairment
Cognitive impairment is associated with increased mortality risk in senior adults [597]. In patients undergoing major elective surgery, there is an association between baseline cognitive impairment and long-term post-operative complications and mortality [598]. Intervention is unlikely to reverse cognitive impairment, except in depression [599]. The mini-COG is the best available tool to evaluate cognitive function in order to assess the patient’s ability to make an informed decision [600].
6.7.1.2.5 Baseline screening using the G8 screening tool
The International Society of Geriatric Oncology (SIOG) PCa Working Group (PCWG) recommends that treatment for senior adults should be based on a systematic evaluation of health status [599].

The G8 (Geriatric 8) health status screening tool is described in Table 6.7.2, the Karnofsky and ECOG Scores in Table 6.7.3 [601].
### Table 6.7.2: G8 screening tool (Adapted from [602])

<table>
<thead>
<tr>
<th>Items</th>
<th>Possible responses (score)</th>
</tr>
</thead>
</table>
| **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 |
| **E** Neuropsychological problems?          | 0 = severe dementia or depression  
1 = mild dementia  
2 = no psychological problems |
| **F** BMI? (weight in kg)/(height in m²)    | 0 = BMI < 19  
1 = BMI 19 to < 21  
2 = BMI 21 to < 23  
3 = BMI ≥ 23 |
| **H** Takes more than three prescription drugs per day? | 0 = yes  
1 = no |
| **P** 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 |
| **Age**                                    | 0: > 85  
1: 80-85  
2: < 80 |
| **Total score**                             | 0-17 |

A G8 score > 14 shows that patients should receive the same treatment as younger patients. Patients with score G8 ≤ 14 should undergo a full geriatric evaluation, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [602]. Patients with reversible impairment (frail patients) should be treated according to the EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines. Patients with irreversible impairment (disabled patients) should receive adapted treatment [599].
Table 6.7.3: Performance Scales - Karnofsky & ECOG Scores [601]

<table>
<thead>
<tr>
<th>Karnofsky Status</th>
<th>Karnofsky Grade</th>
<th>ECOG Grade</th>
<th>ECOG Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no complaints.</td>
<td>100</td>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>Able to carry on normal activities. Minor signs or symptoms of disease.</td>
<td>90</td>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.</td>
</tr>
<tr>
<td>Normal activity with effort.</td>
<td>80</td>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.</td>
</tr>
<tr>
<td>Care for self. Unable to carry on normal activity or to do active work.</td>
<td>70</td>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>Requires occasional assistance, but able to care for most of his needs.</td>
<td>60</td>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care.</td>
<td>50</td>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>Disabled. Requires special care and assistance.</td>
<td>40</td>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>Severely disabled. Hospitalisation indicated though death non-imminent.</td>
<td>30</td>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>Very sick. Hospitalisation necessary. Active supportive treatment necessary.</td>
<td>20</td>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>Moribund.</td>
<td>10</td>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>

6.7.1.2.6 Conclusions

Systematic assessment, using the G8 tool, is recommended by the SIOG PCWG [599]. Patients with G8 score < 14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [599].

Senior adults can be classified into one of four groups regarding health status based on G8 score > 14 (patient considered fit), or score < 14 (patient considered frail or disabled). The treatment policy is then:
- fit or healthy older men should receive standard treatment;
- frail patients may receive standard treatment after resolution of any geriatric problems;
- disabled patients (i.e. non-reversible problems) should receive adapted treatment;
- patients who are too sick with terminal illness should receive only palliative treatment [599].

After resolution of reversible impairments, a similar urological approach should be carried out in fit or frail patients [1, 2]. Older men with PCa should be managed according to their individual health status, which is directed by the presence of any associated comorbidity and not age.
### Guidelines for the evaluation of health status in elderly men

#### Recommendations for assessment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform systematic health status screening in senior adults with localised PCa.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Use the G8 screening tool for health status screening.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment options for senior adults according to their health status:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. offer standard treatment to fit or healthy older men;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. offer standard treatment to frail patients (reversible impairment) after resolution of geriatric problems;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. offer adapted treatment to disabled patients (irreversible impairment);</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. offer only symptomatic palliative treatment to patients who are too sick with terminal illness.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Specific aspects of PCa treatment in older men

#### Localised PCa

#### Deferred treatment (active surveillance, watchful waiting)

Deferred treatment is addressed in Section 6.1. Active treatment mostly benefits patients with intermediate- or high-risk disease and longest expected survival. A recent study assessed the effect of age, health status and patient preferences on outcomes of surgery vs. AS for low-risk PCa. As expected, older age and worse...
baseline health status were associated with a smaller benefit in PCSM and life expectancy with surgery, and increased incremental years with treatment side effects. Older men and men in poor health were likely to have better quality-adjusted life expectancy with AS [603].

6.7.2.1.2 Radical prostatectomy

Senior adults (aged ≥ 75 years) are more likely to present with very advanced disease and have a greater risk of death from PCa, despite higher death rates from competing causes [584]. In the most recent update of the SPCG-4 study, randomising patients with localised PCa to RP vs. WW, the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR, 0.45). However, RP was associated with a reduced risk of metastases and use of androgen deprivation therapy among older men (RR: 0.68 and 0.60, respectively) [333]. Risk of short-term complications after RP is related more to comorbidity severity than age. Conversely, risk of long-term incontinence is influenced more by increasing age [604, 605].

6.7.2.1.3 External beam radiotherapy

External beam radiotherapy and RP have similar cancer control and treatment-related comorbidity, regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [606].

Cardiac status should be assessed because ADT in patients with pre-existing heart conditions is associated with increased morbidity and mortality. Patients with moderate-to-severe comorbidities might not have a significant survival-benefit when combining ADT with EBRT [454].

6.7.2.1.4 Minimally invasive therapies

Minimally invasive energy-ablative therapies are being developed rapidly, but there is still a lack of evidence to support their use.

6.7.2.1.5 Androgen deprivation therapy

In patients with non-metastatic localised PCa not suitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation. In locally advanced T3-T4 disease, immediate ADT may benefit patients with PSA > 50 ng/mL and PSA-DT < 12 months [328, 607].

6.7.2.2 Advanced PCa

6.7.2.2.1 Hormone-naïve metastatic PCa

Androgen deprivation therapy is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG PCWG recommends evaluation of baseline bone mineral density and prevention of osteoporosis by calcium and vitamin D supplements [599].

Routine bisphosphonates or denosumab to prevent skeletal complications in ADT is not recommended, unless there is a risk of fracture [608].

6.7.2.2.2 Metastatic CRPC

In metastatic CRPC, docetaxel is standard in fit and frail older men [609], with comparable response and tolerance to younger patients [610]. Tolerability has not been specifically studied in disabled older men. In elderly and disabled patients, granulocyte colony-stimulating factor prophylaxis should be considered.

Cabazitaxel, abiraterone acetate, enzalutamide, and sipuleucel-T increase survival in chemotherapy-treated and chemotherapy-naïve senior adults [611-617].

Palliative treatment includes surgery, radiopharmaceuticals, EBRT, and medical treatment for pain and symptoms.

6.7.3 Guidelines for the treatment of senior adults (> 70 years of age)

<table>
<thead>
<tr>
<th>Recommendations for assessment</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform systematic health status screening in senior adults with localised PCa.</td>
<td>A</td>
</tr>
<tr>
<td>Use the G8 screening tool for health status screening.</td>
<td>A</td>
</tr>
<tr>
<td>Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.</td>
<td>A</td>
</tr>
<tr>
<td>Treatment options for senior adults according to their health status:</td>
<td>B</td>
</tr>
<tr>
<td>1. Offer standard treatment to fit or healthy older men;</td>
<td></td>
</tr>
<tr>
<td>2. Offer standard treatment to frail patients (reversible impairment) after resolution of geriatric problems;</td>
<td></td>
</tr>
<tr>
<td>3. Offer adapted treatment to disabled patients (irreversible impairment);</td>
<td></td>
</tr>
<tr>
<td>4. Offer only symptomatic palliative treatment to patients who are too sick with terminal illness.</td>
<td></td>
</tr>
</tbody>
</table>
Recommendations for treatment

Localised disease

Offer standard treatment to fit and frail senior adults (after status optimisation) with a life expectancy > 10 years.

Offer individualised treatment based on life expectancy, symptoms and risk factors to senior adults with a life expectancy < 10 years.

In disabled or ‘too-sick’ senior adults, offer immediate androgen deprivation therapy only for symptom palliation.

Offer minimally invasive energy-ablative therapies only to selected fit and frail senior adults with intermediate-risk disease.

Advanced disease (locally advanced/metastatic disease)

Evaluate bone mineral status and prevent osteoporosis-related fractures in senior adults.

Offer new chemotherapeutic and hormonal agents to fit and frail adults.

6.8 Summary of guidelines for the primary treatment of prostate cancer

Table 6.8.1: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

<table>
<thead>
<tr>
<th>Definition</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt; 10 ng/mL and GS &lt; 7 (ISUP grade 1) and cT1-2a</td>
<td>PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b</td>
<td>PSA &gt; 20 ng/mL or GS &gt; 7 (ISUP grade 4/5) or cT2c</td>
<td>any PSA any GS cT3-4 or cN+ any ISUP grade</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.

Guidelines overview - Primary treatment of PCa

Primary treatment of prostate cancer - general recommendations

Discuss several treatment modalities (active surveillance [AS], surgery and radiotherapy) with patients suitable for such treatments.

In patients who are surgical candidates for radical prostatectomy (RP), discuss all approaches (i.e. open, laparoscopic or robotic) as acceptable treatment options since none have clearly shown superiority in terms of functional or oncological results.

Offer external beam radiotherapy (EBRT) to all risk groups of non-metastatic PCa.

Offer intensity-modulated radiation therapy (IMRT) for definitive treatment of PCa by EBRT.

Moderate hypofractionation (HFX) with IMRT including image-guided radiation therapy (IGRT) to the prostate can only be offered to carefully selected patients with localised disease.

Moderate HFX should adhere to radiotherapy-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.

Recommendations

Low-risk PCa

Active surveillance

Offer active surveillance (AS) to patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, prostate-specific antigen (PSA) ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).

Base follow up on digital rectal examination (DRE), PSA and repeated biopsies.

Counsel patients about the possibility of needing further treatment in the future.

Radical prostatectomy

Offer both radical prostatectomy (RP) and radiotherapy (RT) in patients with low- and intermediate-risk PCa and a life expectancy > 10 years.

Do not perform a lymph node dissection (LND) in low-risk PCa.
| **Radiotherapy** | In low-risk PCa, use a total dose of 74 to 78 Gy for external beam radiotherapy (EBRT). In patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP) and with a good International Prostate Symptom Score (IPSS) and a prostate volume < 50 mL, offer low-dose-rate (LDR) brachytherapy. | A |
| **Cryotherapy, HIFU** | Only offer cryotherapy and high-intensity focused ultrasound (HIFU) within a clinical trial setting. The lack of long-term efficacy compared to standard modality must be discussed with patients. | A |
| **Focal treatment** | Do not offer focal therapy of PCa as a therapeutic alternative outside clinical trials. | A |
| **Androgen suppression** | Unsuitable. | A |
| **Watchful waiting** | Offer watchful waiting (WW) to patients not eligible for local curative treatment and with a short life expectancy. | A |

### Intermediate-risk PCa

| **Active surveillance** | Not an option. | A |
| **Radical prostatectomy** | Offer both RP and RT in patients with low- and intermediate-risk disease and a life expectancy > 10 years. Offer nerve-sparing surgery in patients with a low risk of extracapsular disease (refer to nomograms). Use multiparametric magnetic resonance imaging (mpMRI) as a decision tool to select patients for nerve-sparing procedures. Perform an extended LND (eLND) if the estimated risk for positive lymph nodes (LNs) exceeds 5%. Do not perform a limited LND. In patients with pT3,N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it at least improves biochemical-free survival. Inform patients with pT3,N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases. Do not offer adjuvant hormonal therapy (HT) after RP for pN0 disease. | A |
| **Radiotherapy** | In intermediate-risk PCa use a total dose of 76-78 Gy, in combination with short-term androgen deprivation therapy (ADT) (four to six months). In selected intermediate-risk patients, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, offer LDR brachytherapy. | A |
| **Androgen suppression monotherapy** | No place in asymptomatic patients. | A |
| **Watchful waiting** | Offer WW to patients not eligible for local curative treatment and with a short life expectancy. | A |

### High-risk PCa

<p>| <strong>Watchful waiting</strong> | <strong>High risk localised:</strong> Offer WW to patients not eligible for local curative treatment and with a short life expectancy. <strong>High risk locally advanced:</strong> In locally advanced M0 patients unwilling or unable to receive any form of local treatment, offer a deferred treatment policy to asymptomatic patients with a PSA-DT &gt; 12 months and a PSA &lt; 50 ng/mL and non-poorly differentiated tumour. | A |
| <strong>Active surveillance</strong> | Not appropriate. | A |
| <strong>Radical prostatectomy</strong> | Do not offer neoadjuvant hormonal therapy before RP. Offer RP in selected patients with locally advanced (cT3a) disease and a life expectancy &gt; 10 years only as part of multi-modal therapy. Offer nerve-sparing surgery in patients with a low risk of extracapsular disease (refer to nomograms). Perform an eLND in high-risk PCa. | A |</p>
<table>
<thead>
<tr>
<th><strong>High risk localised:</strong> Offer RP in patients with high-risk localised PCa and a life expectancy of &gt; 10 years only as part of multi-modal therapy.</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>In high-risk disease, use mpMRI as a decision-making tool to select patients for nerve-sparing procedures.</td>
<td>B</td>
</tr>
<tr>
<td><strong>High risk locally advanced:</strong> Offer RP in highly selected patients with (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.</td>
<td>C</td>
</tr>
<tr>
<td>In patients with pT3,N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it at least improves biochemical-free survival.</td>
<td>A</td>
</tr>
<tr>
<td>Inform patients with pT3,N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.</td>
<td>A</td>
</tr>
</tbody>
</table>

### Radiotherapy

Inform patients with an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (see Section 6.9.5.1).

In patients with high-risk localised PCa and locally advanced cN0 PCa, use EBRT to a dose of 76-78 Gy, or combined EBRT with brachytherapy boost (either high-dose rate [HDR] or LDR). Radiotherapy should be given in combination with long-term ADT (two to three years).

In patients with locally advanced cN0 PCa, offer RT in combination with long-term ADT (two to three years is recommended).

### Androgen suppression monotherapy

Reserved for those patients unwilling or unable to receive any form of local treatment and that are either symptomatic or asymptomatic with a PSA-DT < 12 months and a PSA > 50 ng/mL and a poorly differentiated tumour.

Do not offer ADT to patients with a PSA-DT > 12 months

### N1 patients

| **cN1** | In patients with cN+ PCa, offer pelvic external beam irradiation in combination with immediate long-term ADT. | B |
| **pN1 after extended lymph node dissection (eLND)** | Offer adjuvant ADT for node-positive (pN+). | B |
| | Offer adjuvant ADT with additional radiotherapy. | A |
| | Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension. | B |

### Metastatic PCa

| **Active surveillance** | Unsuitable. | A |
| **Radical prostatectomy** | Unsuitable outside clinical trial. | A |
| **Radiotherapy to the prostate** | Unsuitable outside clinical trial. | A |
| **Androgen suppression** | Offer surgical or medical castration (luteinising-hormone-releasing hormone [LHRH] agonist or antagonist) as androgen deprivation therapy. | A |
| | Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy. | A |
| | Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with chemotherapy. | A |
| | Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial. | A |
| | In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, urethral obstruction, extra-skeletal metastases). | A |
| | In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications. | A |
| | In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side effects, provided the patient is closely monitored. | B |
Do not routinely offer ADT to asymptomatic men with biochemical recurrence.  
In M1 patients treated with an LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the ‘flare-up’ phenomenon.  
Start anti-androgens used for ‘flare-up’ prevention on the same day as an LHRH analogue is started or for up to seven days before the first LHRH analogue injection if the patient has symptoms. Treat for four weeks.  
Do not offer anti-androgen monotherapy in M1 patients.  
Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.  
In asymptomatic M1 patients, offer intermittent treatment to highly motivated patients, with a major PSA response after the induction period.  
In M1 patients follow the schedules used in published clinical trials on timing of intermittent treatment.  
Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment.  
Resume treatment when the PSA level is > 10-20 ng/mL (or back to the original level, if < 20 ng/mL).  

Guidelines for the treatment of senior adults (> 70 years of age)

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<tr>
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</tr>
<tr>
<td>Use the G8 screening tool for health status screening.</td>
<td>A</td>
</tr>
<tr>
<td>Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.</td>
<td>A</td>
</tr>
</tbody>
</table>

**Treatment options for senior adults according to their health status:**

1. offer standard treatment to fit or healthy older men;  
2. offer standard treatment to frail patients (reversible impairment) after resolution of geriatric problems;  
3. offer adapted treatment to disabled patients (irreversible impairment);  
4. offer only symptomatic palliative treatment to patients who are too sick with terminal illness

<table>
<thead>
<tr>
<th>Recommendations for treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localised disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer standard treatment to fit and frail senior adults (after status optimisation) with a life expectancy &gt; 10 years.</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Offer individualised treatment based on life expectancy, symptoms and risk factors to senior adults with a life expectancy &lt; 10 years.</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>In disabled or ‘too–sick’ senior adults, offer immediate androgen deprivation therapy only for symptom palliation.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Offer minimally invasive energy-ablative therapies only to selected fit and frail senior adults with intermediate-risk disease.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td><strong>Advanced disease (locally advanced/metastatic disease)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluate bone mineral status and prevent osteoporosis-related fractures in senior adults.</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Offer new chemotherapeutic and hormonal agents to fit and frail adults.</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

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

#### 6.9.1 Background

Between 27% and 53% of all patients undergoing RP or RT develop PSA-recurrence (see Sections 6.2 and 6.3). 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 overtreating 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.
6.9.2 Definitions

6.9.2.1 Definition of biochemical recurrence

The PSA level that defines treatment failure depends on the primary treatment. After RP, recurrent cancer is defined by two consecutive PSA values of > 0.2 ng/mL and rising [618-620].

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%) is any PSA increase ≥ 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [621].

Importantly, patients with PSA-recurrence after RP or primary RT have different risks of subsequent symptomatic metastatic disease. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

6.9.3 Natural history of biochemical recurrence

Once a PSA relapse has been diagnosed, it is important to determine, as far as possible, whether the recurrence has developed at local or distant sites. The risk of subsequent metastases and PCSM may be predicted by the initial clinical and pathologic factors (e.g. T-category, PSA, Gleason score) and PSA kinetics (PSA-DT and interval to PSA failure).

6.9.3.1 Post-radical prostatectomy biochemical recurrence

Not all patients with BCR after RP will develop clinical recurrences. In two studies of 1,997 and 2,400 men treated by RP, only 23-34% of those with BCR develop a clinical recurrence and 6% died of PCa [378, 622].

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. A PSA-DT < 3 months, SVI (pT3b), specimen Gleason score 8-10, or time to PSA-recurrence < 3 years indicate a high risk of metastases and PCSM. Conversely, a PSA-recurrence > 3 years following surgery, specimen Gleason score < 7, pathologic organ-confined disease or limited extracapsular extension (pT3a), and PSA-DT > 12 months indicate a low risk of metastases and PCSM [623-626]. Patients in the low-risk subgroup typically respond very well to SRT with a high probability of PSA being undetectable [627]. However, it must be stressed that most patients within the low-risk subgroup have an excellent outcome even without any salvage treatment. Patients within the high-risk subgroup need early and aggressive salvage treatment [628]. Trock et al. demonstrated that SRT was associated with a significant three-fold increase in PCa-specific survival relative to those who received no salvage treatment. The increase in PCa-specific survival associated with SRT was limited to men with a PSA-DT of < 6 months and remained after adjustment for pathological stage and other established prognostic factors. Salvage RT initiated > 2 years after recurrence provided no significant increase in PCa-specific survival [628].

6.9.3.2 Post-radiotherapy biochemical recurrence

In patients experiencing PSA-recurrence after RT, PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 or clinical stage cT3b-T4 also indicate a high risk of metastases and PCSM. Conversely, PSADT > 15 months, biopsy Gleason score < 7, clinical stage < cT3a and time to BCR > 3 years indicate a low risk of metastases and PCSM [625, 629, 630].

Zumsteg et al. have designed a risk score to further subdivide patients who develop PSA recurrence following RT. Those with > 2 high-risk factors (PSA-DT < 3 months, time to BCR < 3 years, biopsy Gleason score 8-10 and clinical stage cT3b-T4) have an increased risk of developing metastases and PCSM as compared to those with 0 or 1 risk factor [630].

6.9.4 Assessment of metastases

6.9.4.1 Bone scan and abdominopelvic computed tomography

Biochemical recurrence after RP or RT precedes clinical metastases by seven to eight years on average, and consequentially the diagnostic yield of common imaging techniques is poor in asymptomatic patients [631]. In men with PSA-only relapse after RP, the probability of a positive BS is < 5%, when the PSA level is < 7 ng/mL [632, 633].

Only 11-14% of patients with BCR after RP have a positive CT and rarely in situations when salvage treatment might be considered [632]. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [634]. Therefore, bone scan and abdominopelvic CT should only be considered in patients with BCR after RP who have a high baseline PSA (> 10 ng/mL) or high PSA kinetics (PSA-DT < 6 months or PSA velocity > 0.5 ng/mL/month) or in patients with symptoms of bone disease [632, 634].
6.9.4.2 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 [635, 636]. Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on BS [637] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative BS [638]. The specificity of choline PET/CT is also higher than BS with less false-positive and indeterminate findings [257]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.4.1.)

Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [249, 639-641]. 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. In a meta-analysis, choline PET/CT detection rates were 65% (95% CI: 58%-71%) when the PSA-DT was < 6 months, and were 71% (95% CI: 66%-76%) and 77% (95% CI: 71%-82%) when the PSA velocity was > 1 and > 2 ng/mL/year, respectively [639].

Despite these limitations, choline PET/CT may change medical management in 18-48% of patients with BCR after primary treatment [642-644]. In a retrospective bi-centric study of 150 patients, 14 of the 55 (25.5%) patients scheduled for palliative treatment were switched to salvage therapy based on choline PET/CT results. Salvage therapy induced a complete biochemical response in 35.7% of these patients at the end of a median follow-up of 18.3 months (range, 10-48 months) [644] suggesting it continues to miss small volume metastasis. In patients not considered fit enough for curative salvage treatments choline PET/CT should be avoided.

After RP, the optimal PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL. Choline PET/CT detection rate was 26% in patients showing PSA < 1 ng/mL but raised up to 44% in the population with PSA values between 1 and 2 (moreover 37% of them were oligo-metastatic) [645]. It has been suggested that a PSA-DT < 6 months and a PSA velocity > 2 ng/mL/year might also select men in whom choline PET/CT could be recommended [646].

After RT, the PSA cut-off level is unclear due to the lack of sufficient data and because the PSA level is more difficult to interpret due to the "physiological" amount of measurable PSA produced by the non-tumoural prostate [640]. In a study of 46 patients with PSA relapse after RT or brachytherapy, the choline PET/CT detection rate was 54.5%, 81%, 89% and 100% when the PSA level was 1-2 ng/mL, 2-4 ng/mL, 4-6 ng/mL and > 6 ng/mL, respectively [647]. In another study of 140 patients the choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [648].

6.9.4.3 Other radionuclide techniques

18F-Fluoride PET and PET/CT have a higher sensitivity than BS in detecting bone metastases [649]. However, 18F-Fluoride PET and PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [650].

68Ga-PSMA PET/CT has shown promising potential in patients with BCR. Detection rates of 58% and 76% have been reported for PSA ranges of 0.2-1 and 1-2 ng/mL, respectively [256]. This suggests that 68Ga-PSMA is substantially more sensitive at low PSA levels than choline PET/CT. Two head-to-head comparisons confirmed this finding [651, 652]. However, studies incorporated varying proportions of initial therapy (RP or RT) and a majority of studies included patients on current ADT. Further prospective studies on homogeneous populations are needed to better define the role of 68Ga-PSMA PET/CT in patients with BCR. Therefore it cannot yet be considered as a standard evaluation tool. However, in case local salvage treatment is planned and 68Ga-PSMA PET/CT is available, it should be considered as a valuable assessment option.

6.9.4.4 Whole-body and axial magnetic resonance imaging

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT [653]. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

6.9.4.5 Assessment of local recurrences

6.9.4.5.1 Local recurrence after radical prostatectomy

The precise localisation of the local recurrence by imaging techniques is needed only if the localisation could change treatment planning. Transrectal US is neither sensitive nor specific in detecting local recurrences after RP. Even with TRUS guidance, the sensitivity of anastomotic biopsies remains low: 40-71% for PSA levels > 1 ng/mL and 14-45% for PSA levels < 1 ng/mL [631].

Choline PET/CT can detect local recurrences, but is less sensitive than MRI [654] and although 68Ga-PSMA PET/CT has improved sensitivity at low PSA levels, it is still unknown if it can reliably detect local
Several studies have reported promising results in the detection of local recurrences using MRI, particularly dynamic contrast-enhanced MRI which showed sensitivities and specificities of 76-90% and 82-100%, respectively [656-659]. However, the mean PSA level in these studies was 0.7-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Two studies evaluated mpMRI in patients with a PSA level < 0.5 ng/mL. One found a sensitivity of only 13% in men with PSA level < 0.3 ng/mL [660], while the other reported a sensitivity of 86% in patients with a PSA level < 0.4 ng/mL [661]. It remains to be seen whether MRI can correctly detect local recurrences in patients with a PSA level < 0.5 ng/mL in order to allow a stereotactic boost to the recurrence site during SRT. Therefore, SRT is usually decided on the basis of BCR, without histological proof of the local recurrence. The dose delivered to the prostatic bed also tends to be uniform as it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Thus, most patients undergo SRT without local imaging.

6.9.4.5.2 Local recurrence after radiation therapy
In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options, it is thus mandatory to obtain histological proof of the local recurrence before treating the patient [631] especially if a local salvage curative treatment is considered.

Transrectal US is not reliable in depicting local recurrences after RT. In contrast, mpMRI has yielded excellent results [631, 662-664] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with choline PET/CT [648], and a nomogram able to predict the probability of extra pelvic disease has been proposed [665]. It is also too soon to know if 68Ga-PSMA PET/CT could play a role in the detection of local recurrences after RT [256].

6.9.4.6 Guidelines for imaging in patients with biochemical recurrence

<table>
<thead>
<tr>
<th>Prostate-specific antigen (PSA) recurrence after radical prostatectomy</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt; 1 ng/mL: no imaging is recommended.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>PSA &gt; 1 ng/mL: positron emission tomography (PET)/computed tomography (CT) imaging is recommended using choline or prostate-specific membrane antigen (PMSA).</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Perform bone scan and/or abdominopelvic CT only in patients with PSA &gt; 10 ng/mL, or with adverse PSA kinetics (PSA-doubling time (DT) &lt; 6 months, PSA velocity &gt; 0.5 ng/mL/month).</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSA recurrence after radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform prostate multiparametric magnetic resonance imaging (mpMRI) only in patients who are considered candidates for local salvage therapy, use mpMRI to localise abnormal areas and guide biopsies.</td>
</tr>
<tr>
<td>Choline PET/CT imaging is recommended to rule out lymph nodes or distant metastases in patients fit enough for curative salvage treatment.</td>
</tr>
<tr>
<td>Perform bone scan and/or abdominopelvic CT only in patients with PSA &gt; 10 ng/mL, or with adverse PSA kinetics (PSA-DT &lt; 6 months, PSA velocity &gt; 0.5 ng/mL/month).</td>
</tr>
</tbody>
</table>

6.9.5 Treatment of PSA-only recurrences
The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial. After RP, the therapeutic options are:
- radiotherapy at least to the prostatic bed;
- (complete) androgen deprivation;
- intermittent androgen deprivation;
- observation.

After RT, the therapeutic options are:
- salvage RP;
- HIFU
- cryotherapy;
- brachytherapy;
- androgen deprivation;
- observation.
6.9.5.1 Radiotherapy (salvage radiotherapy - with or without androgen-deprivation therapy for PSA-only recurrence after radical prostatectomy)

Early SRT provides a possibility of cure for patients with an increasing or persistent PSA after RP. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [505, 666-668], providing patients with a ~80% chance of being progression-free five years later [506].

A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or SRT alone (n = 160) within two years of BCR, showed that salvage RT was associated with a three-fold increase in PCa-specific survival relative to those who received no salvage treatment (p < 0.001). Salvage RT has also been effective in patients with a short PSA-DT [628]. Despite the indication for salvage RT, a “wait and see” strategy is an option in patients with a long PSA-DT of > 12 months [622]. For an overview see Table 6.9.1.

### Table 6.9.1: Selected studies on post-prostatectomy salvage radiotherapy, sorted by pre-salvage radiotherapy PSA level*

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>HT (%)</th>
<th>pre-SRT PSA (ng/mL) median</th>
<th>Median dose (Gy)</th>
<th>bNED/PFS (yr)</th>
<th>5-yr results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegmann, et al. 2011 [669]</td>
<td>301</td>
<td>0</td>
<td>0.28</td>
<td>66.6/70.2</td>
<td>74% (2)</td>
<td>55% vs. 88%  @ 66.6 vs. 70.2 Gy</td>
</tr>
<tr>
<td>Wiegel, et al. 2009 [506]</td>
<td>162</td>
<td>0</td>
<td>0.33</td>
<td>66.6</td>
<td>54% (3.5)</td>
<td>60% vs. 33% @ PSA &lt; 0.5 vs. &gt; 0.5</td>
</tr>
<tr>
<td>Goenka, et al. 2011 [670]</td>
<td>285</td>
<td>31</td>
<td>0.4</td>
<td>&gt; 70 (72%)</td>
<td>37% (7)</td>
<td>39%</td>
</tr>
<tr>
<td>Cremers, et al. 2010 [671]</td>
<td>197</td>
<td>0</td>
<td>0.59</td>
<td>63 /2.25 frct. (88%)</td>
<td>59% (5)</td>
<td></td>
</tr>
<tr>
<td>Bernard, et al. 2010 [672]</td>
<td>364</td>
<td>0</td>
<td>0.6</td>
<td>64.8</td>
<td>50% (5)</td>
<td></td>
</tr>
<tr>
<td>Buskirk, et al. 2006 [673]</td>
<td>368</td>
<td>15</td>
<td>0.7</td>
<td>64.8</td>
<td>46% (5)</td>
<td>63% vs. 51% @ PSA &lt; 0.5 vs. 0.5 - 1.0</td>
</tr>
<tr>
<td>Pazona, et al. 2005 [674]</td>
<td>223</td>
<td>4.5</td>
<td>0.8</td>
<td>63</td>
<td>40/25% (5/10)</td>
<td>42% vs. 30% @ &lt; 1.3 vs. &gt; 1.3</td>
</tr>
<tr>
<td>Pisansky, et al. 2000 [675]</td>
<td>166</td>
<td>4</td>
<td>0.9</td>
<td>64</td>
<td>46% (5)</td>
<td>61% vs. 36% @ PSA ≤ 1 vs. &gt; 1</td>
</tr>
<tr>
<td>Soto, et al. 2012 [676]</td>
<td>441</td>
<td>24</td>
<td>&lt; 1 (58%)</td>
<td>68</td>
<td>63/55% (3) HT/no HT</td>
<td>44/40% HT/no HT</td>
</tr>
<tr>
<td>Stephenson, et al. 2007 [505]</td>
<td>1,540</td>
<td>14</td>
<td>1.1</td>
<td>64.8</td>
<td>32% (6)</td>
<td>37%</td>
</tr>
</tbody>
</table>

* Hormone suppression treatment (HT) can influence the outcome ‘biochemically no evidence of disease (bNED)’ or ‘progression-free survival’ (PFS). Therefore, data sets without HT are highlighted. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.

bNED/PFS = biochemically no evidence of disease/progression-free survival; HT = hormone suppression treatment; n = number of patients; SRT = salvage radiotherapy.

Addition of androgen deprivation to SRT improves outcomes. The Radiation Therapy Oncology Group RTOG 96-01 comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) for 24 months in the post-operative setting reported improved overall survival (82% vs 78% at ten years) [677]. The investigators concluded that 24 months of HT also, significantly reduces metastatic disease, reduces death from CaP (from 7.5% to 2.3%, NNT = 17), reduced overall death (from 22% to 18%) and reduced tumour progression. They found that toxicity was similar in both arms, and that gynaecomastia was extremely common in the bicalutamide group. The GETUG-AFU 16 study [678] confirmed improved bPFS and clinical progression at five years when combining six months of goserelin with SRT, but survival remained unchanged.

6.9.5.1.1 Dose and toxicity

The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the bed of the seminal vesicles dependent upon the pathological stage at RP) [666]. Similarly, a joint AUA/ASTRO Guideline Panel regarded 64-65 Gy as the minimum dose that should be delivered post-RP [679]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control...
at three to five years [672]. In a SR, the pre-salvage RT PSA level and SRT-dose were correlated with BCR, showing that the relapse-free survival decreased by 2.6% per 0.1 ng/mL PSA and improved by 2% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level [666, 680, 681]. However, with dose escalation (72 Gy) or up to a median of 76 Gy, the rate of severe side effects especially for the genitourinary system clearly increases, even with newer planning and treatment techniques [682, 683]. Of note, compared with 3D-CRT, IMRT was associated with a reduction in Grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02), while RT technique had no differential effect on the relatively high level of GU toxicity (five-year: 3D-CRT 15.8% vs. IMRT 16.8%) [682]. After a median salvage IMRT dose of 76 Gy, the five-year risk of Grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [683].

6.9.5.1.2 Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy

The largest retrospective case-matching study to evaluate ART vs. early SRT included pT3N0 R0/R1 patients only (HT was excluded), 390 out of 500 observation-plus-early-SRT patients (median pre-SRT PSA was 0.2 ng/mL) were propensity matched with 390 ART patients. Two and five years after surgery, biochemically no evidence of disease (bNED) rates were 91% and 78% for ART vs. 93% and 82% after salvage RT, respectively. Subgroup analyses did not yield significant differences for the two approaches. It was concluded that early SRT does not impair PCa control, but clearly helps to reduce over-treatment which is a major issue in ART [684]. Both approaches (ART and SRT) together with the efficacy of neoadjuvant HT are currently being compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d’Etudes des Tumeurs Uro-Génitales (GETUG 17).

Decision-making on whether to proceed with adjuvant RT for high-risk PCa - pT3-4 pN0 M0 with undetectable PSA after RP, or to postpone RT as an early salvage procedure in the case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before RP that adjuvant RT may be administered if the patient has negative prognostic risk factors.

6.9.5.2 Hormonal therapy

Currently there is only one underpowered still unpublished RCT comparing the effect of salvage ADT, although retrospective comparative studies are available. The EAU Guidelines Panel conducted a SR including studies published from 2000 onwards [685]. The key findings are summarised below:

Conflicting results on the clinical effectiveness of HT after previous curative therapy of the primary tumour were found. 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) [686]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [687]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic work-up and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. The following factors were found predictive for poor outcomes (CRPC, distant metastases [DM], CSS, OS): short PSA-DT, high Gleason score, high PSA, increased age and comorbidities. In some studies, such as the Boorjian, et al. study [622], high-risk patients, mainly defined by a high Gleason score and a short PSA-DT (most often < 6 months), seem to benefit most from (early) HT, especially in men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [628]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [688]. 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, not all patients with recurrence after primary curative therapy should receive standard HT. Only a minority of them will progress to metastases or PCa-caused death. The objective of HT should be to improve OS, postpone DM, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with comorbidities, the side effects of HT may even decrease life expectancy; in particular, cardiovascular risk factors need to be considered [689, 690]. Early HT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA-DT at relapse (< 6-12 months) or a high initial Gleason score (> 7), and a long life expectancy. In all other situations, the potential benefits of salvage HT should be judiciously considered and balanced against its potential harms.
6.9.5.3 **Observation**

Observation until the development of clinically evident metastatic disease may represent a viable option for patients with low-risk features (PSA-DT > 12 months, time to BCR > 3 years, GS ≤ 7 and stage ≤ T3a) or unfit patients with a life expectancy < 10 years and/or are unwilling to undergo salvage treatment. In unselected relapsing patients, the median actuarial time to the development of metastasis will be eight years and the median time from metastasis to death will be a further five years [378].

6.9.6 **Management of PSA failures after radiation therapy**

Therapeutic options in these patients are ADT or local procedures such as SRP, cryotherapy, interstitial brachytherapy and HIFU [691-700]. Strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of (very) low quality. The following is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

6.9.6.1 **Salvage radical prostatectomy**

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

6.9.6.1.1 Oncological outcomes

In a recent SR of the literature, Chade, *et al.* showed that SRP gave five- and ten-year BCR-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The ten-year CSS and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS [701].

In most contemporary series, organ-confined disease, negative surgical margins (SM), and the absence of seminal vesicle and/or LN metastases were favourable prognostic indicators associated with a better DFS of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [700].

**Table 6.9.2: Oncological results of selected salvage radical prostatectomy case series, including at least 30 patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Median FU (mo)</th>
<th>Pathologic organ-confined (%)</th>
<th>PSM (%)</th>
<th>Lymph-node involvement (%)</th>
<th>BCR-free probability (%)</th>
<th>CSS (%)</th>
<th>Time probability (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonardo, <em>et al.</em> 2009</td>
<td>32</td>
<td>35</td>
<td>53</td>
<td>34</td>
<td>0</td>
<td>75</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Heidenreich, <em>et al.</em> 2010</td>
<td>55</td>
<td>23 (2-56)</td>
<td>73</td>
<td>11</td>
<td>20</td>
<td>87</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Chade, <em>et al.</em> 2011</td>
<td>404</td>
<td>55</td>
<td>55</td>
<td>25</td>
<td>16</td>
<td>37</td>
<td>83</td>
<td>10</td>
</tr>
</tbody>
</table>

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

6.9.6.1.2 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%) [705]. In more recent series, these complications appear to be less common [698, 701].

Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [701].
Table 6.9.3: Perioperative morbidity in selected salvage radical prostatectomy case series, including at least 30 patients

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

* SRP performed before vs. after 1993. 

n = number of patients.

6.9.6.2 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL and biopsy Gleason score ≤ 7, no LN involvement or evidence of distant metastatic disease pre-SRP, and whose initial clinical staging was T1 or T2 [701]. A meta-regression analysis suggested that SRP may be associated with worse continence outcomes than non-surgical approaches [707].

6.9.7 Salvage cryoablation of the prostate

6.9.7.1 Oncological outcomes

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the five-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [708]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the five-year BCR-free survival (BCR-FS) estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [709].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The five-year BCR-FS was 61% following SRP, significantly better than the 21% detected after SCAP. The five-year OS was also significantly higher in the SRP group (95% vs. 85%) [710].

Table 6.9.4: Oncological results of selected salvage cryoablation of the prostate case series, including at least 50 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Median FU (mo)</th>
<th>BCR-free probability (%)</th>
<th>Time probability (yr)</th>
<th>Definition of failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters, et al. 1997</td>
<td>150</td>
<td>17</td>
<td>44</td>
<td>-</td>
<td>Nadir + 0.2</td>
</tr>
<tr>
<td>Bahn, et al. 2003</td>
<td>59</td>
<td>82</td>
<td>59</td>
<td>7</td>
<td>PSA &gt; 0.5</td>
</tr>
<tr>
<td>Ismail, et al. 2007</td>
<td>100</td>
<td>33</td>
<td>73 (low risk)</td>
<td>5</td>
<td>ASTRO</td>
</tr>
<tr>
<td>Pisters, et al. 2008</td>
<td>279</td>
<td>22</td>
<td>58</td>
<td>5</td>
<td>ASTRO and Phoenix</td>
</tr>
<tr>
<td>Williams, et al. 2011</td>
<td>187</td>
<td>7.46 yr</td>
<td>39</td>
<td>10</td>
<td>Nadir +2</td>
</tr>
<tr>
<td>Spiess, et al. 2010</td>
<td>450</td>
<td>40.8</td>
<td>34</td>
<td>-</td>
<td>PSA &gt; 0.5</td>
</tr>
</tbody>
</table>

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

6.9.7.2 Morbidity

According to Cespedes, et al. [714], the risks of urinary incontinence and ED at least twelve months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In a recent study by Pisters, et al., the urinary incontinence rate was 4.4%. The rectal fistulae rate was 1.2% and 3.2% of patients required a TURP for removal of sloughed tissue [709]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.9.5) [715].
Table 6.9.5: Perioperative morbidity, erectile function and urinary incontinence in selected salvage cryoablation of the prostate case series, including at least 50 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Incontinence (%)</th>
<th>Obstruction/Retention (%)</th>
<th>Rectourethral fistula (%)</th>
<th>ED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahn, et al. 2003 [711]</td>
<td>59</td>
<td>8</td>
<td>-</td>
<td>3.4</td>
<td>-</td>
</tr>
<tr>
<td>Ismail, et al. 2007 [708]</td>
<td>100</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Pisters, et al. 2008 [709]</td>
<td>279</td>
<td>4.4</td>
<td>3.2</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>Ahmad, et al. 2013 [717]</td>
<td>283</td>
<td>12</td>
<td>7</td>
<td>1.8</td>
<td>83</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction; n = number of patients.

6.9.7.3 Summary of salvage cryoablation of the prostate
In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, an initial organ-confined PCA cT1c to cT2, initial Gleason score < 7, a pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL.

6.9.8 Salvage brachytherapy for radiotherapy failure
Although there is no role for salvage EBRT following local recurrence after previous definitive RT, for carefully selected patients with primary localised PCs and histologically proven local recurrence, HDR- or LDR brachytherapy remain effective treatment options with an acceptable toxicity profile [718-720]. However, the published series are relatively small and consequently this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR-brachytherapy over a period of nine years [718]. With a median follow-up of 60 months the five-year biochemical control was 51% and only 2% Grade 3 GU toxicities were reported. Comparable with these data, 42 patients were treated in a phase-II trial at MSKCC in New York [721]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after five years was 69% (median follow-up 36 months). Grade 2 late side effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side effects have been reported [722].

Using LDR-brachytherapy with 100palladium (Pd), long-term outcome was reported in 37 patients with a median follow-up of 86 months [719]. The biochemical control rate after ten years was 54%. However, the crude rate of ≥ Grade 2 toxicity was 46% and ≥ Grade 3 toxicity was 11%. These side effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side effects seem to be lower with HDR-brachytherapy [723]. In conclusion, freedom from BCR after salvage HDR and LDR-brachytherapy is promising and the rate of severe side effects in experienced centres seem to be acceptable. Salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

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

Table 6.9.6: Oncological results of selected salvage high-intensity focused ultrasound case series, including at least 20 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Median FU (mo)</th>
<th>BCR-free probability (%)</th>
<th>Negative biopsy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelet, et al. 2000 [725]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gelet, et al. 2004 [726]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uchida, et al. 2011 [727]</td>
<td>22</td>
<td>24</td>
<td>59 (Phoenix) (24 mo.)</td>
<td>92 (only 12 biopsied)</td>
</tr>
<tr>
<td>Berge, et al. 2011 [728]</td>
<td>46</td>
<td>9</td>
<td>60.9 (9 mo)</td>
<td>-</td>
</tr>
</tbody>
</table>

FU = follow-up; mo = months; n = number of patients.
6.9.9.2 **Morbidity**
Again, most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

6.9.9.3 **Summary of salvage high-intensity focused ultrasound**
There is a lack of data which prohibits any recommendation regarding the indications for salvage HIFU.

6.9.10 **Observation**
Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. WW in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSA-DT of > 12 months after RT. The five-year metastasis-free survival rate was 88% with HT vs. 92% with WW (p = 0.74) [729].

6.9.11 **Salvage lymph node dissection**
Novel imaging modalities improve the early detection of nodal metastases [730]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [730-732]. The majority of treated patients showed biochemical recurrence but clinical recurrence-free and cancer specific ten-year survival over 70% has been reported [731, 733]. Neither the template nor the real value of nodal salvage dissection is available. It must however be remembered that the imaging modalities under-evaluate the real nodal involvement. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [576]. Addition of RT to the lymphatic template after salvage LND may improve the BCR rate [734]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival [735].

6.9.11.1 **Guidelines for salvage lymph node dissection**

**Recommendation**
Discuss salvage lymph node dissection (LND) with men experiencing nodal recurrence after local treatment but it should be considered experimental and biochemical recurrence after salvage LND occurs in the majority of cases.

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

<table>
<thead>
<tr>
<th>Local salvage treatment</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations for biochemical recurrence after radical prostatectomy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer patients with a prostate-specific antigen (PSA) rise from the undetectable range and favourable prognostic factors (≤ pT3a, time to biochemical recurrence &gt; 3 year, PSA-doubling time [DT] &gt; 12 months, Gleason score ≤ 7), active surveillance and possibly delayed salvage radiotherapy.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Treat patients with a PSA rise from the undetectable range with salvage radiotherapy (SRT). The total dose of SRT should be at least 66 Gy and should be given early (PSA &lt; 0.5 ng/mL).</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td><strong>Recommendations for biochemical recurrence after radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Due to the increased rate of side effects, perform SRP in experienced centres.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Offer/discuss high intensity focused ultrasound, cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and with histologically proven local recurrence. Inform patients about the experimental nature of these approaches.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td><strong>Recommendations for systemic salvage treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not routinely offer androgen-deprivation therapy (ADT) to asymptomatic men with biochemical recurrence.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Do not offer ADT to patients with a PSA-DT &gt; 12 months.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>If salvage ADT (post-primary radiotherapy) is started, offer intermittent therapy to responding patients.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>
6.10 Treatment: Castration-resistant PCa (CRPC)

Table 6.10.1: Definition of Castration-resistant PCa (CRPC)

| Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either; | a) Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or, | b) Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [736]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC. |

6.10.1 Non-metastatic castration-resistant PCa

Frequent post-treatment PSA surveillance has resulted in earlier detection of progression. Although approximately one-third of men with a rising PSA will develop bone metastases within two years [737], there are no available studies suggesting a benefit for immediate treatment.

In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free and OS [737, 738]. 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 [739] suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL and again after every doubling of the PSA based on PSA-testing every three months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level.

6.10.2 Metastatic castration-resistant PCa

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

6.10.2.1 Conventional androgen deprivation in castration-resistant PCa

Eventually men with PCa 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 [740, 741]. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients.

Table 6.10.2: Randomised phase III controlled trials - first-line treatment of metastatic castration-resistant PCa*

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Selection Criteria</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 99-16 2004 [742]</td>
<td>docetaxel/EMP, every 3 weeks, 60 mg/m², EMP 3 x 280 mg/day</td>
<td>mitoxantrone, every 3 weeks, 12 mg/m² prednisone 5 mg BID</td>
<td>OS: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) PFS: 6.3 vs. 3.2 mo. (p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>TAX 327 2008 [609, 743]</td>
<td>docetaxel, every 3 weeks, 75 mg/m² prednisone 5 mg BID Or docetaxel, weekly, 30 mg/m² prednisone 5 mg BID</td>
<td>mitoxantrone, every 3 weeks, 12 mg/m², Prednisone 5 mg BID</td>
<td>OS: 19.2 for 3 weekly vs.17.8 mo. for weekly and 16.3 in the control group. (p = 0.004, HR: 0.79 95% CI: 0.67-0.93)</td>
<td></td>
</tr>
</tbody>
</table>
6.10.3  First-line treatment of metastatic castration-resistant PCA

6.10.3.1  Abiraterone
Abiraterone was evaluated in a phase III trial (COU-AA-302) [744] which included 1,088 chemo-naïve mCRPC patients. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone. The main stratification factors were Eastern Cooperative Oncology Group (ECOG) PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and radiographic PFS (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) [746]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly Grade 1-2. Sub-set analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [750].

6.10.3.2  Enzalutamide
A randomised phase III trial (PREVAIL) [747] included a similar patient population and compared enzalutamide and placebo. Men with visceral metastases were accepted although the numbers were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naïve mCRPC population of 1,717 men and showed significant improvement in both co-primary endpoints, rPFS (HR: 0.186; CI: 0.15-0.23, p < 0.001), and OS (HR: 0.706; CI: 0.67-0.74, p = 0.0001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension and again it was equally well tolerated in men > 75 years [751] as well as in those with or without visceral metastases [752]. For the subgroup of visceral metastases, there seems to be limited benefit concerning OS [752]. Enzalutamide has also been compared with bicalutamide in a phase II study [753] revealing a significant improvement in PFS (15.7 months vs. 5.8 months, HR 0.44, p < 0.0001).

6.10.3.3  Docetaxel regimen
A significant improvement in median survival of 2-2.9 months occurred with docetaxel-based chemotherapy
compared to mitoxantrone + prednisone therapy [742, 743]. The standard first-line chemotherapy is docetaxel 75 mg/m² three-weekly doses combined with prednisone 5 mg BID, up to ten cycles. Prednisone can be omitted if there are contraindications or no major symptoms.

Several poor prognostic factors have been described before docetaxel treatment: PSA > 114 ng/mL, PSA-DT < 55 days, or the presence of visceral metastases [754]. A better risk group definition was subsequently presented, again based on the TAX 327 study cohort: the independent prognostic factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine. Patients were categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), showing three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [755].

Age by itself is not a contraindication to docetaxel [610] but attention must be paid to closer monitoring and comorbidities as discussed in Section 6.7.2.2.2.2 [756]. In men with mCRPC who are thought to be unable to tolerate the standard regime the data shows that docetaxel 50 mg/m² every two weeks seems well tolerated with less Grade 3-4 AEs and suggest a prolonged time to treatment failure [757].

### 6.10.3.4 Sipuleucel-T

In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [738]. 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, leading to a significant HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was equivalent 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. In Europe, sipuleucel-T is not available.

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Selection criteria</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABIRATERONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fizazi, et al.</td>
<td>abiraterone + prednisone HR</td>
<td>placebo + prednisone</td>
<td>Previous docetaxel. ECOG 0-2. PSA or radiographic progression.</td>
<td>OS: 15.8 vs. 11.2 mo (p &lt; 0.0001). FU: 20.2 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radiologic PFS: no change</td>
</tr>
<tr>
<td></td>
<td>[614]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Bono, et al.</td>
<td></td>
<td></td>
<td></td>
<td>OS: 14.8 vs. 10.9 mo. (p &lt; 0.001 HR: 0.65; 95% CI: 0.54-0.77). FU: 12.8 mo.</td>
</tr>
<tr>
<td>[611]</td>
<td></td>
<td></td>
<td></td>
<td>Radiologic PFS: 5.6 vs. 3.6 mo.</td>
</tr>
<tr>
<td><strong>RADIUM-223</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parker, et al.</td>
<td>radium-223</td>
<td>Placebo</td>
<td>Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.</td>
<td>OS: 14.9 vs. 11.3 mo. (p = 0.002, HR: 0.61; 95% CI: 0.46-0.81). All secondary endpoints show a benefit over best standard of care</td>
</tr>
<tr>
<td>[758]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CABAZITAXEL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahl, et al.</td>
<td>cabazitaxel + prednisone</td>
<td>mitoxantrone + prednisone</td>
<td>Previous docetaxel. ECOG 0-2.</td>
<td>OS: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI: 1.33-3.33). FU: 25.5 months</td>
</tr>
<tr>
<td>[617]</td>
<td></td>
<td></td>
<td></td>
<td>OS ≥ 2y 27% vs. 16% PFS: -</td>
</tr>
<tr>
<td>deBono, et al.</td>
<td></td>
<td></td>
<td></td>
<td>OS: 15.1 vs. 12.7 mo. (p &lt; 0.0001, HR: 0.70; 95% CI: 0.59-0.83). FU: 12.8 mo.</td>
</tr>
<tr>
<td>[613]</td>
<td></td>
<td></td>
<td></td>
<td>PFS: 2.8 vs. 1.4 mo. (p &lt; 0.0001, HR: 0.74; 95% CI: 0.64-0.86)</td>
</tr>
</tbody>
</table>
ENZALUTAMIDE

| Scher, et al. 2012 [612] | enzalutamide | Placebo | Previous docetaxel. ECOG 0-2. | OS: 18.4 vs. 13.6 mo. (p < 0.001 HR: 0.63; 95% CI: 0.53-0.75). FU: 14.4 mo. | Radiologic PFS: 8.3 vs. 2.9 mo. (HR: 0.40; 95% CI: 0.35-0.47 p < 0.0001) |

*Only studies reporting survival outcomes as primary endpoints have been included.
OS = overall survival; PFS = progression-free survival.

6.10.4 Second-line treatment for mCRPC
All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.10.3.

6.10.4.1 Cabazitaxel
Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [613]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) + prednisone (10 mg/day), respectively. Overall survival was the primary end-point, which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO Grade 3-4 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 [759]. In two post marketing randomised phase 3 trials, firstly, cabazitaxel was shown not to be superior to docetaxel in the first line setting and, secondly, it was seen that in the second line setting, 20 mg/m² cabazitaxel is not inferior to 25 mg/m² in terms of OS, but less toxic. Therefore, the lower dose should be preferred [760, 761]. In any case, cabazitaxel should be administered by physicians with expertise in handling neutropenia and sepsis, preferably with prophylactic granulocyte colony-stimulating factor at least in the high-risk patient population [762].

6.10.4.2 Abiraterone acetate after prior docetaxel
Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [611] and the final results have been reported more recently [614]. A total of 1,195 patients with mCRPC were randomised 2:1 to abiraterone acetate + prednisone or placebo + prednisone. All patients had progressive disease based on the PCWG2 criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, p < 0.0001). The benefit was observed in all subgroups and all the secondary objectives were in favour of abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common Grade 3-4 AEs did not differ significantly between the arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly Grade 1-2 (fluid retention, oedema and hypokalaemia).

6.10.4.3 Enzalutamide after docetaxel
The planned preliminary analysis of the AFFIRM study was published in 2012 [612]. 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 30% of the population. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, p < 0.001). This led to the recommendation that the study be halted and unblinded. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. 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.

6.10.4.4 Radium-223
The only bone-specific drug that is associated with a survival benefit is radium-223, an α-emitter. In a large
phase III trial (ALSYMPCA), 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo, plus standard of care. The primary end-point was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70; p < 0.001) [758]. It was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, this did not differ significantly from that in the placebo arm [758]. Radium-223 was effective and safe no matter if the patients were docetaxel pre-treated, or not [763].

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

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open. Either further HT (enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) are reasonable options albeit with low levels of evidence. PARP inhibitors have shown high rates of response in men with somatic homologous recombination deficiency (HRD) in initial studies. Men previously treated with both docetaxel and at least one novel hormonal agent and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate [764]. Patients without HRD did not clearly benefit from olaparib. Although not yet available they offer an exciting opportunity to tailor therapy based on the mutation profile contained within a tumour.

In general however, and in unselected patients, subsequent treatments can be expected to have a smaller response [765, 766] with evidence of cross-resistance between enzalutamide and abiraterone [767].

6.10.6 **Monitoring of treatment**

Baseline examinations should include history and clinical examination as well as baseline bloods (PSA, FBC, renal function, LFTs, ALP), bone scan and CT of chest abdomen and pelvis [768]. Prostate-specific antigen alone is not reliable enough [769] for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA [770]. Instead PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [742]. A majority of experts at a recent consensus meeting suggested regular review and repeat 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 [768]. This reflects that the agents with a proven OS survival benefit all have potential toxicity and considerable cost and patients with no objective benefit should have treatment modified. This panel stressed that such treatments should not be stopped for PSA progression alone. Instead at least two of 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 [771]. These recommendations also seem valid for clinical practice outside trials.

6.10.7 **When to change treatments**

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. As the number of effective treatments increases and without head to head trials or data assessing the effectiveness of different sequencing options, it is not clear how to choose the appropriate “second-line” treatment. In the absence of other data, the inclusion criteria from licensing trials have been used to prioritise treatment sequencing.

The Eastern Cooperative Oncology group PS have been used to stratify patients. Generally men with a PS of 0-1 are likely to tolerate treatments and those with PS of 2 or more are less likely to benefit. However, it is important that treatment decisions are individualised. This applies particularly where symptoms related to disease progression are determining PS. In such cases it may be appropriate to trial novel treatments to establish if treatment would improve PS. A summary of the issues regarding sequencing are discussed in a paper published following the St. Gallen Consensus Conference [768].

6.10.8 **Symptomatic management in metastatic castration-resistant PCa**

Castration-resistant PCa is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is often required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [772]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur.

6.10.8.1 **Common complications due to bone metastases**

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [773],...
even as a single fraction [774]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [775]. 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 [776]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [777, 778]. 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 consultation should be planned to discuss a possible decompression, followed by EBRT [779]. Otherwise, EBRT, with or without systemic therapy, is the treatment of choice.

6.10.9 Preventing skeletal-related events

6.10.9.1 Bisphosphonates
Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anticancer treatments but docetaxel were available. 643 patients who had CRPC [780] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for fifteen consecutive months, or placebo. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at fifteen and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (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.

6.10.9.2 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) [779]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA nor the EMA have approved denosumab for this indication [781].

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with metastatic CRPC 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 (NTX) and bone-specific alkaline phosphatase (BAP) were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p < 0.0001 for both). However, these findings were not associated with any survival benefit and in a recent post-hoc re-evaluation of endpoints, denosumab showed identical results when comparing skeletal-related events and symptomatic skeletal events [782].

The potential toxicity (e.g., osteonecrosis of the jaw) of these drugs, must always be kept in mind [773, 779]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection [783].

6.10.10 Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant PCa

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No definitive strategy regarding first treatment choice (which drug/drug family first) can be devised.</td>
<td>4</td>
</tr>
<tr>
<td>No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy, chemotherapy or radium-223) as no clear predictive factors exist.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure that testosterone levels are confirmed to be &lt; 50 ng/mL, before diagnosing castration-resistant PCa (CRPC).</td>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>Do not treat patients for non-metastatic CRPC outside of a clinical trial.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Counsel, manage and treat patients with metastatic (m)CRPC in a multidisciplinary team.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Treat patients with mCRPC with life prolonging agents. Base the choice of first line treatment on the performance status, symptoms, comorbidities, location and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>
6.10.11  **Guidelines for cytotoxic treatment in castrate-resistant PCa**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counsel, manage and treat patients with metastatic castration-resistant PCa (mCRPC) in a multidisciplinary team.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m² every three weeks.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include cabazitaxel, abiraterone, enzalutamide and radium-223.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Base second-line treatment decisions of mCRPC on pre-treatment performance status, comorbidities and extent of disease.</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

6.10.12  **Guidelines for supportive care of castrate-resistant PCa**

These recommendations are in addition to appropriate systemic therapy.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

7. FOLLOW-UP

7.1  **Follow-up: After local treatment**

7.1.1  **Definition**

Local treatment is defined as RP or RT, either by EBRT or low- or high-dose brachytherapy, or any combination of these. Unestablished alternative treatments, such as HIFU and cryosurgery do not have a well-defined, validated PSA cut-off to define BCF, but do follow the general principles as presented in this section.

7.1.2  **Why follow-up?**

Recurrence occurs after primary therapy in many patients who have previously received treatment with intent to cure. Reasons for follow-up vary depending on treatment, patient age, comorbidity and the patient’s own wishes. Patients who receive curative therapy are followed up to:

* assess immediate- and long-term oncological results, side effects or complications of therapy, functional outcomes and to provide psychological support to PCa survivors;
* discuss the possibility of second-line treatment with curative intent; early HT or WW with the patient.

7.1.3  **How to follow-up?**

The procedures indicated at follow-up visits vary according to clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. Prostate specific antigen level and DRE are the only tests that should be performed routinely. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications must be individualised, which is beyond the scope of these Guidelines. The examinations used most often for cancer-related follow-up after curative surgery or RT are discussed below.

7.1.3.1  **Prostate-specific antigen monitoring**

Measurement of PSA is a cornerstone in follow-up after local treatment. Expectations differ after RP and RT, but PSA recurrence often precedes clinical recurrence [784, 785]. A single, elevated, serum PSA level should
be confirmed before starting second-line therapy based solely on PSA elevation.

### 7.1.3.2 Definition of prostate-specific antigen progression

The PSA level for definition of treatment failure differs between RP and RT. International consensus defines recurrent cancer after RP by two consecutive PSA rises ≥ 0.2 ng/mL [786]. However, others have argued for a higher cut-off of 0.4 ng/mL for patients at high risk of clinical progression [785].

Ultrasensitive PSA assay remains controversial for routine follow-up after RP. Men with a ultrasensitive PSA nadir < 0.01 ng/mL have a 4% likelihood of early biochemical relapse [787]. Detectable post-operative ultrasensitive PSA does not predict BCR in all cases, although it adds prognostic value. In men with ultrasensitive PSA > 0.05 ng/mL, 66.8% remained free of biochemical disease at five years [788]. If survival is improved by early adjuvant treatment after RP (before PSA reaches > 0.2 ng/mL), higher PSA nadir levels may help identify suitable candidates.

At the 2006 RTOG-ASTRO Consensus conference, a new definition of radiation failure was proposed to establish better correlation between definition and clinical outcome, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [621]. It applies to patients with or without HT.

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 BCF after these alternative local treatments.

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

Prostate-specific antigen is expected to be undetectable within six weeks after successful RP [789]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease.

A rapidly increasing PSA level suggests distant metastases, whereas a later, slowly increasing, level most likely suggests local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [790]. Local treatment failure and distant metastases occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [791].

Thus, in patients with favourable pathology (< pT3, pN0, Gleason score < 8), PSA measurement and disease-specific history could be a single test in follow-up after RP.

### 7.1.3.4 PSA monitoring after radiotherapy

Prostate-specific antigen level falls slowly after RT compared with RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT [792], although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. After RT, PSA-DT is correlated with site of recurrence; patients with local recurrence have a doubling time of thirteen months compared to three months for those with distant failure [793].

### 7.1.3.5 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [791]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Prostate-specific antigen measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT or RP, but PSA measurement may be the only test in cases with favourable pathology (< pT3, pN0, Gleason < 8) after RP [794].

### 7.1.3.6 Transrectal ultrasound, bone scintigraphy, computed tomography, magnetic resonance imaging, and \(^{11}\)C-choline positron emission tomography computed tomography

Imaging techniques have no place in routine follow-up of localised PCa. They are only justified in patients with BCF or in patients with symptoms for whom the findings affect treatment decisions. (See Section 6.9.4.5 for a more detailed discussion).

### 7.1.3.6.1 Transrectal ultrasonography/magnetic resonance imaging guided biopsy.

Biopsy of the prostate bed and urethrovesical anastomosis or of the remaining prostate after radiotherapy, are only indicated if local recurrence affects treatment decisions.

### 7.1.4 When to follow-up?

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. Patients should be followed up more closely during the initial post-treatment period when risk of failure is highest. Prostate-specific antigen measurement, disease-specific history and DRE are recommended at three, six and twelve months post-operatively, every six months thereafter until three years, and then annually.

The first post-treatment clinic visit mainly focusses on detecting treatment-related complications.
and assist patients in coping with their new situation. Tumour or patient characteristics may allow alterations to this schedule. Patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimen-confined tumour. Advanced age or associated comorbidity may make further follow-up in asymptomatic patients superfluous.

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

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>After radical prostatectomy serum prostate-specific antigen (PSA) level &gt; 0.2 ng/mL is associated with residual or recurrent disease.</td>
<td>2a</td>
</tr>
<tr>
<td>After radiotherapy, an increase in PSA &gt; 2 ng/mL above the nadir, rather than a specific threshold value, is the most reliable sign of recurrence.</td>
<td>2a</td>
</tr>
<tr>
<td>Palpable nodules and increasing serum PSA are signs of local recurrence.</td>
<td>2a</td>
</tr>
</tbody>
</table>

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum prostate-specific antigen (PSA) measurement supplemented by digital rectal examination (DRE). These should be performed at three, six and twelve months after treatment, then every six months until three years, and then annually.</td>
<td>B</td>
</tr>
<tr>
<td>Imaging to detect local recurrence is only recommended if it affects treatment planning. Biopsy is usually not necessary before second-line therapy.</td>
<td>B</td>
</tr>
<tr>
<td>Do not routinely offer bone scans and other imaging modalities to asymptomatic patients if there are no signs of biochemical relapse. In case patients have bone pain or other symptoms of progression, re-staging should be considered irrespective of serum PSA level.</td>
<td>B</td>
</tr>
</tbody>
</table>

### 7.2 Follow-up: During hormonal treatment

#### 7.2.1 Introduction
Follow up must be individualised as BCF might be associated with rapid symptomatic progression or evolve without progression on imaging or symptoms over years.

#### 7.2.2 Purpose of follow-up
The main objectives of follow-up in these patients are to ensure treatment compliance, to monitor treatment response and side effects, and to guide the treatment at the time of CRPC. Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up during HT.

#### 7.2.3 Methods of follow-up

##### 7.2.3.1 Clinical follow-up
Clinical follow-up is mandatory on a regular basis, and cannot be replaced, neither by laboratory test biology nor imaging modalities. Of utmost importance in metastatic situations is to advise patients about early signs of spinal cord compression, check for occult cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk.

##### 7.2.3.1.1 Prostate-specific antigen monitoring
Prostate-specific antigen is a key marker for following the course of androgen sensitive PCa. Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa in locally advanced and metastatic PCa [795], as in salvage ADT for relapse following treatments with curative intent [796].

For intermittent ADT Section 6.6.4.3 may be consulted.

A rise in PSA level usually precedes the onset of clinical symptoms by several months. Importantly, taking into account the PSA level alone is insufficient to define progression as clinical progression (usually bone pain) with a stable PSA has been reported.

##### 7.2.3.1.2 Creatinine, haemoglobin and liver function monitoring
Creatinine monitoring is good clinical practice as an increase may be linked to bilateral ureteral obstruction or bladder retention. Liver function tests may suggest treatment toxicity (especially NSAA), or rarely disease
progression. A decline in haemoglobin after three months of ADT is independently associated with a shorter progression-free and OS rate [797] and might explain significant fatigue. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [798]. Therefore, it may be helpful to determine bone-specific isoenzymes as none are directly influenced by HT.

7.2.3.1.3 Bone scan, ultrasound and chest X-ray
Asymptomatic patients with a stable PSA level should not undergo imaging at regular intervals [799]. New symptomatic bone lesions require a bone scan, as well as a PSA progression suggesting CRPC status, if a treatment modification is considered. The Prostate Cancer Clinical Trials Working Group has clarified the definition of bone scan progression as the appearance of at least two new lesions [742], later confirmed.

Suspicion of disease progression indicates the need for additional imaging modalities, guided by symptoms or possible subsequent treatments. In CRPC, imaging must be individualised with the aim of maintaining the patient’s QoL.

7.2.3.1.4 Testosterone monitoring
This should be considered part of clinical practice for men on LHRH therapy. Most patients receiving LHRH analogues will achieve castrate serum testosterone levels (< 50 ng/mL). However, approximately 13-38% of patients fail to achieve this goal and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [525], known as the ‘acute on-chronic effect’ or ‘breakthrough response’.

The timing of measurements is not clearly defined. A three to six-month testosterone level assessment is suggested to ensure castration is achieved and maintained. If not, switching to another agonist or antagonist, or to an orchiectomy should be considered. In patients with rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

7.2.3.1.5 Monitoring of metabolic complications
Androgen deprivation therapy has a greater range of complications than might be expected. The most severe are metabolic syndrome, cardiovascular morbidity and bone problems, (see Section 8.2.4.5). The patient’s general practitioner should probably be more involved at this stage.

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and regularly), as for blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. A cardiology consultation should be considered in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. Monitoring serum levels of vitamin D and calcium is important (see Section 6.7.2.2.1). It is suggested that routine bone monitoring should be performed every two years during castration [800], or yearly if there are other risk factors [801, 802]. However, there is no high level evidence that this recommendation improves bone complications due to ADT, and prospective trials are needed.

Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc.) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [797, 798]. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

7.2.4 When to follow-up
After the initiation of ADT, it is recommended that patients are followed at three to six months intervals. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

7.2.4.1 Stage M0 - M1 patients
If there is a good treatment response, i.e. PSA response (< 4 ng/mL), symptomatic improvement, good psychological coping, good treatment compliance, follow-up visits are scheduled every three to six months.

7.2.4.2 Castration-refractory PCa
Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualised follow-up scheme.
Guidelines for follow-up during hormonal treatment

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate patients at three to six months after the initiation of treatment.</td>
<td>A</td>
</tr>
<tr>
<td>As a minimum, tests should include serum prostate-specific antigen (PSA) measurement, digital rectal examination (DRE), serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and side effects.</td>
<td>A</td>
</tr>
<tr>
<td>In patients undergoing intermittent androgen deprivation, monitor PSA and testosterone at fixed intervals during the treatment pause (monthly or at three-month intervals).</td>
<td>A</td>
</tr>
<tr>
<td>Adapt follow-up to the individual patient, according to stage of disease, prior symptoms, prognostic factors and the treatment given.</td>
<td>A</td>
</tr>
<tr>
<td>In patients with stage M0 disease with a good treatment response, schedule follow-up every six months. As a minimum requirement, include a disease-specific history, DRE and serum PSA determination in the diagnostic work-up.</td>
<td>A</td>
</tr>
<tr>
<td>In patients with stage M1 disease with a good treatment response, schedule follow-up every three to six months. As a minimum requirement, include a disease-specific history, DRE, serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year.</td>
<td>A</td>
</tr>
<tr>
<td>Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.</td>
<td>A</td>
</tr>
<tr>
<td>When disease progression occurs, or if the patient does not respond to treatment, adapt/individualise follow up.</td>
<td>A</td>
</tr>
<tr>
<td>In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa (CRPC) requires a testosterone level &lt; 50 ng/mL (&lt; 1 mL/L).</td>
<td>B</td>
</tr>
<tr>
<td>Do not offer routine imaging to otherwise stable patients.</td>
<td>B</td>
</tr>
</tbody>
</table>

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first will summarise consequences of therapies for PCa. Based on two SRs, the second will evaluate the evidence for adverse effects of treatments over the longer-term (twelve months +) and also make evidence-based recommendations for 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 prostate cancer can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of ‘quality of life’ [803]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team ranging from urologist, medical oncologist, radiation oncologist, oncology nurse to psychologists and many others. Attention to the psychosocial concerns of men with prostate cancer is integral to quality clinical care, and this includes the needs of carers and partners [762]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient’s QoL. Taking QoL into consideration relies on understanding the patient’s wishes and preferences so that optimal treatment proposals can be formulated and discussed.

8.2 Adverse effects of prostate cancer therapies

8.2.1 Surgery

Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as RALP. Recent SRs have documented complication rates after RALP [388, 390-393], and can be compared with contemporaneous reports after RRP [398]. From these reports, the mean continence rates at twelve months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP. There is, as yet, no evidence from retrospective studies of differences in urinary incontinence at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or ED outcomes. The major limitations of the included studies
were the retrospective study design and the use of different assessment tools preventing comparison between techniques and series. Recently, a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen centres using RALP or RRP was published. At twelve months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [394]. A recent RCT comparing RALP and RRP, has reported outcomes at twelve weeks in 326 patients [334]. Functional outcomes were similar in the two groups, but longer follow up is needed to report on longer term effects. The intra-and peri-operative complications of retropubic RP and RALP are listed in Table 8.2.1.

### Table 8.2.1: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [388])

<table>
<thead>
<tr>
<th>Predicted probability of event</th>
<th>RALP (%)</th>
<th>Laparoscopic RP (%)</th>
<th>RRP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder neck contracture</td>
<td>1.0</td>
<td>2.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>1.0</td>
<td>4.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Infection</td>
<td>0.8</td>
<td>1.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Organ injury</td>
<td>0.4</td>
<td>2.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Ileus</td>
<td>1.1</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0.6</td>
<td>0.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predicted rates of event</th>
<th>RALP (%)</th>
<th>Laparoscopic RP (%)</th>
<th>RRP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavien I</td>
<td>2.1</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Clavien II</td>
<td>3.9</td>
<td>7.2</td>
<td>17.5</td>
</tr>
<tr>
<td>Clavien IIIa</td>
<td>0.5</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Clavien IIIb</td>
<td>0.9</td>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Clavien IVa</td>
<td>0.6</td>
<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Clavien V</td>
<td>&lt; 0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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

**8.2.1.1 Early complications of extended lymph node dissection**

Pelvic eLND increases morbidity in the treatment of PCa. 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 [804]. 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%) [805, 806]. Briganti et al. [807] also showed more complications after extended compared to limited LND. 20% of men suffer a complication of some sort after eLND. Thromboembolic events occur in less than 1% of cases.

**8.2.2 Radiotherapy**

**8.2.2.1 Side effects of external beam radiotherapy**

Retrospective studies suggest that RT affects erectile function to a lesser degree than surgery of patients [808], and this has been borne out by the recent ProtecT study results (see below). A meta-analysis has shown that the one-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after EBRT + EBRT, 0.55 after EBRT, 0.34 after nerve-sparing RP, and 0.25 after standard RP. When studies with more than two years of follow-up were selected (i.e. excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches [809]. Studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT [810, 811]. In a retrospective evaluation of 30,552 and 55,263 men, who had undergone either EBRT or RP, the risk of being diagnosed with rectal cancer increased by 1.7-fold in comparison with the surgery group [810]. Another analysis [811] showed that the relative risk of developing bladder cancer increased by 2.34-fold in comparison with a healthy control population. On the other hand, a re-analysis of SEER data including more than 100,000 patients, demonstrated a risk of about 0.16% (i.e. 160 cases per 100,000 patients) of radiation-induced malignant tumours [812]. The Memorial Sloan-Kettering Cancer Center group have also reported corresponding data on late toxicity from their experience in 1,571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of ten years [813]. Both acute gastrointestinal and GU toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) Grade 2 or more
gastrointestinal toxicity was 5% with IMRT vs. 13% with 3D-CRT. The incidence of Grade 2 or higher late GU toxicity was 20% in patients treated with 81 Gy vs. 12% in patients treated with lower doses. The overall incidences of Grade 3 toxicity were 1% for gastrointestinal toxicity and 3% for GU toxicity. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity. Interestingly, with dose escalation, GU toxicity may become the predominant type of morbidity [813].

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%) [814]. A small RCT has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity [815]. This observation requires further study in a larger number of patients. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for BPH increases the risk of post-implantation incontinence and urinary morbidity. Prevention of morbidity depends on careful patient selection, and expert assessment of IPSS score, backed up by urodynamic studies if needed is key to this.

A small RCT has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice [816].

Table 8.2.2: Acute gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer morbidity scale (adaptations with regard to the original RTOG scale in italics) according to Huang et al. [817]*.

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.</td>
<td>Diarrhoea requiring parasympatholytic drugs. Mucous discharge not necessitating sanitary pads. Rectal or abdominal pain requiring analgesics.</td>
<td>Diarrhoea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distension (flat plate radiograph demonstrates distended bowel loops).</td>
</tr>
<tr>
<td>GU</td>
<td>Frequency of urination or nocturia twice pretreatment habit. Dysuria or urgency not requiring medication.</td>
<td>Frequency of urination is less frequent than every hour (day: 12-16 times; nocturia 5-8 times). Dysuria, urgency, bladder spasm requiring local anaesthetic.</td>
<td>Frequency of urination is more frequent than every hour (day: &gt;16 times; nocturia: &gt; 8 times). Dysuria, bladder spasm, urgency requiring frequent regular narcotic. Gross haematuria complaints requiring permanent or suprapubic catheter.</td>
</tr>
</tbody>
</table>

Table 8.2.3: Late gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scale (adaptations with regard to the original RTOG/EORTC scale in italics) according to Huang et al. [817]*

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild diarrhea</td>
<td>Moderate diarrhea</td>
<td>Watery diarrhea</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Mild cramping</td>
<td>Intermittent, severe cramping.</td>
<td>Obstruction requiring surgery.</td>
<td>Perforation</td>
</tr>
<tr>
<td>Bowel movements 2-5 per day</td>
<td>Bowel movements (5 per day).</td>
<td>Bleeding requiring surgery or 2 laser treatments or transfusions.</td>
<td>Fistula</td>
</tr>
<tr>
<td>Slight rectal discharge or bleeding</td>
<td>Moderate excessive, rectal discharge.</td>
<td>Intermittent, frequent bleeding (3 single laser treatments or transfusion).</td>
<td>Abdominal pain or tenesmus requiring tube decompression or bowel diversion.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GU</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency during day 0.5-1 h</td>
<td>Frequency during day: 1-2 h</td>
<td>Frequency during day: 2 h</td>
<td>Frequency during day: Necrosis</td>
</tr>
<tr>
<td>Nocturia 2-3/night</td>
<td>Nocturia 4-6/night</td>
<td>Nocturia 6/night</td>
<td>Severe haemorrhagic cystitis</td>
</tr>
<tr>
<td>Slight dysuria or microscopic haematuria requiring no medication</td>
<td>Moderate dysuria or intermittent (mild, moderate) haematuria requiring medication†</td>
<td>Severe dysuria</td>
<td>Bladder capacity &gt; 100 mL</td>
</tr>
<tr>
<td>Slight epithelial atrophy, minor telangiectasia</td>
<td>Moderate telangiectasia</td>
<td>Frequent (severe) haematuria</td>
<td></td>
</tr>
<tr>
<td>Bladder capacity &gt; 300 mL</td>
<td>Bladder capacity: 150-300 mL</td>
<td>Severe telangiectasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder capacity: 100-150 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benign urethral strictures requiring TURP, dilation, or suprapubic or permanent catheter</td>
<td></td>
</tr>
</tbody>
</table>

* The difference between grade 1 and grade 2 GI pain, mucosal loss, or bleeding is most easily made when grade 2 is defined as morbidity requiring specific medication: grade 1 = stool softener, diet modification, occasional (< 2/wk) non-narcotic drug, occasional antidiarrhoeal agent (2/wk), occasional use of incontinence pads (1-2 d/wk); grade 2 = regular (>2/wk) use of (non)narcotic drugs for pain, regular (2/wk) antidiarrhoeals, steroid suppositories, one laser.

† With the exception of antibiotics.


GI = gastrointestinal; GU = genito-urinary; TURP = transurethral resection of the prostate.

8.2.3 Local treatments other than surgery or radiotherapy

8.2.3.1 Cryosurgery

In Ramsay et al.’s systematic review and meta-analysis [511], there was evidence that the rate of urinary incontinence at one year was lower for CSAP than for RP, but the size of the difference decreased with longer follow-up. There was no significant difference between CSAP vs. EBRT in terms of urinary incontinence at one year (< 1%), CSAP had a similar ED rate (range 0-40%) to RP at one year. There was insufficient data to compare CSAP vs. EBRT in terms of ED. There was a general trend for CSAP to have fewer procedural complications, apart from urinary retention. The only difference that reached statistical significance was for urethral stricture, which was less frequent after CSAP than after RP. However, the data underlying this comparison are weak and are, of course, not based on a RCT.

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 statistically significant incontinence rates than RP [511]. The safety profile for HIFU was generally good, the commonest reported complications being dysuria (22-30%), acute urinary retention (range 2-24%), urethral sloughing (up to 22%) and UTI (up to 17%). However, HIFU appeared to have a slightly higher incidence of urethral stricture than EBRT which was statistically significant. The quality of the evidence was poor, due to high risks of bias across studies and heterogeneity of outcome definition, measurement and reporting.
The incontinence rates at one year for focal CSAP were very low. Procedural complication rates were generally low, with the commonest complication being acute urinary retention (range 1.2-8.0%).

8.2.4 **Hormonal therapy**

There is a lack of data on the effects of HT on QoL, with only a single, large, prospective, RCT comparing orchiectomy + flutamide or placebo in M1 patients. Combined therapy resulted in a lower QoL in the first six months, with more frequent diarrhoea and worse emotional functioning, compared with castration alone [818]. A small RCT evaluated the HRQoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. Both sexual and cognitive function significantly declined with ADT, while emotional distress significantly increased in the no treatment patient group [819]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [820]. Another retrospective, non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than orchiectomised patients. The stage at diagnosis had no effect on health outcomes [821].

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 twelve months [822]. 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 [823], preserved libido and erectile function [824].

Intermittent androgen deprivation has been discussed elsewhere (see Section 6.6 - Metastatic PCa - Hormonal therapy).

8.2.4.1 **Sexual function**

Loss of libido and ED are common. The management of acquired ED is mostly non-specific [825].

8.2.4.2 **Hot flushes**

Hot flushes are the most common side-effect of ADT. They appear three months after starting ADT, usually persist long-term and have a significant impact on QoL.

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications. Soy phytoestrogens have shown an efficacy in breast cancer patients, but have not been evaluated in men. Progesterone-based treatments have demonstrated efficacy with 80% of patients showing an improvement [826].

Serotonin re-uptake inhibitors (e.g. venlafaxine or sertraline) appear to be effective in men, but less than HT based on a prospective randomised trial comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or CPA, 100 mg daily [827]. After six months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

With a placebo effect influencing up to 30% of patients [828], the efficacy of clonidine, veralipride, gabapentine [829] and acupuncture [830] must be compared in prospective RCTs.

8.2.4.3 **Other systemic side-effects of androgen-deprivation therapy**

Androgen-deprivation therapy is associated with significant side effects which may lead to significantly increased morbidity or even mortality.

8.2.4.4 **Non-metastatic bone fractures**

Due to increased bone turnover and decreased BMD in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% relative risk with long-term ADT) [831]. Hip fractures in men are associated with a significant risk of death [832]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture. The WHO FRAX tool ([http://www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) are common and occur during the first year of ADT [833]. Both changes increase the fracture risk.

8.2.4.4.1 **Lifestyle changes before starting long-term androgen-deprivation therapy**

Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption, and to normalise their BMI. Calcium and vitamin D supplements...
should be considered if low values are detected (normal values: calcium: 2.2-2.6 nmol/L, vitamin D: 100-160 nmol/L). A daily intake of at least 1,200 mg/day of calcium and 1,000 UI of vitamin D is useful.

8.2.4.4.2 Hormonal treatment modalities
Bicalutamide monotherapy could be a bone-protective treatment [834, 835], but is limited by its suboptimal efficacy (see Section 6.6 - Metastatic PCa - Hormonal Therapy). The intermittent modality might be associated with less bone impact [565].

8.2.4.4.3 Bisphosphonates
Bisphosphonates increase BMD in the hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid remains unclear: quarterly [836] or yearly [837] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [838]. A quarterly regimen could be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [839].

In contrast to breast cancer, a significant benefit in OS has only been demonstrated in PCa in a post-hoc analysis for the oral first-generation clodronate with an absolute 8% OS increase after eight years of follow-up [840]. This benefit has never been observed with more recent bisphosphonates.

Denosumab (a fully human monoclonal antibody against receptor activator of NF-κB ligand [RANKL])
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 two years, using a 60 mg subcutaneous regimen every six months [841]. 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 four weeks), a delay in bone metastases of 4.2 months has been shown [782] without any impact on OS, but with an increase in side effects. Therefore, this later regimen cannot be recommended.

8.2.4.5 Metabolic effects
Lipid alterations are common and may occur as early as the first 3 months of treatment [833]. ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. Once again, exercise is strongly recommended for its protective effect. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [842], 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 [843]:
- 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 [844].

8.2.4.6 Cardiovascular morbidity
Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [845]. Several studies showed that ADT, after only six months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [846]. The RTOG 92-02 [847] and 94-08 [415] trials confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 [848]. However, an increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [849] or presenting with a metabolic syndrome [850].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [851]. However, the methodology used in these studies does not provide convincing evidence to show a clear superiority of these compounds.

These data resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [689]. Preventive advice includes non-specific measures such as loss of
weight, increased exercise, improved nutrition and smoking cessation.

8.2.4.7 Fatigue
Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure [852, 853], with prolonged efficacy [854] and improved specific survival [855].

Anaemia may be a cause of fatigue. Anaemia requires an etiological diagnosis (medullar invasion, mainly inflammatory, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusions are required if severe anaemia is present. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [856].

8.2.4.8 neurological side effects
Castration seems also to be associated with an increased risk of stroke [857], and is suspect to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [858].

8.3 Overall quality of life in men with prostate cancer
Living longer with prostate cancer, does not necessarily equate to living well [803, 762]. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for prostate cancer [859]. Radical treatment for prostate cancer 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. loss of muscle mass, sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae increased cardiovascular and bone fracture risk [860, 861]. Direct symptoms from advanced or metastatic cancer e.g. pain, hypercalcaemia, spinal cord compression, pathological fractures, also adversely affect health [862, 863]. Men’s QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [864, 865].

The concept of ‘quality of life’ is subjective and can mean different things to different men, but there are some generally common features across virtually all patients. Drawing from these common features, specific tools or ‘patient reported outcome measures’ (PROMs) have been developed and validated for men with prostate cancer. These questionnaires assess common issues that affect men after prostate cancer diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated SRs around cancer-specific QoL outcomes in men with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

Table 8.3.1: PROMs assessing cancer specific quality of life

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Domains / items</th>
</tr>
</thead>
<tbody>
<tr>
<td>(FACT-G) [866]</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy-Prostate</td>
<td>12 cancer site specific items to assess for prostate related symptoms. Can be combined with FACT-G or reported separately.</td>
</tr>
<tr>
<td>(FACT-P) [867]</td>
<td></td>
</tr>
<tr>
<td>European Organisation for Research and Treatment</td>
<td>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.</td>
</tr>
<tr>
<td>of Cancer QLQ-C30 (EORTC QLQ-C30) [868]</td>
<td></td>
</tr>
<tr>
<td>European Organisation for Research and Treatment</td>
<td>Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.</td>
</tr>
<tr>
<td>of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [869]</td>
<td></td>
</tr>
<tr>
<td>Expanded prostate cancer index composite (EPIC)</td>
<td>Urinary, bowel, sexual, and hormonal symptoms.</td>
</tr>
<tr>
<td>[870]</td>
<td></td>
</tr>
<tr>
<td>Expanded prostate cancer index composite short</td>
<td>Urinary, sexual, bowel, and hormonal domains.</td>
</tr>
<tr>
<td>form 26 (EPIC 26) [871]</td>
<td></td>
</tr>
<tr>
<td>UCLA Prostate Cancer Index (UCLA PCI) [872]</td>
<td>Urinary, bowel, and sexual domains.</td>
</tr>
</tbody>
</table>
8.3.1 Long-term (≥12 months) quality of life outcomes in men with localised disease.

Men undergoing local treatments

Recently the results of the Prostate Testing for Cancer and Treatment (ProtecT) trial (n = 1,643 men) were published [875]. The study reported no difference in EORTC QLQ-C30 assessed global QoL, up to five years of follow-up in men aged 50-69 years with T1-T2 disease randomised for treatment with AM, RP or RT [875]. 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 six years of follow-up. Minimal clinically important differences for the 50 item EPIC questionnaire are not to our knowledge available. For men receiving RT, 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 six years of follow-up in the ProtecT trial.

The findings regarding RP and RT are supported by other observational studies, the most important being The Prostate Cancer Outcomes Study (PCOS) [876] that studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT. The study reported that at five 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 five years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at fifteen years.

With respect to brachytherapy cancer-specific QoL outcomes, the best available evidence come from one small RCT (n = 200) evaluating bilateral nerve sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsened 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 five years of follow-up when comparing to pre-treatment values [877]. It should be noted of this trial within group tests only were reported.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advise eligible patients for active surveillance, that global quality of life is equivalent for up to five years compared to radical prostatectomy or radiotherapy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.</td>
<td>1b</td>
<td>C</td>
</tr>
</tbody>
</table>

8.3.2 Improving quality of life in men who have been diagnosed with prostate cancer

Men undergoing local treatments

In men with localised disease, nurse led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, dyadic adjustment, depression, managing bowel and urinary function problems) provided positive short-term effects (four months) on sexual function (effect size 0.45) and long-term (twelve months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [878].

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 [405]. 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 nine months of follow-up [406]. 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. A detailed discussion can be found in the EAU Male Sexual Dysfunction Guidelines [879].

Men undergoing systemic treatments

Similar to men treated with a radical approach (see above) 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 [880].

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 three months in men treated with ADT [852]. 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 [881, 882]. These findings are supported by a recent SR which reported improvements up to twelve weeks in cancer-specific QoL in a meta-analysis of high quality trials (SMD 0.33; 95%; CI: 0.08-0.58) [883].

**Recommendations**

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<th>Recommendations</th>
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<tr>
<td>Offer men on androgen deprivation therapy, twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.</td>
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<tr>
<td>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.</td>
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10. CONFLICT OF INTEREST

All members of the EAU - ESTRO - ESUR - SIOG Prostate Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/.

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