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1. INTRODUCTION

1.1 Aims and scope
The European Association of Urology (EAU) 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.

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

Section 6.3: Treatment - Definitive Radiotherapy, has been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the EAU PCa Guidelines Panel are (in alphabetical order): Prof. Dr. M. Bolla, Dr. A. Henry, Prof. Dr. M. 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/prostate-cancer/?type=panel.

1.2.1 Acknowledgement
The EAU 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 2016 document presents a full update of the 2015 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 2016 EAU PCa Guidelines.

Key changes for the 2016 print:
• Chapter 4 - Classification and staging systems, the new 2014 International Society of Urological Pathology (ISUP) Consensus Conference findings have been included.
• Section 5.2.4 Diagnosis - The role of imaging; the key findings of the systematic review on the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results, have been included [3]. The recommendations have been adapted accordingly.
• Section 6.2 - Radical prostatectomy, a new Section 6.2.6 - Indication and extent of pelvic lymph node dissection has been included.
• Section 6.4 - Options other than surgery and radiotherapy for the primary treatment of localised PCa, has been revised and restructured.
• Section 6.6 - Treatment: Metastatic PCa, has been completely revised.
• Section 6.10 - Treatment of PSA-only recurrence after treatment with curative intent,
  o Section 6.10.5.2 - Hormonal therapy; the key findings of a systematic review on ‘The role of hormonal treatment in PCa patients with non-metastatic disease recurrence after local curative treatment’ [4] have been included.
• Section 6.10.11 - Salvage lymph node dissection has been included as a new topic.
• Section 6.11 -Treatment: Castration-resistant PCa (CRPC), has been completely revised.

Changed recommendations and evidence summaries can be found in sections:
5.1.1 Guidelines for screening and early detection

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<td>Do not subject men to PSA testing without counselling on the potential risks and benefits.</td>
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PSA = prostate-specific antigen.

5.3.5 Guidelines for staging of PCa

**Intermediate-risk PCa**

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<td>In predominantly Gleason pattern 4, metastatic screening, include at least a cross-sectional abdominopelvic imaging, and a CT/MRI and bone-scan for staging purposes.</td>
<td>2a</td>
<td>A*</td>
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<tr>
<td>In predominantly Gleason pattern 4, use prostate mpMRI for local staging and metastatic screening.</td>
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**High-risk localised PCa/ High-risk locally advanced PCa**

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<td>Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.</td>
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mpMRI = multiparametric magnetic resonance imaging; CT = computed tomography.

6.4.5 Summary of evidence and guidelines for experimental therapeutic options to treat clinically localised PCa

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<td>There is no reliable long-term comparative data to indicate that CSAP or HIFU leads to equivalent oncological outcomes compared with radical prostatectomy or EBRT.</td>
<td>3</td>
</tr>
<tr>
<td>PSA 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 follow-up and re-treatment criteria.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only offer cryotherapy and HIFU within a clinical trial setting.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

HIFU = high-intensity focused ultrasound.

6.6.7 Guidelines for hormonal treatment of metastatic prostate cancer

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

6.10.4.6 Guidelines for imaging in patients with biochemical failure

<table>
<thead>
<tr>
<th>PSA recurrence after RT</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<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>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

PET/CT = positron emission tomography/computed tomography.

6.10.11.1 Guidelines for salvage lymph node dissection

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss salvage 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.</td>
<td></td>
</tr>
</tbody>
</table>

LND = lymph node dissection.
6.11.10 Summary of evidence and recommendation for life-prolonging treatments of mCRPC

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clear-cut recommendation can be made for the most effective drug for secondary</td>
<td>3</td>
</tr>
<tr>
<td>treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.</td>
<td></td>
</tr>
</tbody>
</table>

2. METHODS

2.1 Data identification
For the 2016 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. systematic reviews with meta-analysis, randomised controlled trials, and prospective comparative studies) published in the English language. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between January 1st 2014 to April 24th 2015. A total of 1,792 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/prostate-cancer/?type=appendices-publications.

Specific sections of the text have been updated based on a systematic review 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:

- Section 5.2.4.2 - Multiparametric MRI (mpMRI)
  What is the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results? [3].

- Section 6.10.5.2 - Hormonal therapy
  The role of hormonal treatment in PCa patients with non-metastatic disease recurrence after local curative treatment: A systematic review [4].

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 (2). 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 on line at the above address. In addition, the International Society of Geriatric Oncology (SIOG) and the European Society for Radiotherapy & Oncology (ESTRO) have endorsed the PCa Guidelines.

2.2 Review
The following sections were subjected to peer review prior to publication:

- 6.6. Treatment - Metastatic prostate cancer;
- 6.11. Treatment - Castration-resistant prostate cancer (CRPC).

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

Ongoing systematic reviews include:

- What is the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results? [3].
- Antibiotic prophylaxis for prostate biopsies: Risk factors for infection - what is the optimal antibiotic prophylaxis?
- What are the benefits and harms of extended, limited or no lymph node dissection during radical prostatectomy for prostate cancer? [5];
- How does biochemical recurrence following curative treatment for prostate cancer impact on overall survival, cancer-specific survival and development of metastatic disease? [6].
3. EPIDEmiOLOGY AND AETIOLOGY

3.1 Epidemiology
Prostate cancer is the most common non-skin cancer in elderly males (> 70 years of age) in Europe. It is a major health concern, especially in developed countries with a greater proportion of elderly men in the general population. The incidence is highest in Northern and Western Europe (> 200 per 100,000 men), while rates in Eastern and Southern Europe have showed a continuous increase [7]. There is a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe [8]. Overall, during the last decade, the 5-year relative survival percentages for PCa steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 [8].

With the expected increase in the life expectancy of men and the subsequent rise in the incidence of PCa, the disease’s economic burden in Europe is also expected to increase. It is estimated that the total economic costs of PCa in Europe exceed €8.43 billion [9], with a high proportion of the costs occurring in the first year after diagnosis. In European countries with available data (UK, Germany, France, Italy, Spain, the Netherlands), this amounted to €106.7-179.0 million for all PCa patients diagnosed in 2006.

3.2 Risk factors and chemoprevention
Epidemiological studies have shown strong evidence for a genetic predisposition to PCa, based on two of the most important factors, racial/ethnic background and family history [10, 11]. Genome-wide association studies have identified 100 common susceptibility loci who contribute to the risk for PCa [12].

A small subpopulation of men with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before the age of 55 [11]. More than 70 PCa susceptibility loci, explaining ~30% of the familial risk for this disease, have been identified [13]. Patients with hereditary PCa usually have a disease onset six to seven years earlier than spontaneous cases, but do not differ in other ways [11].

The frequency of incidentally- and autopsy-detected cancers is roughly the same in different parts of the world [14]. This finding is in sharp contrast to the incidence of clinical PCa, which varies widely between different geographical areas, being high in the USA and Northern Europe and low in South-East Asia. If Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men [15].

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as diet, sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation [16, 17] and occupational exposure have all been discussed as being aetiologically important [17]. Prostate cancer ought to be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to the following specific features:

• high prevalence;
• long latency;
• endocrine dependency;
• availability of serum markers (prostate-specific antigen [PSA]);
• the histological precursor lesion prostatic intraepithelial neoplasia [16].

However, there is currently no strong evidence to suggest that dietary interventions can reduce the risk of PCa. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) showed a weak correlation between insulin-like growth factor-I (IGF-1) levels and high intake of protein form dairy products and an increased risk of PCa [18]. The outcome of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was negative, and therefore vitamin E and selenium are not recommended for the prevention of PCa [19]. Similarly, a meta-analysis of eight randomised controlled trials (RCTs) comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [20].

Metabolic syndrome is weakly and non-significantly associated with the risk of PCa, but associations vary with geography. Among single components of the syndrome (body mass index, dysglycaemia or dyslipidaemia, high triglycerides, low high-density lipoprotein (HDL) cholesterol) only hypertension and waist circumference > 102 cm were associated with a significantly greater risk of PCa, increasing the risk by 15% ($p = 0.035$) and 56% ($p = 0.007$), respectively [21]. Currently, there are no data to suggest that medical intervention would effectively reduce progression of PCa.

The role of medication in the development of PCa has been investigated in several subgroups. A recent study in hypogonadal men receiving testosterone therapy did not show an increased risk of PCa [22].
Furthermore there are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa [23, 24].

Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing the risk of developing PCa. Although it seems that 5-ARIs have a potential benefit in 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 increased risk of high-grade PCa [25-27]. None of the available 5-ARIs have been approved for this indication.

Several studies have been published on a putative correlation between statin use and PCa incidence: a recent meta-analysis and the results of the REDUCE study did not confirm a preventive effect of statins on PCa risk [21, 28].

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on the risk of progression. There is, as yet, insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk. But such lifestyle modifications might be associated with other non-specific benefits and must therefore be encouraged.

3.2.1 Guideline for preventative measures
At this moment in time no definitive recommendation can be provided for preventive measures due to the lack of conclusive data.

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 to make recommendations on their treatment. Throughout this Guideline the 2009 Tumour, Node, Metastasis classification for staging of PCa (Table 4.1.1) [29] and the EAU risk group classification essentially based on D'Amico's classification system for PCa is used (Table 4.1.2) [30]. 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 [29]

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumour not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within the prostate¹</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one half of one lobe or less</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves more than half of one lobe, but not both lobes</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostatic capsule²</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>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 nodes³</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M - Distant metastasis⁵</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s)</td>
</tr>
</tbody>
</table>

¹ Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
² Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.
³ The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.
⁴ Laterality does not affect the N-classification.
⁵ When more than one site of metastasis is present, the most advanced category should be used.

### 4.2 Gleason score and ISUP 2014 grade groups

The (2005 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 [31].

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 [32, 33] has introduced the concept of the grade groups of PCa, 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 codify the clinically highly significant distinction between Gleason score 7 (3 + 4) and 7 (4 + 3) PCa.

The grade groups represent a compression of Gleason scores ≤ 6 in grade group 1 and Gleason scores 9-10 in grade group 5, whereas Gleason score 7 is expanded to grade group 2, i.e. 7 (3 + 4) and grade group 3, i.e. 7 (4 + 3). The ISUP 2014 prostate cancer grade groups therefore range from 1-5, see table 4.2.1.
Table 4.2.1 International Society of Urological Pathology 2014 grade groups

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Grade group</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>
<th>Localised</th>
<th>Locally advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSA &lt; 10 ng / mL and GS &lt; 7 and cT1-2a</td>
<td>PSA 10-20 ng /mL or GS 7 or cT2b</td>
<td>PSA &gt; 20 ng / mL or GS &gt; 7 or cT2c</td>
<td>any PSA</td>
<td>any GS cT3-4 or cN+</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.

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 [34]. 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 [35]. However, there is still no level 1 evidence that PSA mass screening is cost-effective in reducing PCa mortality [36].

Currently, screening for PCa is one of the most controversial topics in the urological literature [37]. Three large prospective RCTs published data on screening in 2009 [38-40]. Heated discussions and debates resulted in many conflicting positions and policy papers. Some authors argue that the use of current American Urological Association (AUA) guidelines [41] or the U.S. Preventive Services Task Force recommendations for screening [42] may lead to a substantial number of men with aggressive disease being missed [43, 44]. Recently 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 [45]. 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 [36], which has been updated since [46] presents the main overview. 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 these 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. the biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [26, 27].

The impact on the patient’s overall QoL is still unclear [47-49], 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) [50]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after noncompliance 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 [51].

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Number needed to screen</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1,410</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>979</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>781</td>
<td>27</td>
</tr>
</tbody>
</table>

An individualised risk-adapted strategy for early detection might be offered to a well-informed man with at least 10-15 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 with a family history of PCa (both paternal and maternal [52]) and age > 45 years, or African-Americans [53]. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [54, 55] are also at increased risk of PCa metastasis or death several decades later. The long-term survival and QoL benefits of such an approach remains to be proven at a population level. Recently, as for breast cancer, a genetic abnormality likely to be associated with an increased risk has been shown prospectively, especially for BRCA2 [56]. Several new biological markers such as TMPRSS2-Erg fusion, PCA3, kallikreines [57, 58] or several genetic markers [59-62] have been shown to add sensitivity and specificity on top of PSA, lowering over-diagnosis. At this time there is too limited data to base a recommendation on. Also a population-based survival benefit has not yet been demonstrated.

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:

• from the PCPT cohort: PCPTRC 2.0 [http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp];
• from the ERSPC cohort: [http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators];
• from a local Canadian cohort: [http://sunnybrook.ca/content/?page=occ-prostatecalc] (among others).

Since none has clearly shown superiority it remains a personal decision which one to use [63].

Informed men requesting an early diagnosis should be given a PSA test and undergo a digital rectal examination (DRE) [64]. 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 2 years for those initially at risk, or postponed up to 8-10 years in those not at risk [65].

The age at which early diagnosis should be stopped remains controversial, but an individual’s life expectancy must definitely be taken into account. Men who have less than a 15-year life expectancy are unlikely to benefit based on data from the 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 [66].

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 7.1, Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only
way to decrease overtreatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

From a public health point of view, mass screening of PCa is not indicated. However, early diagnosis on an individual basis is possible based on DRE and PSA testing. Individual patient screening requires informed consent from the patient following a full discussion with their physician on the pros and cons of the complete procedure, taking into account the patient’s risk factors, age and life expectancy. The interval for follow-up screening depends on age and baseline PSA level.

5.1.1 Guidelines for screening and early detection

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not subject men to 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 10-15 years.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Offer early PSA testing in 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 2 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 8 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 based on data from the PIVOT and the ERSPC trials.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

ERSPC = European Randomized Study of Screening; PCa = prostate cancer; PIVOT = Prostate Cancer Intervention Versus Observation Trial; PSA = prostate-specific antigen.

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 [67]. Suspect DRE in patients with PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [68]. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy [69, 70].

5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [71]. 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) [72].

There are no agreed standards defined for measuring PSA [73]. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [74]. Table 5.2.1 demonstrates the occurrence of Gleason ≥ 7 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 [75].
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 ≥ 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) [76];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [77].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treated PCa [78], 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 [79-82].

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 [83]. 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) [84].

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 [85, 86].

5.2.2.5 PCA3 marker
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 Progena 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 [87-90].

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 unconfirmed [91]. Currently, the main indication for the Progena test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain [92].

5.2.2.6 Guidelines for risk-assessment of asymptomatic men

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer further risk-assessment to asymptomatic men with a PSA between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: • risk-calculator; • an additional serum or urine-based test (e.g. PHI, 4Kscore or PCA3) or imaging.</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

PSA = prostate specific antigen; PHI = Prostate Health Index test.
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 [93]. Risk stratification is a potential tool for reducing unnecessary biopsies [93].

Limited PSA elevation alone should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory [94, 95]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [96].

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 [97, 98].

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 for risk estimates);
- suspicious DRE, 5-30% cancer risk [67, 68];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 40% risk [99];
- extensive (multiple biopsy sites, i.e., ≥ 3) high grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [99, 100];
- a few atypical glands immediately adjacent to high grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [101];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade prostate carcinoma [102];
- positive multiparametric MRI findings (see Section 5.2.4).

Additional information may be gained by the Progensa DRE urine test for PCA3, the serum 4K and PHI test 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 [92]. 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 recent 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 [103]. Given the limited currently available data, no recommendation can be made regarding its routine application.

<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 [104].

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 [105]. 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 [106].

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 12 core biopsies are recommended [107], with > 12 cores not being significantly more conclusive [108, 109].
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 [110].

5.2.3.6 **Seminal vesicle biopsy**
Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA > 15 ng/mL, the odds of tumour involvement are 20-25% [111]. 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 multiparametric magnetic resonance imaging (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 [112].

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 [113]. Increased quinolone resistance [114] is associated with a rise in severe post-biopsy infection [115].

5.2.3.9 **Local anaesthesia prior to biopsy**
Ultrasound-guided periprostatic block is recommended [116]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [117].

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 5.2.2 [118]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [119].

<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 **Role of imaging**
5.2.4.1 **TRUS and US-based techniques**
Grey-scale TRUS is not reliable at detecting PCa [121]. Thus, there is no evidence that US-targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography and contrast-enhanced US are being investigated. Currently there is not enough evidence for their routine use [122].

5.2.4.2 **Multiparametric magnetic resonance imaging (mpMRI)**
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 excellent sensitivity for the detection and localisation of Gleason score ≥ 7 cancers (see Table 5.2.3) [123-126].
Many single-centre studies suggest that mpMRI 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 [127]. The association of systematic biopsies and biopsies targeted on mpMRI abnormalities (MRI-Tbx) may also better predict the final pathological grade found at prostatectomy [128].

As a result, some authors proposed performing mpMRI before prostate biopsy, to increase the detection of aggressive cancers and reduce the over-detection of non-significant foci [129-132]. One recent meta-analysis confirmed that, in men with an abnormal mpMRI, MRI-Tbx had a higher detection rate of clinically significant PCa compared to TRUS biopsy (sensitivity 0.91, [95% CI: 0.87-0.94] vs. 0.76, [95% CI: 0.64-0.84]) and a lower rate of detection of insignificant PCa (sensitivity 0.44, 95% CI: 0.26-0.64 vs. 0.83, 95% CI: 0.77-0.87). However, sub-group analysis showed that MRI-Tbx markedly improved the detection of significant PCa in the repeat biopsy setting (relative sensitivity 1.62 [95% CI: 1.02-2.57]) but not in men with an initial biopsy (relative sensitivity 0.97 [95% CI: 0.94-1.01]) [133]. Another systematic review reached similar conclusions [122]. Two recent RCTs not included in the meta-analyses and performed in patients undergoing an initial biopsy, yielded contradictory results as to whether or not the association of systematic biopsies and MRI-Tbx had a higher detection rate than systematic biopsies alone [134, 135].

It remains uncertain whether a negative mpMRI can justify omitting biopsy because of the heterogeneity and potential selection bias of published studies [122, 127]. It is therefore not possible to recommend using targeted biopsies only [3].

Multiparametric MRI remains limited by its inter-reader variability and the heterogeneity in definitions of positive and negative examinations. The first version of the Prostate Imaging Reporting and DataSystem (PIRADS) scoring system [136] failed to improve inter-reader interpretation as compared to subjective scoring [137, 138]. An updated version (PIRADS V2) has been proposed recently but needs to be evaluated further [139].

5.2.4.3 **Guidelines for imaging**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before repeat biopsy, perform 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>

**mpMRI** = multiparametric magnetic resonance imaging.

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 PCa detection rate [140]. 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 [141, 142]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [112] 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 [143-145]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [143]. Table 5.2.4 lists the recommended terminology for reporting prostate biopsies [141].
Table 5.2.4: Recommended terminology for reporting prostate biopsies [141]

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign/negative for malignancy</td>
<td>If appropriate, include a description.</td>
</tr>
<tr>
<td>Active inflammation</td>
<td></td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
<td></td>
</tr>
<tr>
<td>High-grade PIN</td>
<td></td>
</tr>
<tr>
<td>High-grade PIN with atypical glands</td>
<td>suspicious for adenocarcinoma (PINATYP)</td>
</tr>
<tr>
<td>Focus of atypical glands/lesion</td>
<td>suspicious for adenocarcinoma/ataypical small acinar proliferation, suspicious for cancer</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

PIN = prostatic intraepithelial neoplasia.

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 2005 Gleason score (i.e., 2005 ISUP Modified Gleason System) [31]. A global Gleason score comprising all biopsies is also reported as well as the ISUP 2014 grade group (see Section 4.2). Intraductal carcinoma, lymphovascular invasion and extraprostatic extension must each be reported, if identified.

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 [146-148]. 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 [149]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [150] 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:

- 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: extraprostatic extension, seminal vesicle invasion, lymphovascular invasion, intraductal carcinoma, peri-neural invasion;
- ISUP 2014 grade group (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 [151]. 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 [152].

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 [153]. 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 [31]. 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>Recommendation</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 RP specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.5). As a result of the complex information provided on each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.6). Synoptic reporting results in more transparent and complete pathology reporting [154].

Table 5.2.5: Mandatory elements provided by the pathology report

| Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma. |
| Grading according to Gleason score (or therapy-related changes) and ISUP 2014 grade group. |
| Tumour (sub)staging and surgical margin status: location and extent of extraprostatic extension, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion, location and extent of positive surgical margins. |
| Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour. |

Table 5.2.6: Example checklist: reporting of prostatectomy specimens

| Histopathological type                                                                 |
| • Type of carcinoma, e.g. conventional acinar, or ductal |
| Histological grade                                                                 |
| • Primary (predominant) grade |
| • Secondary grade |
| • Tertiary grade (if applicable) |
| • Global Gleason score / ISUP 2014 grade group |
| • Approximate percentage of Gleason grade 4 or 5 |
| Tumour quantitation (optional)                                                        |
| • Percentage of prostate involved |
| • Size/volume of dominant tumour nodule |
| Pathological staging (pTNM)                                                          |
| If extraprostatic extension is present:                                               |
| • indicate whether it is focal or extensive |
| • specify sites |
| • Indicate whether there is seminal vesicle invasion |
| If applicable, regional lymph nodes:                                                 |
| • location |
| • number of nodes retrieved |
| • number of nodes involved |
If carcinoma is present at the margin:

- specify sites

Other

- Presence of lymphovascular / angio-invasion
- Location of dominant tumour
- Presence of intraductal carcinoma

5.2.6.2.1 Gleason score in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2005 modified) Gleason system [31] is the strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is incorporated in nomograms that predict disease-specific survival after prostatectomy [155].

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 [156] 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 extraprostatic extension. It is useful to report the location and extent of extraprostatic extension because the latter is related to recurrence risk [157].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive extraprostatic extension. Some describe focal as a few glands [158] or extension as < 1 high-power field (HPF) [159], whereas others measure the depth of extent in millimetres [160].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute extraprostatic extension. 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 [161, 162] and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as extraprostatic extension (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [163].

5.2.6.3 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [159, 164-167]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [164]. 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 [168].

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 [165] 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 [169].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of extraprostatic extension [170]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [159]. 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 [171], or number of blocks with positive margin involvement.
5.2.7 Guidelines for the clinical diagnosis of PCa

<table>
<thead>
<tr>
<th>Recommendation</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 ISUP 2005 modified Gleason grading system for grading of PCa.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Base the decision to perform a biopsy on PSA testing and 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. PHI, 4Kscore or PCA3] 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 10-12 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>1a</td>
<td>A</td>
</tr>
<tr>
<td>Use a local anaesthetic by periprostatic infiltration for prostate needle biopsies.</td>
<td>3</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>2a</td>
<td>B</td>
</tr>
</tbody>
</table>

DRE = digital rectal examination; ISUP = International Society of Urological Pathology; PCa = prostate cancer; PCA3 = prostate cancer gene 3; PHI = Prostate Health Index; PSA = prostate-specific antigen.

5.3 Diagnosis: Clinical staging
The extent of PCa is evaluated by DRE and PSA, and may be supplemented with bone scanning and 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. DRE is positively correlated with tumour stage in < 50% of cases [172], 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. Prostate specific antigen is produced by benign and malignant tissue, thus, there is no direct relationship between serum PSA and clinicopathological tumour stage [173]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [174]. An increase in tumour-positive biopsies is an independent predictor of extraprostatic extension, margin involvement, and lymph node invasion [175]. Serum PSA, Gleason score, and T stage are more useful together than alone in predicting final pathological stage [155, 176]. These models may help to select candidates for nerve-sparing surgery and lymphadenectomy (Section 7.2).

Seminal vesicle invasion is predictive of local relapse and distant metastatic failure. Seminal vesicle biopsies can improve pre-operative staging accuracy [177]. This is not recommended for first-line examination, but is 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 [178, 179]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [180].

Transperineal 3D prostate mapping biopsy (PMB) is an alternative to transrectal biopsies because it provides more accurate tumour localisation, extent and Gleason grading [181], and has acceptable morbidity.

5.3.1.3 Transrectal ultrasound (TRUS)
Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [182, 183].
Combined DRE and TRUS can detect T3a PCa more accurately than either method alone [184]. Even 3D-TRUS, colour Doppler and contrast agents may help in local staging [185, 186], but all TRUS techniques are largely operator-dependent and cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine staging.

5.3.1.4 Multiparametric magnetic resonance imaging (mpMRI)
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 extracapsular extension (ECE), SVI, and overall stage T3 detection showed 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 [187]. Multiparametric magnetic resonance imaging has poor sensitivity since it cannot detect microscopic extraprostatic extension. Its sensitivity increases with the radius of extension within periprostatic fat. In one study, the ECE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [188]. In another study, mpMRI sensitivity, specificity and accuracy for detecting T3 stage were 40, 95 and 76%, respectively, for focal (i.e. microscopic) extraprostatic extension, and 62, 95 and 88% for extensive extraprostatic extension [189].

The use of high field (3T) or functional imaging in addition to T2-weighted imaging improves sensitivity for ECE or SVI detection, but the experience of the reader remains of paramount importance [190]. Magnetic resonance imaging, although not perfect for local staging, may improve prediction of the pathological stage when combined with clinical data [191, 192].

Given its low sensitivity for focal (microscopic) extraprostatic extension, mpMRI is not recommended for local staging in low-risk patients [191, 193, 194]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [195].

5.3.2 N-staging
5.3.2.1 PSA level and biopsy findings
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 [155, 196, 197]. Measurement of PSA alone is unhelpful in predicting lymph node metastases. Nomograms or Partin tables can define patients at low risk (< 10%) of nodal metastasis, although nomograms may be more accurate in establishing the extent of nodal involvement [176, 198]. The simple Roach formula can also be used [199]. Patients with low- and intermediate-risk PCa may be spared N-staging before potentially curative treatment [155].

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 [200].

5.3.2.2 Nodal staging using computed tomography and multiparametric magnetic resonance imaging
Abdominal CT and mpMRI indirectly assess nodal invasion by measuring lymph node diameter. Their sensitivity is low and microscopic invasion cannot be detected. Using a 10-mm threshold, CT or mpMRI sensitivity is < 40% [201-213]. Among 4,264 patients, 654 (15.3%) had positive lymph nodes at lymphadenectomy but only 105 (2.5%) had a positive CT scan. Median estimated CT sensitivity, specificity, NPV and PPV were 7%, 100%, 85% and 100%, respectively [212].

Fine-needle aspiration biopsy (FNAB) may be useful in cases with positive imaging, even if it has a false-negative rate of 40% [214].

For CT or mpMRI, detection of microscopic lymph node invasion is < 1% in patients with a Gleason score < 8, PSA < 20 ng/mL, or localised disease [209, 215, 216]. Computed tomography and mpMRI should not be used for nodal staging in low-risk patients and be reserved for high-risk cancer.

5.3.2.3 Lymphadenectomy
The currently available most optimal method for N-staging is open or laparoscopic lymphadenectomy (see Section 7.2.6).

Primary removal of sentinel lymph nodes aims to improve accuracy of detecting tumour bearing nodes while reducing morbidity associated with extended pelvic lymph node dissection (LND) [217, 218]. Image guidance allows intraoperative sentinel node (SN) detection visually [219]. Difficulty in accessing the SN and the lack of data from large multicentre cohorts are major limitations of this technique. Therefore, for the time being, this remains experimental [220].
5.3.3 M-staging
5.3.3.1 Bone scan
Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. However, it suffers from relatively low specificity [221]. Thus, in patients with equivocal findings, the lesions need to be assessed by other imaging modalities.

The NPV for bone scanning is 87-100% [214, 222-230]. Its diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score [222-235] and these three factors were the only independent predictors of BS positivity in a study of 853 patients [236]. The BS positivity rate is extremely low (< 1%) in low-risk patients [235, 237-239]. In contrast, it is 6.6 - 38.5% in patients with a PSA level of 20-50 ng/mL [222, 225-228, 230, 231, 237-239], 19 - 90.7% in patients with stage > T3 [222, 226, 228, 229, 231, 237] and 16.9 - 29.6% in patients with Gleason > 8 tumours [233, 234, 237, 239]. The proportion of positive BSs in patients with PSA levels of 10 - 20 ng/mL (1-33.3%) or Gleason 7 (2.8 - 22%) is quite variable from one study to another [214, 221, 222, 223, 225-229, 238-240]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive BS [238, 240].

Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score or clinical stage [212].

5.3.4 New imaging modalities
5.3.4.1 Nodal metastases
11C- or 18F-choline positron emission tomography (PET)/CT have good specificity for lymph node metastases, but a sensitivity of between 10-73% [241, 242].

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic lymph node metastases were 62% (95% CI: 51 - 66%) and 92% (95% CI: 89 - 94%), respectively [243]. 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 [244]. Therefore, choline PET/CT has no place for up-front staging in nodal metastasis. Currently, prostate-specific membrane antigen-PET CT (PSMA PET/CT) remains investigational.

Magnetic resonance imaging sensitivity is low for lymph node metastases and similar [245, 246] or inferior [247] to that of choline PET/CT.

5.3.4.2 Bone metastasis
18F-fluoride PET or PET/CT shows similar specificity and superior sensitivity to bone scanning [241, 248-252]. However, unlike choline PET/CT, it does not detect lymph nodes metastases, and it is less cost-effective compared to bone scanning [252].

It remains unclear whether 11C-choline PET/CT is more sensitive than conventional bone scanning, but it has higher specificity, with fewer indeterminate bone lesions [241, 243, 253].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scanning and targeted radiography in detecting bone metastases in high-risk PCa [254-256]. Whole-body mpMRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [257]. A recent meta-analysis found that mpMRI 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) [258].

Table 5.3.1 Sensitivity and specificity for detecting bone metastases on a per-patient basis [258]

<table>
<thead>
<tr>
<th>Bone Modality scan</th>
<th>Sensitivity%</th>
<th>Specificity%</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Modality scan</td>
<td>78</td>
<td>85</td>
<td>95% (0.73-0.83)</td>
</tr>
<tr>
<td>PET</td>
<td>91</td>
<td>99</td>
<td>95% (0.83-0.96)</td>
</tr>
<tr>
<td>mpMRI</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, these techniques are currently limited by their lack of availability. The clinical benefit of detecting bone metastases at an earlier time-point using more sensitive techniques also remains unclear in the initial staging setting. Bone scan is therefore usually preferred in most centres.
5.3.5 **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 CT and TRUS 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, metastatic screening, include at least a cross-sectional abdominopelvic imaging and a CT/MRI and bone-scan for staging purposes.</td>
<td>2a</td>
<td>A*</td>
</tr>
<tr>
<td>In predominantly Gleason pattern 4, use prostate mpMRI for local staging and metastatic screening.</td>
<td>2b</td>
<td>A</td>
</tr>
</tbody>
</table>

<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>

*Upgraded following panel consensus.

CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PET = positron emission tomography; TRUS = transrectal ultrasound.

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 [259] and 45% of them are candidates for deferred management. There are two distinct strategies for conservative management that aim to reduce overtreatment: AS and watchful waiting (WW) (Table 7.1.1).

6.1.1.1 **Definition**

6.1.1.1.1 **Active surveillance**

Active surveillance aims to achieve correct timing for curative treatment, rather than delayed application of palliative treatment [260]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, while considering individual life expectancy.

6.1.1.1.2 **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 [259]**

<table>
<thead>
<tr>
<th></th>
<th>Active surveillance</th>
<th>Watchful waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment intent</td>
<td>Curative</td>
<td>Palliative</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Predefined schedule</td>
<td>Patient-specific</td>
</tr>
<tr>
<td>Assessment/markers used</td>
<td>DRE, PSA, re-biopsy, mpMRI</td>
<td>Not predefined</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>&gt; 10 years</td>
<td>&lt; 10 years</td>
</tr>
<tr>
<td>Aim</td>
<td>Minimise treatment-related toxicity</td>
<td>Minimise treatment-related toxicity</td>
</tr>
<tr>
<td></td>
<td>without compromising survival</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Only for 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.*

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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 15 years follow-up [259].

6.1.2.1 Active surveillance
The aim is to reduce over-treatment in patients with clinically confined, very-low-risk PCa, without compromising curative treatment [260]. Active surveillance is only proposed for highly selected low-risk patients. Current data are from ongoing prospective or retrospective cohorts, without any available RCTs.

One of the largest cohorts with the longest follow-up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [261]. These men presented with stage T1c or T2a PCa and PSA ≤ 10 ng/mL, age ≤ 70 years and a Gleason score ≤ 6 or age > 70 years with a score of ≤ 7. Initially, six biopsies were performed, but in recent years the 12-core protocol was introduced. After a median follow-up of 6.4 years (21% followed for more than 10 years), the 10- and 15-year OS were 80% and 62%, respectively. At 10 and 15 years, disease-specific survival (DSS) rates were 98.1% and 94.3%, respectively. Twenty-eight men (2.8%) developed metastases during follow-up (all but 2 being Gleason ≥ 7), and 15 died. Sixty-three and-a-half percent and 55% of men were still alive on AS at 10 and 15 years, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years in (43.5%), a Gleason score progression on repeat biopsies (35%) and patient preference (6%).

Several studies have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review including > 3,900 patients [262]. There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated.

Selection criteria for AS published so far [262, 263] include: Gleason 6, when specified, < 2 - 3 positive cores with < 50% cancer involvement of every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc. The later threshold remains controversial [263, 264]. A consensus meeting 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, extraprostatic extension or lymphovascular invasion in needle biopsy [265]. Some studies enrolled men with a PSA < 20 ng/mL, or up to T2b PCa, as well as men with a Gleason score 7 (3 + 4), a PSA < 10 ng/mL, a PSAD < 0.15 ng/mL/g, a T1c, and < 2 positive cores [266, 267]. These latter criteria are, as yet, not considered acceptable for an AS strategy, and should therefore not be used. A comprehensive review of the currently available patient selection- and follow-up criteria has been published [263].

Biological markers, including urine PCA3, transmembrane protease, serine 2 - ETS-related gene (TMPRSS2-ERG) fusion, or PSA isoforms such as the PHI index appear promising as does genomics on the tissue sample itself [268-270]. However, further study data will be needed before such markers can be used in standard clinical practice. Re-biopsy to exclude sampling error is still considered standard practice, [263] even if this could be modified in the future [271] as re-biopsy is associated with increased rates of infectious complications [272].

Imaging with mpMRI is of particular interest due to its high NPV value for lesion upgrading and for staging anterior prostate lesions [273, 274]. A systematic review has been recently published [274] highlighting its important place in AS programmes.

Follow up in AS should be based on repeat biopsy, [263] serial PSA measurements and clinical examination (DRE). The optimal biopsy regimen is still unclear. As yet, mpMRI cannot replace follow-up biopsies and should not be used alone as an assessment tool to prompt active treatment [274].

The decision to suggest 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 the published cohorts. A PSA change (especially a PSA-DT < 3 years) is a less powerful indication for changed management based on its weak link with grade progression [275]. Active treatment may also be instigated upon a patient’s request. This occurs in around 10% of patients on AS [276]. Overall, no major perturbation of health-related QoL and psychological well-being is apparent in the first years [277]. The same findings have been observed for WW [278].
### 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 [279]</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 [280]</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 [281]</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 [282]</td>
<td>99</td>
<td>45</td>
<td>0/2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Roemeling et al, 2007 [283]</td>
<td>278</td>
<td>41</td>
<td>89</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Khatami et al, 2007 [284]</td>
<td>270</td>
<td>63</td>
<td>NR</td>
<td>85</td>
<td>98.1</td>
</tr>
<tr>
<td>Klotz et al, 2015 [261]</td>
<td>993</td>
<td>77</td>
<td>NR</td>
<td>90</td>
<td>99.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2,130-3,000</td>
<td>43</td>
<td>90</td>
<td>99.7</td>
<td></td>
</tr>
</tbody>
</table>

* Patients receiving active therapy following initial active surveillance. CSS = cancer-specific survival; n = number of patients; 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 [285]. Watchful waiting is possible in patients with localised PCa and limited life expectancy.

Studies on WW have included patients with up to 25 years follow-up, with endpoints of OS and DSS. Several series have shown a consistent DSS rate of 82-87% at 10 years [286-291], and 80-95% for T1/T2 and Gleason score ≤ 7 [292]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [288, 290, 291], and two reported 20-year DSS rates of 57% and 32%, respectively [288, 290]. Of note is that these studies did not use the revised Gleason classification, which is associated with a slight increase in the grading. Practically, many patients classified as Gleason 6 in older studies would now be classified as Gleason 7. Therefore, the current Gleason 6 population has less aggressive disease compared to the patients classified in the above-mentioned cohorts.

Patients with well-, moderately- and poorly differentiated tumours had 10-year cancer-specific survival (CSS) rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [292]. Observation was most effective in men aged 65-75 years with low-risk PCa [293].

In patients with stage cT1a PCa, 10-year CSS rates were 96% and 94% for grade 1 and 2 tumours, respectively [286]. Metastasis-free survival (MFS) rate was 92% and 78% for patients with grade 1 and 2 tumours, respectively, indicating a higher risk of progression for moderately-differentiated tumours. Similar results were found in other studies of stage cT1a disease [294, 295].

Gleason 6-10 tumours carry a continuously increasing mortality risk up to 15 years follow-up after WW [296]. 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 6.1.4) [297, 298].

### Table 6.1.4: 15-year mortality risk for localised PCa in relation to Gleason score in patients aged 55-74 years [297-299]

<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 15 years.

Six hundred and ninety-five patients with T1/T2 PCa were randomised to WW or RP (Table 6.1.5) [299]. Although the study started after PSA screening was introduced, only 5% of men were diagnosed by screening.
After a median follow-up of 12.8 years, there was a significant decrease in cancer specific (CS) mortality, overall mortality, metastatic progression, and local progression in the RP group vs. the WW group.

Table 6.1.5: Outcome of Scandinavian Prostate Cancer Group Study Number 4 at 15 years follow-up [299]

<table>
<thead>
<tr>
<th></th>
<th>RP <em>(n = 347)</em> (%)</th>
<th>Watchful waiting <em>(n = 348)</em> (%)</th>
<th>Relative risk <em>(95% CI)</em></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 <em>(0.61-0.92)</em></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Metastatic progression</td>
<td>21.7</td>
<td>33.4</td>
<td>0.59 <em>(0.45-0.79)</em></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Local progression</td>
<td>21.5</td>
<td>49.3</td>
<td>0.34 <em>(0.26-0.45)</em></td>
<td>nr</td>
</tr>
</tbody>
</table>

CI = confidence interval; nr = not reported; RP = radical prostatectomy.

The overall difference was not modified by PSA level (below or above 10 ng/mL) or Gleason score (below or above 7) at diagnosis. Age at randomisation had a profound impact, with a benefit in OS and MFS only in those aged < 65 years.

Another study randomised 731 men with clinically organ-confined PCa (PSA < 50 ng/mL and age < 75 years) to RP or WW [300]. Fifty percent of the patients had non-palpable PCa, compared to only 12% in the other trial [299]. Despite a 10-year life expectancy which was an inclusion criterion, > 33% of the men died within 10 years, suggesting that the population was less fit than expected, and reduced the ability to assess the survival benefit for active treatment [300].

After a mean follow-up of 10 years, there was no significant difference between the treatments for overall mortality (47% for RP vs. 49.9% for the WW group and PCa-specific survival, 5.8% for the RP group vs. 8.4% for the WW group). There were no significant differences in OS when considering patient age, Gleason score, performance status (PS), and Charlson comorbidity index (CCI) score. 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. There was a relative-risk and absolute-risk reduction of 31% and 10.5%, respectively, for patients with intermediate/high-risk PCa. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%).

Data from a 1995 study showed a tendency for a higher probability of metastases in the deferred treatment group and shorter CSS was reported after deferred therapy compared with immediate hormone therapy (HT) in presumed localised PCa after 15 years of follow-up [301]. Another study showed higher mortality in men with localised PCa treated with 150 mg/day bicalutamide compared with placebo [302].

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 [303]. Swedish data show a higher prevalence of deferred treatment in low-risk disease of 46% [304].

Many small, localised, well-differentiated tumours do not progress, and radical therapy may lead to substantial overtreatment. This was confirmed by a recent analysis at 5 and 10 years follow up in 19,639 patients aged > 65 years who were not given curative treatment. Most men with a comorbidity index score (CCI) score ≥ 2 died from competing causes at 10 years whatever their initial age. However, men without comorbidity or CCI score 1 had a low risk of death at 10 years, especially for well- or moderately differentiated lesions (Table 8.7) [305]. For CCI score ≥ 2, tumour aggressiveness had little impact on OS, suggesting that patients could have been spared biopsy and diagnosis of cancer. Thus, evaluation of initial comorbidity and survival probability before proposing biopsy or treatment is important [306].

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 [307]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa were treated with androgen-deprivation therapy (ADT) immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS hazard ratio (HR) was 1.21 (95% CI: 1.05-1.39), favouring immediate treatment. The time from randomisation to progression of hormone-refractory disease did not differ significantly, nor did CSS.

The median time to start of deferred treatment was 7 years. One hundred and twenty-six patients died without needing treatment (44% of deaths). Immediate ADT resulted in a modest but significant increase in OS, but no significant difference in PCa mortality or symptom-free survival, raising 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 ≤ 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 time to PSA relapse after response to immediate ADT correlated significantly with baseline PSA.

6.1.4 Deferred treatment for metastatic PCa (stage M1)
The only candidates for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. Median survival is ~2 years, 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 [308, 309]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.1.5 Guidelines for active surveillance and watchful waiting

**Recommendation - active surveillance**

<table>
<thead>
<tr>
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<tr>
<td>4</td>
<td>A*</td>
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</table>

Discuss surgery and radiotherapy as treatment options with patients suitable for such treatments.

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

Follow-up should be based on DRE, PSA and repeated biopsies.

Patients should be counselled on the possibility of needing further treatment in the future.

**Recommendation - watchful waiting for localised prostate cancer**

<table>
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<tr>
<th>LE</th>
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</table>

Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.

While on watchful waiting, base the decision to start non-curative treatment on symptoms and disease progression (see Section 6.1.2.2).

**Recommendation - watchful waiting for locally advanced prostate cancer**

<table>
<thead>
<tr>
<th>LE</th>
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<td>1b</td>
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</table>

In locally advanced M0 patients unwilling or unable to receive any form of local treatment, offer a deferred treatment policy using ADT as monotherapy to asymptomatic patients with a PSA doubling time > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.

*Upgraded following panel consensus.

ADT = androgen-deprivation therapy; DRE = digital rectal examination; PSA = prostate-specific antigen.

6.2 Treatment: Radical prostatectomy

6.2.1 Introduction

Radical prostatectomy (RP) involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain negative margins. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP by any approach must be eradication of disease, while preserving continence and, whenever possible, potency [310]. Patients should not be denied this procedure on the grounds of age alone [306] but they should have at least 10 years of life expectancy. Increasing age is linked to increased incontinence risk (see Section 6.6). Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [305]. An estimation of life expectancy is paramount in counselling a patient about surgery [311] (see also Section 6.6 - Management of PCa in older men).

Currently, RP is the only treatment for localised PCa to show a benefit for OS and CSS, compared with WW, as shown in one prospective randomised trial [312]. The SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality, with a relative risk (RR) of death at 18 years of 0.71 (95% CI: 0.59-0.86). The number needed to treat (NNT) to prevent one death at 18 years of follow-up was 8; it decreases to 4 for men younger than 65 years of age. Radical prostatectomy was also associated with a reduction in PCa-specific mortality (PCSM) at 18 years (RR: 0.56; 95% CI: 0.41-0.77). The benefit of surgery with respect to death from PCa was largest in men younger than 65 years (RR = 0.45) However, RP was also associated with a reduced risk of metastases among older men (RR = 0.68).

The benefits in OS and CSS were not reproduced in the overall study population (mean age 67 years) of another prospective randomised trial using the same methodology (PIVOT trial). After a median follow-up of 10 years, neither all-cause mortality (HR = 0.88; 95% CI: 0.71-1.08) or specific mortality (HR: 0.63; 95%
CI: 0.36-1.09) were reduced [300]. It must be highlighted that the populations included in these 2 RCTs are different, the SPCG trial includes a larger proportion of intermediate- or high-risk patients.

Robot-assisted laparoscopic prostatectomy (RALP) is displacing radical retropubic prostatectomy (RRP) as the most used surgical approach for clinically localised PCa in the USA and is being increasingly used in Europe and other parts of the world. This trend has occurred despite the lack of high-quality evidence to support the superiority of RALP. A recent systematic review demonstrated that robotic surgery had lower peri-operative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy, although there was considerable methodological uncertainty. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes [313]. A recent, prospective, controlled, non-randomised trial of patients undergoing prostatectomy in 14 centres using RALP or RRP showed no difference in rates of positive surgical margins. At 12 months post-operatively, continence rates did not differ, but ED rates were significantly different with 70.4% after RALP and 74.7% after RRP [314].

Increased surgical experience has lowered the complication rates of RP and improved cancer cure [315-318]. 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 [319, 320]. More evidence for a volume-outcome relationship was provided by a recent systematic review [321].

There is a lack of studies comparing the different surgical modalities as well as of longer-term outcomes allowing comparison of more robust criteria, such as PCa mortality and overall mortality [313, 322-326]. Even though there appears to be a clear volume-outcome relationship, suggesting that referral of patients to high-volume centres would seem reasonable, the impact of a shift in practice has yet to be fully determined [321]. 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 the balance of benefits and side effects of each therapy modality has been considered together with the patient.

6.2.2 Low-risk PCa
Patients with low-risk PCa should be informed about the results of two randomised trials comparing retropubic RP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.57 [95% CI: 0.40-0.81]) and distant metastases (RR: 0.40; 95% CI: 0.21-0.73) were significantly reduced in low-risk PCa at 18 years. However, death from PCa (RR: 0.54; 95% CI, 0.26-1.13) was not reduced. In the PIVOT trial, a preplanned subgroup analysis of men with low-risk PCa showed that RP did not significantly reduce all-cause mortality (HR: 1.15; 95% CI: 0.80-1.66), or death from PCa (RR: 0.54; 95% CI: 0.26-1.13) at 10 years.

The decision to offer RP in cases of low-risk cancer should be based upon the probabilities of clinical progression, side-effects and potential benefit to survival [327]. It might therefore be reasonable to propose AS to selected patients whose tumours are most likely to be insignificant. Apart from disease characteristics, age and comorbidities impact the choice for surgery vs. WW. Individual patient preferences should always be considered in shared decision making. Extended pelvic lymph node dissection (eLND) is not necessary as the risk for pN+ does not exceed 5% [328].

6.2.3 Intermediate-risk, localised PCa
Patients with intermediate-risk PCa should be informed about the results of two randomised trials comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71; 95% CI: 0.53-0.95), death from PCa (RR: 0.38; 95% CI: 0.23-0.62) and distant metastases (RR: 0.49; 95% CI: 0.32-0.74) were significantly reduced in intermediate-risk PCa at 18 years. In the PIVOT trial, according to a preplanned subgroup analysis of 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: 0.21-2.1) at 10 years.

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCa-specific survival rates of 13% and 19.6%, respectively [329].

The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [328]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [328]. In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes.
6.2.3.1 Oncological results of radical prostatectomy in low- and intermediate-risk prostate cancer

Table 6.2.1 presents data from two prospective studies.

Table 6.2.1: Oncological results of radical prostatectomy in organ-confined disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of RP</th>
<th>Median follow-up (mo)</th>
<th>Risk category</th>
<th>12-year CSS (%)</th>
<th>18-year CSS (%)</th>
</tr>
</thead>
</table>

CSS = cancer-specific survival; n = number of patients; 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 [330]. When managed with non-curative intent, high-risk PCa is associated with 10-year and 15-year PCSM rates of 28.8 and 35.5%, respectively [329].

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 lymph nodes is 15-40% [328].

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 Gleason 8-10 lesions. Patients with high-grade tumours confined to the prostate at histopathological examination have a good prognosis after RP. A high rate of downgrading exists between the biopsy Gleason score and the Gleason score of the resected specimen [331]. These men, in particular, may benefit most from potentially curative resection.

Several retrospective case series have demonstrated good outcomes after RP in the context of a multimodal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy Gleason score > 8. Biochemical PFS (BPFS) at 5- and 10-years follow-up ranged between 35-51% and 24-39%, respectively, while the CSS at 5-, 10- and 15-years follow-up was 96%, 84-88% and 66%, respectively [331-334].

6.2.4.1.2 Prostate-specific antigen > 20 ng/mL

D’Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP [335]. Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a BPFS at 5-, 10- and 15-years follow-up, ranging between 40-63%, 25-48% and 25%, respectively. The CSS at 5, 10 and 15 years ranged between 93-97%, 83-91% and 71-78%, respectively [333-338]. Spahn et al. published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively [336].

6.2.4.2 Locally advanced PCa

The surgical treatment of clinical stage T3 PCa has traditionally been discouraged [339], mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse [340, 341].

In recent years, however, there has been a renewed interest in surgery for locally advanced PCa and several retrospective case series have been published [342-344]. In up to 50% of cases this is part of multimodality treatment.

Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease [345, 346] and therefore help with patient selection. In expert centres, it has been shown that continence can be preserved in most cases, and in some cases, potency can also be preserved [347].

Retrospective case series demonstrated 5-, 10- and 15-year BPFS ranging between 45-62%, 43-51% and 38-49%, respectively. Cancer-specific survival at 5-, 10- and 15-years ranged between 90-99%, 85-92% and 62-84%, respectively. Five- and 10-year OS ranged between 90-96% and 76-77%, respectively [342-344, 346-350].
Only a limited number of cohort studies provided survival data for surgery of cT3b-T4 PCa. In these studies, the CSS was 88-92% at 5 years and 87-92% at 10 years, while the OS was 73-88% at 5 years and 65-71% at 10 years [351-353].

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 preoperative staging. cN+ was not a significant predictor of cancer-specific mortality (CSM) \( p = 0.6 \) [354]. Due to the limited evidence, local treatment of cN+ patients, in association with a multimodal approach, should be discussed with patients on an individual basis.

### 6.2.5 Rationale for RP in patients with cN0 but pathologically confirmed lymph node invasion (pN1) PCa

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% [355, 356]. Furthermore, two retrospective observational studies have shown a dramatic improvement in CSS and OS in favour of completed RP vs. abandoned RP in patients who were found to be N+ at the time of surgery [357, 358]. This highlights the fact that frozen section should no longer be considered and supports the role of RP as an important component of multimodal strategies of pN+ PCa. These findings have been corroborated in a contemporary retrospective analysis [358]. Radical prostatectomy resulted in superior survival of patients with pN+ PCa after controlling for lymph node tumour burden and frozen sections of lymph nodes intraoperatively are no longer recommended [359].

Recent studies described survival outcomes after surgery in pN1 PCa, with 5-, 10- and 15-year CSS ranging from 84-95%, 51-86% and 45%, respectively. The OS at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively [237, 355-358, 360, 361].

### 6.2.6 Indication and extent of pelvic lymph node dissection

It is generally accepted that extended pelvic lymph node dissection (eLND) provides important information for prognosis which cannot be matched by any other currently available procedure [245].

The individual risk of finding positive lymph nodes can be estimated using preoperative nomograms. Only a few of these nomograms are based on eLND templates. A risk of nodal metastases over 5% (Briganti nomogram, MSKCC, or Roach nomogram) is an indication to perform nodal sampling by an extended nodal dissection [328, 362, 363].

#### 6.2.6.1 Technique of lymph node dissection

Extended LND includes removal of the nodes overlaying 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, 75% of all anatomical landing sites are cleared [364]. A recent prospective mapping study confirmed that a template including the external iliac, obturator and internal iliac areas was able to correctly stage 94% of patients. Nevertheless, in pN+ patients, this template was associated with a 24% incomplete clearance from positive nodes [244]. Adding the common iliac area and the presacral area decreased this risk to 3%. It is recommended that for each region the nodes should be sent in separate containers for histopathological analysis.

**Sentinel node analysis**

Sentinel node (SN) mapping studies have shown that aside from the obturator and external iliac lymph nodes, the prostate also drains to the presacral nodes and most commonly to the internal iliac nodes [244, 364]. Adding SN mapping to extended nodal dissection aids in directing dissection to nodes most likely to contain nodal metastases. Sentinel node mapping in PCa is still an experimental method and the optimal technology, radioactive or fluorescence tracers, or both, has not been determined yet [365] (see Section: 5.3.2.3).

#### 6.2.6.2 Early complications

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended vs. limited LND, three-fold higher complication rates have been reported by some authors [366]. 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. Other authors have reported more acceptable complication rates [367]. Similar rates of lymphoceles have been observed in RARP series, however, in one subgroup analysis lymphoceles were more common in the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [368, 369]. Briganti et al., [366] showed more complications after extended compared to limited LND. In 20% of men a complication was reported after eLND. Lymphoceles occurred in 10% of cases. Thromboembolic events occurred in less than 1% of cases.
6.2.6.3 Outcome of pN1

Prognostic indicators
The number of involved nodes [370], the tumour volume within the lymph node, and capsular perforation of the nodal metastases are predictors of early recurrence after prostatectomy for nodal metastasised PCa [371]. A lymph node density (defined as the percentage of positive lymph nodes in relation to the total number of analysed/removed lymph nodes) over 20% was found to be associated with poor prognosis [372].

Survival in pN1
Recent studies described survival outcomes after surgery in pN1 PCa, with 5-, 10- and 15-year CSS rates ranging from 84-95%, 51-86% and 45%, respectively. The OS at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively [237, 256-258, 293, 373, 374]. The number of removed nodes was correlated with disease specific survival in men with nodal metastases [237, 360, 370, 375-379]. In one population based study with a 10-year follow-up, patients undergoing excision of at least 10 nodes (node-negative patients) had a lower risk of PCa-specific death at 10 years than those who did not undergo lymphadenectomy [380]. In another series, it was demonstrated that a more extensive LND was associated with improvement in CSS in patients with lymph node invasion [370]. Retrospective findings suggest, but do not prove that men with nodal metastases may benefit from more extended nodal dissection. Better staging in men with a higher nodal yield may have resulted in the observed improved survival. Clinical recurrence (imaging confirmed) is observed in 33% of men after prostatectomy for lymph node metastasised PCa after a median follow up of 17 years [354].

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 10-year CSS rate of 80% [355, 356]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective randomised trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more frequently performed eLND. The benefits should be judged against the side effects of long-term HT. Follow-up of PSA and delaying the initiation of HT until PSA level rises is therefore an acceptable option in selected cases with < 2 microscopically involved lymph nodes in an extended nodal dissection.

Adjuvant radiotherapy
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 [361]. 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 lymph nodes) and GS 7-10 and pT3-4 or R1 as well as men with 3-4 positive nodes were more likely to benefit from RT after surgery [361]. In A SEER retrospective population-based analysis, adding RT to RP showed a non-significant trend to improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [359]. No recommendations can be made on 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 that found a benefit for adding RT to androgen ablation in pN1 patients [361]. However the optimal field (prostatic fossa only or whole pelvis) remains unclear.

Adjuvant chemotherapy
The TAX3501 trial compared the role of leuprolide (18 months) with and without docetaxel (6 cycles) in men after prostatectomy for high-risk PCa. The trial ended prematurely due to poor accrual and overall only 19.7% of patients were found to have nodal metastases. Adjuvant chemotherapy after prostatectomy should only be considered in a clinical trial.
6.2.7 **Guidelines for eLND in prostate cancer and pN+ patients**

<table>
<thead>
<tr>
<th>Recommendation</th>
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<th>GR</th>
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<tbody>
<tr>
<td>Do not perform LND in low-risk PCa.</td>
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<td>A</td>
</tr>
<tr>
<td>Perform an eLND in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Perform an eLND in high-risk PCa.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Do not perform a limited LND.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Upon detection of nodal involvement during RP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Offer adjuvant ADT for node-positive (pN+);</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>• Discuss adjuvant ADT with additional radiotherapy (see Section 6.2.6.3);</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>• Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes show microscopic involvement with a PSA &lt; 0.1 ng/mL and absence of extranodal extension.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; eLND = extended lymph node dissection; LND = lymph node dissection; PCa = prostate cancer; RP = radical prostatectomy.

6.2.8 **Complications and functional outcomes of radical prostatectomy**

The intra-and peri-operative complications of retropubic RP and RALP are listed in Table 6.2.2 [381] and section 7.8.3 - Radical prostatectomy.

**Table 6.2.2: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [313])**

<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>
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</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 Na</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.

Post-operative incontinence and ED are common problems following surgery for PCa. A recent systematic review found that the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP [326]. 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, nonrandomised trial of patients undergoing prostatectomy in 14 centres using RALP or RRP was published. At 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [314].

6.2.9 **Indications for nerve-sparing surgery**

Nerve-sparing RP can be performed safely in most men with localised PCa [382, 383]. Clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa, any GS > 7 on biopsy. An externally validated nomogram predicting side-specific extracapsular extension can help guide decision making [384, 385]. Multiparametric MRI might be helpful for 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.
The early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. Placebo-controlled prospective studies have shown no benefit from daily early administration of vardenafil or sildenafil vs. on-demand vardenafil or sildenafil in the post-operative period [386, 387]. Conversely, another placebo-controlled prospective study has shown that sildenafil has a significant benefit on the return of normal spontaneous erections [388].

6.2.10 **Guidelines for radical prostatectomy**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss AS and radiotherapy with suitable patients.</td>
<td>4</td>
<td>A*</td>
</tr>
<tr>
<td>Offer RP to patients with low- and intermediate-risk PCa and a life expectancy &gt; 10 years.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk of extracapsular disease (T1c, GS &lt; 7 and PSA &lt; 10 ng/mL, or refer to Partin tables/nomograms).</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>In intermediate- and high-risk disease, use multiparametric MRI as a decision tool to select patients for nerve-sparing procedures.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy of &gt; 10 years.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>Offer RP in a multimodality setting to selected patients with locally advanced (cT3a) PCa, and a life expectancy &gt; 10 years.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1).</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 for pN0.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Offer any surgical approach (i.e. open, laparoscopic or robotic) to patients who are surgical candidates for radical prostatectomy.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

*Upgraded based on panel consensus

AS = active surveillance; DFS = disease-free survival; GS = Gleason score; MRI = magnetic resonance imaging; OS = overall survival; PCa = prostate cancer; RP = radical prostatectomy.

6.3 **Treatment: definitive radiotherapy**

6.3.1 **Introduction**

There are no published RCTs comparing RT with WW or AS. The only randomised trial in the modern era is the ProtecT study which has not yet reported its first results [389].

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold 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 [390]:

- 2009 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 [391]);
- 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 a 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 randomised trials 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.
which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [392]. Tomotherapy is another evolving technique for the delivery of IMRT, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

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 randomised studies (see below) have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year survival without biochemical relapse [393-402]. 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 [403].

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 III for the rectum is about 2-3% and for the genito-urinary tract is 2-5% [395, 402, 404-417] (see also Section 6.8.4.1 Post-treatment quality of life in patients with localised PCa).

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 study 2011 [393]</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 Median 9 yr</td>
<td>Disease specific mortality (DSM) vs. other cause of death</td>
<td>High risk / PSA &gt; 10 16 % DSM @ 70 Gy 4% DSM @ 78 Gy (p = 0.05) Higher risk 15% DSM @ 70 Gy 2% DSM @ 78 Gy (p = 0.03)</td>
<td></td>
</tr>
<tr>
<td>PROG 95-09 study [394]</td>
<td>393</td>
<td>T1b-T2b PSA 15 ng/mL 75% GLS &lt; 6 including proton boost 19.8 vs. 28.8 Gy</td>
<td>70.2 vs.79.2 Gy Median 8.9 yr for survivors</td>
<td>10-year ASTRO Biochemical failure (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>
<td></td>
</tr>
<tr>
<td>MRC RT01 study [390]</td>
<td>843</td>
<td>T1b-T3a, N0, M0 PSA &lt; 50 ng/mL neoadjuvant HT</td>
<td>64 vs. 74 Gy Median 10 yr</td>
<td>Biochemical progression free survival (BFS); OS</td>
<td>43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)</td>
<td></td>
</tr>
<tr>
<td>Dutch randomised phase III trial [402]</td>
<td>664</td>
<td>T1b-T4 143 pts. with (neo)adjuvant HT</td>
<td>68 vs. 78 Gy Median 110 mo.</td>
<td>Freedom biochemical (Phoenix) and/or clinical failure (FFF) @ 10 yrs</td>
<td>43% FFF @ 68 Gy 49% FFF @ 78 Gy (p = 0.045)</td>
<td></td>
</tr>
<tr>
<td>French GETUG 06 randomised trial [397]</td>
<td>306</td>
<td>T1b-T3a, N0, M0 PSA &lt; 50 ng/mL</td>
<td>70 vs. 80 Gy Median 61 mo.</td>
<td>BCF (ASTRO)</td>
<td>39% BF @ 70 Gy 28% BF @ 80 Gy</td>
<td></td>
</tr>
</tbody>
</table>
Retrospective NCDB study [403]

<table>
<thead>
<tr>
<th></th>
<th>16,714</th>
<th>intermediate risk</th>
<th>high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13,538</td>
<td>73% ( T \leq 2a )</td>
<td>40% ( T \geq 2b )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76% ( \text{GLS} \leq 7a )</td>
<td>67% ( \text{GLS} \geq 7b )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 75.6 Gy vs. ( \geq 75.6 \text{ Gy} ) 49% HT</td>
<td>&lt; 75.6 Gy vs. ( \geq 75.6 \text{ Gy} ) 77% HT</td>
</tr>
<tr>
<td>Median</td>
<td>85-86 mo.</td>
<td>OS</td>
<td>propensity adjusted HR: 0.84 favouring dose escalation (( p &lt; 0.001 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>propensity adjusted HR: 0.82 favouring dose escalation (( p &lt; 0.001 ))</td>
</tr>
</tbody>
</table>

BCF = biochemical failure; HT = hormone therapy; OS = overall survival.

6.3.3.2 Hypofractionation (HFX)

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 [400].

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 [401]. 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 [418-424]. A systematic review 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 [425]. 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 genito-urinary and rectal toxicity, and long-term side effects may not all be known yet [425-427].

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. For extreme HFX, it seems prudent to restrict this therapy to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.
### Table 6.3.2: Phase 3 randomised trials of moderate hypofractionation for intact 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>Lukka et al.</td>
<td>466</td>
<td>60% GS 6 31% GS 7 9% GS 8-10</td>
<td>52.5 Gy/20 fx 66 Gy/33 fx</td>
<td>62</td>
<td>68</td>
<td>5 yr FFBF 40% (NS) 5 yr FFBF 43%</td>
<td>Gr ≥ 3 2% (NS) Gr ≥ 3 1%</td>
</tr>
<tr>
<td></td>
<td>470</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeoh et al.</td>
<td>108</td>
<td>n.s.</td>
<td>55 Gy/20 fx 64 Gy/32 fx</td>
<td>66.8</td>
<td>90</td>
<td>7.5 yr FFBF 53% (p &lt; 0.05)</td>
<td>Late GU; HR: 1.58 (95% CI: 1.01-2.47) favouring hypofractionation</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td></td>
<td></td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dearnaley et al.</td>
<td>151</td>
<td>n.s.</td>
<td>57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx</td>
<td>73.4</td>
<td>51</td>
<td>n.s.</td>
<td>Gr ≥ 2 GU 0% (NS) Gr ≥ 2 GI 1% (NS) Gr ≥ 2 GU 2% Gr ≥ 2 GI 4% Gr ≥ 2 GU 2% Gr ≥ 2 GI 4%</td>
</tr>
<tr>
<td></td>
<td>153</td>
<td></td>
<td></td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>153</td>
<td></td>
<td></td>
<td>74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuban et al.</td>
<td>102</td>
<td>29% low 70% intermediate 1% high</td>
<td>72 Gy/30 fx 75.6 Gy/42 fx</td>
<td>80.2</td>
<td>56</td>
<td>5 yr FFBF 96% (NS) 5 yr FFBF 92%</td>
<td>5 yr Gr ≥ 2 GU 19% (NS) 5 yr Gr ≥ 2 GI 14% (NS) 5 yr Gr ≥ 2 GU 19% 5 yr Gr ≥ 2 GI 6%</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td></td>
<td></td>
<td>71.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arcangeli et al.</td>
<td>83</td>
<td>26% GS 7 74% GS &gt;7</td>
<td>62 Gy/20 fx 80 Gy/40 fx</td>
<td>81.4</td>
<td>70</td>
<td>5 yr FFBF 85% (p = 0.065) * p ss for GS ≥ 4 + 3 5 yr FFBF 79%</td>
<td>3 yr Gr ≥ 2 GU 16% (NS) 3 yr Gr ≥ 2 GI 17% (NS) 3 yr Gr ≥ 2 GI 11% 3 yr Gr ≥ 2 GI 14%</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td></td>
<td></td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollack et al.</td>
<td>151</td>
<td>34% GS 6 47% GS 7 19% GS 8-10</td>
<td>70.2 Gy/26 fx 78 Gy/36 fx</td>
<td>84</td>
<td>68</td>
<td>5 yr BCDF 23% (NS) 5 yr BCDF 21%</td>
<td>5 yr Gr ≥ 2 GU 13% (p = 0.16) 5 yr Gr ≥ 2 GI 9% (NS) 5 yr Gr ≥ 2 GU 13% 5 yr Gr ≥ 2 GI 9%</td>
</tr>
<tr>
<td></td>
<td>152</td>
<td></td>
<td></td>
<td>78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluwini et al.</td>
<td>403</td>
<td>30% GS ≤ 6 45% GS &gt; 7 25% GS 8-10</td>
<td>64.6 Gy/19 fx 78 Gy/39 fx</td>
<td>90.4</td>
<td>49</td>
<td>n.s.</td>
<td>3 mo. ≥ 2 GU 23% 3 mo. ≥ 2 GI 13% 3 mo. ≥ 2 GU 22% 3 mo. ≥ 2 GI 13%</td>
</tr>
<tr>
<td></td>
<td>391</td>
<td></td>
<td></td>
<td>78</td>
<td></td>
<td></td>
<td></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; CI = confidence interval; FFBF = freedom from biochemical failure; FU = follow-up; fx = fractions; GI = gastrointestinal; Gr = grade; GS = Gleason score; GU = genito-urinary; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; NS = not significant; n.s. = not stated; ss = statistically significant.

### 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 randomised trials [429-433] (Table 7.3.3). 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 2 or 3 months before (for neoadjuvant), but the concomitant component is crucial to potentiate RT. Long-term ADT, ranging from 2 to 3 years is recommended for locally advanced disease [399, 434] rather than short term (6-months) [433]. Dose
escalation phase III randomised trials are on going to assess its impact on DFS. Cardiovascular mortality may be related to ADT, not RT, as addressed in Section 12.9.3.3.

Whether these results should be applied to patients with intermediate- or high-risk localised PCAs is unclear. The Boston trial has shown an improved 8-year OS rate for patients without moderate or severe comorbidity assigned to 6 months of complete ADT (p = 0.01) [432], and the RTOG 94-08 study showed an increased 10-year OS rate for intermediate risk only with 4 months of complete ADT (p = 0.003) [398].

The EORTC trial 22961, an equivalence trial with 970 patients (78% T3-4, 92% N0) combined RT (70 Gy) with either 6 months or with 3 years of LHRH analogue treatment. With a median follow-up of 6.4 years, both cancer-specific and overall mortality were significantly lower with long-term androgen suppression [399].

In the RTOG 9910 trial, 1,579 intermediate-risk PCAs patients were randomised to LHRH antagonist therapy for 8 weeks before RT (70.2 Gy in 2-D or 3-D techniques) followed by either another 8 or 28 weeks of anti-hormonal treatment. Extended androgen suppression did not significantly improve 10-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 [435].

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</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 [429]</td>
<td>2010</td>
<td>T1-2 poorly differentiated and M0, or T3-4 N0-1 M0</td>
<td>415</td>
<td>EBRT ± ADT</td>
<td>LHRH agonist for 3 yr (adjuvant)</td>
<td>70 Gy RT</td>
<td>Significant benefit at 10 years for combined treatment (HR: 0.60, 95% CI: 0.45-0.80, p = 0.0004).</td>
</tr>
<tr>
<td>RTOG 85-31 [430]</td>
<td>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 Gleason score 7-10</td>
</tr>
<tr>
<td>Granfors [436]</td>
<td>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 lymph-node-positive tumours</td>
</tr>
<tr>
<td>D’Amico [432]</td>
<td>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>Denham 2011 [433]</td>
<td>2011</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 yrs: HR: 0.84, 0.65-1.08; p = 0.18)</td>
</tr>
<tr>
<td>RTOG 94-13 [437]</td>
<td>2007</td>
<td>T1c-4 N0-1 M0</td>
<td>1292</td>
<td>ADT timing comparison</td>
<td>2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant 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 therapy groups (interaction suspected)</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Risk Group</td>
<td>Sample Size</td>
<td>Treatment Details</td>
<td>10-yr Survival Rate</td>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
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<td>-------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>RTOG 86-10</td>
<td>2008</td>
<td>T2-4 N0-1</td>
<td>456</td>
<td>EBRT ± ADT, Goserelin plus flutamide 2 mo. before, plus concomitant therapy</td>
<td>65-70 Gy RT</td>
<td>No significant difference at 10 yr</td>
<td></td>
</tr>
<tr>
<td>RTOG 92-02</td>
<td>2008</td>
<td>T2c-4 N0-1 M0</td>
<td>1554</td>
<td>Short vs. prolonged ADT, LHRH agonist given for 2 years as adjuvant after 4 mo. as neoadjuvant</td>
<td>65-70 Gy RT</td>
<td>p = 0.73 p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with Gleason score 8-10</td>
<td></td>
</tr>
<tr>
<td>EORTC 22961</td>
<td>2009</td>
<td>T1c-2ab N1 M0, T2c-4 N0-1 M0</td>
<td>970</td>
<td>Short vs. prolonged ADT, LHRH agonist for 6 mo. vs. 3 yrs</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>
<td></td>
</tr>
<tr>
<td>Pisansky</td>
<td>2014</td>
<td>Intermediate risk (94% T1-T2, 6% T3-4)</td>
<td>1579</td>
<td>Short vs. prolonged ADT, LHRH antagonist 8 + 8 vs. 8 + 28 wk</td>
<td>70.2 Gy 2D / 3D</td>
<td>67 vs. 68% p = 0.62, confirms 8 + 8 weeks LHRH as a standard</td>
<td></td>
</tr>
<tr>
<td>SPCG-7/ SFUO-3</td>
<td>2014</td>
<td>T1b-2 Grade 2-3, T3 N0 M0</td>
<td>875</td>
<td>ADT ± EBRT, LHRH agonist for 3 mo plus continuous flutamide</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>
<td></td>
</tr>
<tr>
<td>PRO7/ SWOG</td>
<td>2015</td>
<td>T3-4 (88%), PSA &gt; 20 ng/mL (64%), GLS 8-10 (36%) N0 M0</td>
<td>1205</td>
<td>ADT ± EBRT, Continuous LHRH agonist</td>
<td>65-70 Gy 3D-CRT vs. no RT</td>
<td>10-years OS = 49% vs. 55% favouring combined treatment (HR: 0.7, p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Mottet 2012</td>
<td>2012</td>
<td>T3-4 N0 M0</td>
<td>273</td>
<td>ADT ± EBRT, LHRH agonist for 3 yr</td>
<td>70 Gy 3D-CRT vs. no RT</td>
<td>Significant reduction of clinical progression; 5-years OS 71.4% vs. 71.5%</td>
<td></td>
</tr>
</tbody>
</table>

LHRH = luteinising-hormone-releasing hormone; 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 progression-free survival (PFS) in a cohort of 413 high-risk patients. Patients were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years, plus four cycles of docetaxel and estramustine or to goserelin alone (arm 2). Local therapy was administered at 3 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 3 months of treatment) was obtained in 34% in the ADT + DE arm and 15% in the ADT arm. With a median follow-up period of 4.6 years, the 4-year PFS was 85% in arm 1 vs. 81% in arm 2 (p = 0.26), but the data need to mature [442].

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

Zelefsky et al. [443] 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%). 3D-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 10 years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before RT. The 10-year 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 6-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 (4-6 months) [398, 444, 445]. 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 EBRRT + short-term ADT did not improve OS in high-risk localised PCa, in the Boston and RTOG 94-13 and 86-10 trials [431, 432, 437], 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 lymph nodes). With a median follow-up time of 8 years, OS was significantly improved in the patients allocated to ADT + RT (HR, 0.70; 95% CI: 0.57 to 0.85; p < 0.001). Deaths from PCa were significantly reduced by the addition of RT to ADT (HR: 0.46; 95% CI: 0.34 to 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 [440].

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to 3 years of ADT using an LHRH agonist (leuprorelin), with or without RT (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic lymph nodes). After a median follow-up period of 67 months, there was a significant improvement in the 5-year DFS (p < 0.001), metastatic disease-free survival (p < 0.018), and locoregional PFS (p < 0.0002), but the effect on OS was not reported [441].

Another study compared hormonal treatment alone (i.e. 3 months of continuous androgen blockade followed by continuous flutamide treatment (n = 439) with the same treatment combined with RT (n = 436) [438]. The 10 (15) year cumulative PCSM was 18.9% (30.7%) and 8.3% (12.4%) (HR: 0.35; [p < 4.1E-10 for 15 year results]), and overall mortality was 35.3% (56.7%) and 26.4% (43.4%) (HR: 0.70; p = 0.0006 for 15-year results), respectively.

6.3.3.7 Lymph node irradiation
6.3.3.7.1 Prophylactic lymph node irradiation in clinically N0 prostate cancer (estimated cN0)
There is no level 1 evidence for prophylactic whole-pelvic irradiation, since randomised trials have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77-06 study (n = 484 with T1b-T2) [446], the Stanford study (n = 91) [447], and the GETUG 01 trial (n = 444 with T1b-T3 N0 pNx M0) [448]. In the RTOG 94-13 study [437], 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
lymphadenectomy may be needed to improve the selection of patients who may be able to benefit from pelvic lymph node irradiation and to supplement the use of the Briganti tables [328] and/or the Roach formula [449]. The results of pelvic lymphadenectomy, 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 trails 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 randomised phase II in the UK, 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 [399], 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 5-year (54%) and 9-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 [450]. Patients with pelvic lymph node 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 STAMPEDE trial suggests that pelvic RT could be beneficial for N1 disease, but this is not based on a randomised comparison [451] (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 [452]; the other study suggested a clearer advantage for protons [453].

One randomised trial 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 [394]. Thus, unequivocal information that shows an advantage of protons over IMRT proton therapy is still not available.

Studies from the SEER database, and from Harvard [454, 455], 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 [455].

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 [456].

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 brachytherapy for localised PCa
There is a consensus on the following eligibility criteria for LDR monotherapy [457]

- Stage cT1b-T2a N0, M0;
- Gleason score 6 with ≤ 50% of biopsy cores involved with cancer or;
- Gleason 3 + 4 score with ≤ 33% of biopsy cores involved with cancer;
- An initial PSA level of ≤ 10 ng/mL;
- A prostate volume of < 50 cm³;
- An International Prostatic Symptom Score (IPSS) ≤ 12.

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. Guidelines on the clinical and technical aspects of brachytherapy have been published and are strongly recommended [457-459]. There have been no randomised trials comparing brachytherapy as
monotherapy with other curative treatment modalities. Outcome data are available from a number of large population cohorts with mature follow-up [460–467]. The BDFS for Gleason 6 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [460–467].

A significant correlation has been shown between the implanted dose and recurrence rates [468]. 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 4 years than patients who received less than 140 Gy (92% vs. 68%). There is no benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [460].

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5–22%), post-implantation transurethral resection of the prostate (TURP), which is required in up to 8.7% of cases, and incontinence (0–19%) [469]. A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity [470]. 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 benign prostatic hyperplasia increases the risk of post-implantation incontinence and urinary morbidity.

Erectile dysfunction develops in about 40% of the patients after 3-5 years. In a retrospective analysis of 5,621 men who had undergone LDR monotherapy [471], the urinary, bowel, and erectile morbidity rates were 33.8%, 21%, and 16.7%, respectively, with invasive procedure rates of 10.3%, 0.8%, and 4%, respectively. A small randomised trial 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 [472].

LDR brachytherapy combined with EBRT for intermediate- and high-risk PCa
In cases of intermediate- or high-risk localised PCa, brachytherapy, supplemental EBRT [473] and neoadjuvant hormonal treatment [474] may be considered. Dose-escalated EBRT has been compared with EBRT followed by a LDR brachytherapy boost in intermediate-risk and high-risk patients in a randomised trial [475]. 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 (prescribed dose 115 Gy). The full paper is pending.

6.3.5.2 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. Guidelines advising on clinical and technical issues are available and recommended [476]. High-dose-rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [477]. Higher doses of supplemental EBRT than this may best be delivered with IMRT [478].

Data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) [479]. In a retrospective analysis of modern series [463, 480], BDFS rates of 85.8%, 80.3% and 67.8% in men with low-risk, intermediate-risk, and high-risk PCa, respectively, were reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar with high-dose EBRT and HDR brachytherapy in terms of diarrhoea and insomnia [481]. However, the frequency of ED was significantly increased with HDR brachytherapy (86 vs. 34%). A single randomised trial of EBRT vs. EBRT and HDR brachytherapy boost has been reported [482]. A total of 218 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 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 BDFR (p = 0.04) with 5-, 7- and 10-year estimates of biochemical control 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-completed 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 2 years, possibly due to a dose lower than the current standard used [482]. A systematic review 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, randomised trial [483].
### 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>

### 6.3.5.3 Side effects of percutaneous irradiation and brachytherapy

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients [484]. A meta-analysis has shown that the 1-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing RP, and 0.25 after standard RP. When studies with more than 2 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 [485].

Studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT [486, 487]. 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 [486]. Another analysis [487] 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 [488]. 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 10 years [489]. 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 [489].

### 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 5 years [490]. Three prospective randomised trials have assessed the role of immediate post-operative RT (adjuvant RT [ART]), as follows:

**6.3.6.1 EORTC 22911**

EORTC 22911 [491], 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 RRP. Grade 4 toxicity was not observed (Criteria: see Tables 6.8.1 and 6.8.2). The rate of grade 3 GU toxicity was 5.3% vs. 2.5% in the observation group after 10 years. For patients younger than 70 years, the study concluded that immediate post-operative RT after surgery significantly improved the 10-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 10 years after immediate irradiation (HR: 0.45; p < 0.0001). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after 10 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 5 years for pT3 with negative margins and other risk factors [491].

**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 [492].

6.3.6.3 SWOG 8794 trial
Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, p = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; p = 0.023) [493, 494].

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 [491, 492, 494] after recovery of urinary function;
or
• Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [495, 496] (see Section 6.10.5.1).

Table 6.3.4: Overview of all three randomised trials for adjuvant radiation therapy after RP*

<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 follow-up (mo)</th>
<th>Biochemical Progression-free survival (bNED)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 8794 [494]</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 [491]</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 [492]</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; NS = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

6.3.7 Immediate (adjuvant) post-operative external irradiation after radical prostatectomy (pN1)
In a retrospective matched-pair analysis with 364 pN+ patients, men who received adjuvant RT in addition to ADT after RP had a 16% better 10-year CSS as compared to those without ADT [497]. In a recent study comparing lymph node positive prostatectomy patients who received either adjuvant ADT alone (n = 721) or ADT + ART (n = 386), the multimodal treatment reduced 8-year PCSM (13.8% vs. 7.6%, p = 0.08) [361]. Subgroup analysis in this retrospective study demonstrated a significant benefit from additional ART for patients with intermediate risk (1-2 positive nodes, GLS 7-10 and pT3b/4 or positive surgical margins; 6.9% vs. 15.8%, p = 0.03) and for patients with high risk (3-4 positive nodes irrespective of further risk parameters; 3.5% vs. 21.2%, p = 0.02). The results could be confirmed with the end-point OS. These data need prospective validation, but could be helpful in individual decision making.
6.3.8 Summary of evidence and guidelines for definitive radiotherapy

**Summary of evidence**

| LE | The highest effect of adjuvant radiotherapy is seen in patients with pT3R1 PCa. |
| LE | 1a |

**Recommendation**

<p>| LE | GR | Discussion |</p>
<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>A</td>
<td>Discuss AS and surgery with all patients who would be suitable for these treatment options.</td>
</tr>
<tr>
<td>2a</td>
<td>A</td>
<td>Offer EBRT to all risk groups of non-metastatic PCa.</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>In low-risk PCa, use a total dose of 74 to 78 Gy.</td>
</tr>
<tr>
<td>2a</td>
<td>A</td>
<td>In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume &lt; 50 mL, offer LDR brachytherapy.</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>In intermediate-risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (4-6 months).</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>In patients with high-risk localised PCa, use a total dose of 76-78 Gy in combination with long-term ADT (2-3 years).</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>In patients with locally advanced cN0 PCa, offer radiotherapy in combination with long-term ADT (2-3 years).</td>
</tr>
<tr>
<td>2a</td>
<td>A</td>
<td>Offer IMRT for definitive treatment of PCa by EBRT.</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>In patients with cN+ PCa offer pelvic external irradiation in combination with immediate long-term ADT.</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>In patients with pT3,N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it improves at least biochemical-free survival.</td>
</tr>
<tr>
<td>2b</td>
<td>A</td>
<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 (see Section 6.10.5.1).</td>
</tr>
</tbody>
</table>

**ADT = androgen deprivation therapy; AS = active surveillance; CRT = conformal radiotherapy; EBRT = external-beam radiation therapy; IMRT = intensity-modulated radiotherapy; IPSS = International Prostate Symptom Score; PCa = prostate cancer; PSA = prostate-specific antigen; TURP = transurethral resection of prostate; WHO = World Health Organization.**

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 [498-501]. In this Section, we will consider both whole gland and focal treatment, looking particularly at high-intensity focused US (HIFU) and cryosurgery (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 [498-501].

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.

Patients who are potential candidates for CSAP are those who have organ-confined PCa and those identified...
as having minimal tumour extension beyond the prostate [498-500]. The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobes under the pubic arch. Prostate-specific antigen serum levels should be < 20 ng/mL, and the biopsy Gleason score should be < 7. Potential candidates for CSAP are:

- 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.

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 beyond 10 years.

### 6.4.2.1 Results of cryosurgery for PCa

A comparative assessment of primary ablative therapies for localised PCa, including CSAP, was recently undertaken [502]. The systematic review and network meta-analysis compared CSAP vs. RP and EBRT. Data from 3,995 patients across 19 studies (including 1 RCT, 4 non-randomised comparative studies, and 14 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 1-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 studies, the findings in relation to cancer-specific outcomes were considered inconclusive. The review noted significant inconsistencies in outcome definition, measurement and reporting in the evidence base, in particular biochemical recurrence.

In Ramsay et al.’s systematic review and meta-analysis [502], there was evidence that the rate of urinary incontinence at 1 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 for urinary incontinence at 1 year. CSAP had a numerically lower rate of ED at 1 year compared with RP but this was not statistically significant. 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.

### 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 [503]. 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. The procedure is time-consuming, with about 10 g prostate tissue treated per hour. Potential candidates are patients with low-to-moderate risk in investigational settings. 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 [504]. As a consequence of the lower PSA cut-off for recurrence than in the Phoenix criteria (PSA nadir + 2 ng/mL), the outcome may be approximately 10% lower using the Stuttgart criteria than the Phoenix criteria [505].

A recent systematic review and comparative assessment by network meta-analysis [502] compared HIFU vs. RP and EBRT as primary treatment for localised PCa. Data from 4,000 patients across 21 studies (including 1 non-randomised comparative study and 20 case series) were included.

There was some evidence that BCF rates were significantly higher at 1 year with HIFU than with EBRT. However, the difference was no longer statistically significant at 5 years. Similar statistically significant findings were observed with regard to DFS at 1 year, with worse outcomes for HIFU than for EBRT. The differences were no longer significant at 3 years. The biochemical result was in contrast to OS at 4 years, which was higher when using HIFU. In terms of toxicity, there were insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at 1 year HIFU had lower statistically significant incontinence rates than RP. The safety profile for HIFU was generally good, apart from a potential numerical increase in rates of urinary retention and dysuria. 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.
In an earlier systematic review and meta-analysis [506], 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters [506]. No controlled trial 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 [507-509]. 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 [510-512].

6.4.4.1 Pre-therapeutic assessment of patients
The high number of random and systematic errors associated with TRUS-guided random biopsy regimens mean that this procedure is not sufficiently accurate for selecting candidates for focal therapy. Transperineal biopsy or MRI may be useful tools. For characterising men considering focal therapy, transperineal prostate biopsy using a template-guided approach is recommended [513-515]. When used with a 5 mm sampling frame, this approach can rule in or out PCa foci with volumes of 0.5 mL and 0.2 mL with 90% certainty [516]. Thus, the exact anatomical localisation of the index lesion - defined as the biologically most aggressive - can be accurately determined.

6.4.4.2 Patient selection for focal therapy
The primary objective of treatment must be the eradication of measurable and biologically aggressive disease with minimal toxicity. However, although treatment is usually intended to be a single session, re-treatment may be necessary. There are no standardised follow-up schedules and re-treatment indications. Based on published data, the following criteria identify possible candidates for currently ongoing trials of focal treatment:

- candidates for focal therapy should ideally undergo transperineal template mapping biopsies; mpMRI with or without TRUS biopsy may be an option in experienced hands;
- focal therapy should be limited to patients with a low to moderate risk in investigational settings;
- retrospective data have shown the presence of grade I-III toxicity in 13% of cases [517];
- patients should be counselled and cautioned that no data on functional and oncological outcomes are available;
  1. the therapy is investigational;
  2. the long-term consequences are unknown;
  3. the optimal method for follow-up and the criteria for salvage therapy are not clear;
  4. focal therapy is not without toxicity.

Early reports suggest the feasibility of MRI-guided focal salvage cryotherapy after local RT [518] and focal electroporation [519].

6.4.4.3 Results of focal therapy for localised PCa
Ramsay et al.'s [502] systematic review 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 (5 studies reporting on focal CSAP, 3 studies on focal HIFU, and 1 study reporting on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at 3 years. The incontinence rates at 1 year for focal CSAP were very low (<1%), whilst the ED rate (range 0-40%) was similar to RP. Procedural complication rates were generally low, with the commonest complication being acute urinary retention (range 1.2-8.0%). For focal HIFU vs. RP or EBRT, there were no comparable data on oncological, continence nor potency outcomes at 1 year or more. The commonest reported complications were dysuria (22-30%), acute urinary retention (range 2-24%), urethral sloughing (up to 22%) and urinary tract infection (up to 17%).
6.4.5 Summary of evidence and guidelines for experimental therapeutic options to treat clinically localised PCa

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The available short-term data does not prove equivalence.</td>
<td>2b</td>
</tr>
<tr>
<td>There is no reliable long-term comparative data to indicate that CSAP or HIFU leads to equivalent oncological outcomes compared with radical prostatectomy or EBRT.</td>
<td>3</td>
</tr>
<tr>
<td>PSA 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 follow-up and re-treatment criteria.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only offer cryotherapy and HIFU within a clinical trial setting.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Do not offer focal therapy of PCa as a therapeutic alternative outside clinical trials.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

HIFU = high-intensity focused ultrasound.

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) [520].

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 [521]. 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 levels compared to 50 ng/dL [522-524]. 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 orchiectomy
Bilateral orchiectomy, or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [525] and it is the quickest way to achieve a castration level which is usually reached within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

6.5.3 Oestrogens
Treatment with oestrogens results in testosterone suppression but is not associated with bone loss [526]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses [527, 528] 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 2-3 days after administration and lasts for about 1 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 2-4 weeks.
Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [530] and comparable to orchiectomy [531] [530].

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 [532].

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
Luteinizing-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.

6.5.5.1 Abarelix
Abarelix has shown to be equally effective as LHRH agonists in achieving and maintaining castration levels and in reducing serum PSA levels [533, 534]. However, the FDA issued a warning as regards allergic reactions with its long-term use, resulting in the suspension of its further development. It is still licensed in metastatic and symptomatic PCa, for which no other treatment option is available, or as a short-term induction modality (http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21320_plenaxis_lbl.pdf).

6.5.5.2 Degarelix
Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. 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 3 [535]. An extended follow-up has been published, suggesting a better PFS compared to monthly leuprorelin [535]. 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 CPA) and hepatotoxicity.

6.5.6.1.1 Cyproterone acetate (CPA)
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 randomised trial [536] 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 [537]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.5.6.1.2 Megestrol acetate and medroxyprogesterone acetate
Very limited information is available, but these drugs are associated with a poor overall efficacy.

6.5.6.2 Non-steroidal anti-androgens
Non-steroidal anti-androgen monotherapy has been promoted on the basis of improved QoL compared to castration. Anti-androgens do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [538]. Non-androgen pharmacological side-effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profile
than flutamide and nilutamide [539]. All three agents share a common potential liver toxicity (occasionally fatal) therefore, patients’ liver enzymes must be monitored regularly.

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 5-6 hours, leading to a three times daily use. The recommended 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 [538, 540].

6.5.7 New compounds (for castrate-resistant patients only)
During castration, the occurrence of castration-resistance (CRPC) is systematic. It is considered to be mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see Section 6.11 - 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 adaptative mechanism [541]. 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 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 for relatively high costs. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred [542]. 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 systematic review of ADT in PCa has recently been published [520].

6.6.2 Prognostic factors
Median survival of patients with newly diagnosed metastases is at least 42 months [543] 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 [544], alkaline phosphatase [545] 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 [546].
Based on a large SWOG 9346 cohort, PSA level after 7 months of ADT was used to create 3 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 13 months median survival [547]. This grouping, however, requires independent confirmation.

6.6.3 First-line hormonal treatment
Primary ADT has been the standard of care for the past decades [520]. There is no level 1 evidence for, or against, a specific type of ADT, whether orchietomy, an LHRH analogue or antagonist, except in patients with impending spinal cord compression for whom either a bilateral orchidectomy, 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 [548]. 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 4 weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing ‘flare-up’ per-se is unknown [549].

6.6.4 Combination therapies
6.6.4.1 Complete androgen blockade (CAB)
There are conflicting results from several studies comparing CAB with monotherapy. The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [550]. Systematic reviews 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) [551, 552] beyond 5 years of survival [553] 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 (NSAA) monotherapy
Based on a Cochrane systematic review [554] 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 (IAD)
Three independent reviews [555-557] and a meta-analysis [558] looked at the clinical efficacy of IAD. All of these reviews included eight RCTs of which only three were conducted in patients with M1 disease only. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 [559] 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-analysis 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. 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 very recently published prospective trials came to the same conclusions [560, 561].

Other possible long-term benefits of IAD include bone protection [562] and a protective effect against metabolic syndrome. This possible protective effect has been challenged recently [563] and deserves more studies. Testosterone recovery was observed in most studies [564] leading to intermittent castration. Finally, IAD is associated with a very significant decrease in treatment costs. IAD is feasible and accepted by the patients [564].

The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies [556, 564]. Nevertheless, there is consensus amongst authors on some statements:
• IAD is based on intermittent castration. Therefore, only drugs leading to castration are suitable.
• Most data has been published on CAB (rather than IAD).
• LHRH antagonist might be a valid alternative to an agonist.
• The induction cycle cannot be longer than 9 months, otherwise testosterone recovery is unlikely.
• ADT should be stopped only if patients have fulfilled all of the following criteria:
  - well-informed and compliant patient;
  - no clinical progression;
  - clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.
• Strict follow-up is mandatory, with clinical examination every 3-6 months. The more advanced the disease, the closer the follow-up should be. The same laboratory should be used to measure PSA.
• Treatment is resumed when the patient progresses clinically, or has a PSA rising above a predetermined (empirically set) threshold: usually 10-20 ng/mL in metastatic patients.
• The same treatment is used for at least 3-6 months.
• Subsequent cycles of treatment are based on the same principles until the first sign of castration resistance become 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 [556].

IAD might be an option in patients with metastatic disease after a standardised induction period.

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. Current insights are mainly based on flawed, underpowered RCTs, with mixed patient populations (i.e. locally advanced, M1a, M1b status), and a variety of ADT treatments and follow-up schedules.

ADT was shown to be the most cost-effective therapy if started at the time the patient developed symptomatic metastases [542].

A Cochrane review extracted four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [554]. 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 adjuvant after RP [565]. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications.

The ASCO guidelines conclude that it is not possible to make a recommendation on when to start initial HT in advanced asymptomatic PCa [566]. The ESMO guidelines do not comment on this topic [567].

6.6.5 Hormonal treatment combined with chemotherapy
Three large RCT were conducted, two of which were fully published by September 2015 [546, 568]. The third and most recent trial presented initial findings at a conference [569]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks) (within 3 months of ADT initiation). The primary objective in all 3 studies was OS. The key findings are summarised in Table 6.6.1.

Table 6.6.1. Key findings - Hormonal treatment combined with chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Med FU months</th>
<th>Median OS (months)</th>
<th>HR</th>
<th>P value</th>
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<td>ADT + D</td>
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<td></td>
<td></td>
<td></td>
<td>ADT</td>
<td></td>
<td></td>
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<tr>
<td>Gravis [568]</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 [546]</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 [569]</td>
<td>M1 [61%] / N+ [15%] / relapse</td>
<td>1,184 / 593 (D)</td>
<td>81 / 76</td>
<td>593 (D + ZA)</td>
<td>71</td>
<td>NR</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 4 bone metastases, with at least 1 outside the spine and pelvis; n = number of patients; ZA = zoledronic acid.
In the GETUG 15 trial [568], all patients had newly diagnosed M1 PCa, either primary or after a primary treatment. They were stratified based on previous treatment, and Glass risk factors [544]. In the 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 [546].

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). Patients were included with either M1, or N1 or having 2 criteria out of three: T3/4, PSA ≥ 40 ng/mL, Gleason 8-10. Also relapsed patients after local treatment were included if they had one of the following criteria: PSA ≥ 4ng/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) [569, 571].

In the three trials toxicity was mainly haematologic 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 [572, 573].

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 [572]. Docetaxel is used at the standard regimen of 75mg/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 [574] and the Munich cancer registry [575] 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 6 months ADT and with ≤ 3 bone spots confirmed the feasibility and after a median 34 months follow up, suggested a better CSS [576]. 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 systematic review clearly highlighted that at this time this approach must, as yet, be considered as experimental [577].

6.6.8 Guidelines for the first-line treatment of metastatic prostate cancer

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Modality</th>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castration combined with chemotherapy</td>
<td>Docetaxel combined with castration</td>
<td>Offer castration combined with chemotherapy 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>Castration alone</td>
<td>Surgical, LHRH agonist, OR LHRH antagonist</td>
<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></td>
<td></td>
<td>Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castration combined with any local treatment</td>
<td>Radiotherapy/Surgery</td>
<td>Use castration combined with local treatment in an investigational setting only.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

PROSTATE CANCER - UPDATE MARCH 2016
6.6.9  

**Guidelines for hormonal treatment of metastatic prostate cancer**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>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.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

**Anti-androgens**

- 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 7 days before the first LHRH analogue injection if patient has symptoms. Treat for four weeks.  
  - Do not offer anti-androgen monotherapy in M1 patients.  
  - 1a A

**Intermittent treatment**

- In asymptomatic M1 patients, offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.  
  - Stop treatment when the PSA level is < 4 ng/mL after 6 to 7 months of treatment.  
  - Resume treatment when the PSA level is > 10-20 ng/mL (or to the initial level if < 20 ng/mL).  
  - 4 C

**Drugs**

- In M1 patients, offer combined treatment with LHRH agonists and NSAA.  
  - Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.  
  - 2 B

**ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone; NSAA = non-steroidal anti-androgen; PSA = prostate specific antigen.**

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 [578]. A similar increase is expected in Europe [7].

The Surveillance, Epidemiology and End Results (SEER) database shows that 71% of PCa-related deaths occur in men aged ≥ 75 years [579], probably due to the higher incidence of advanced/metastatic disease [580-582].

Despite the high incidence and mortality rates in senior adults, they may be undertreated [583, 584]. 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 [585].

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 [305]. 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 [586]. This can be explained by the observations from a study in which patients did not receive active local treatment for their
PCa [305]. At 10 years, most men with a Charlson Comorbidity Index (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) [587] is the best tool for assessing mortality risk unrelated to PCa [588].

**Table 6.7.1: Cumulative Illness Score Rating-Geriatrics (CISR-G)**

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

- **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
- Vulnerable: one or two Grade 3 scores
- Frail: > 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 [589-591]. 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 [592]. Nutritional status can be estimated from body weight during the previous 3 months:

- Good nutritional status < 5% weight loss;
- Risk of malnutrition: 5-10% weight loss;
- Severe malnutrition: > 10% weight loss.

6.7.1.2.4 Cognitive impairment
Cognitive impairment is associated with increased mortality risk in senior adults [593]. In patients undergoing major elective surgery, there is an association between baseline cognitive impairment and long-term post-operative complications and mortality [594]. Intervention is unlikely to reverse cognitive impairment, except in depression [68].

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 systematic evaluation of health status [66]. 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 [595].

### Table 6.7.2: G8 screening tool (Adapted from [596])

<table>
<thead>
<tr>
<th>Items</th>
<th>Possible responses (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?</td>
<td>0 = severe decrease in food intake&lt;br&gt;1 = moderate decrease in food intake&lt;br&gt;2 = no decrease in food intake</td>
</tr>
<tr>
<td>B Weight loss during the last 3 months?</td>
<td>0 = weight loss &gt; 3 kg&lt;br&gt;1 = does not know&lt;br&gt;2 = weight loss between 1 and 3 kg&lt;br&gt;3 = no weight loss</td>
</tr>
<tr>
<td>C Mobility?</td>
<td>0 = bed or chair bound&lt;br&gt;1 = able to get out of bed/Chair but does not go out&lt;br&gt;2 = goes out</td>
</tr>
<tr>
<td>E Neuropsychological problems?</td>
<td>0 = severe dementia or depression&lt;br&gt;1 = mild dementia&lt;br&gt;2 = no psychological problems</td>
</tr>
<tr>
<td>F BMI? (weight in kg)/(height in m²)</td>
<td>0 = BMI &lt; 19&lt;br&gt;1 = BMI 19 to &lt; 21&lt;br&gt;2 = BMI 21 to &lt; 23&lt;br&gt;3 = BMI ≥ 23</td>
</tr>
<tr>
<td>H Takes more than three prescription drugs per day?</td>
<td>0 = yes&lt;br&gt;1 = no&lt;br&gt;0.0 = not as good&lt;br&gt;0.5 = does not know&lt;br&gt;1.0 = as good&lt;br&gt;2.0 = better</td>
</tr>
<tr>
<td>P In comparison with other people of the same age, how does the patient consider his/her health status?</td>
<td>0: &gt; 85&lt;br&gt;1: 80-85&lt;br&gt;2: &lt; 80</td>
</tr>
</tbody>
</table>

G8 score > 14 shows that patients should receive the same treatment as younger patients. Patients with G8 ≤ 14 should undergo full geriatric evaluation, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [596]. Patients with reversible impairment (vulnerable patients) should be treated according to EAU Guidelines. Patients with irreversible impairment (frail patients) should receive adapted treatment [66].
### Table 6.7.3: Performance Scales - Karnofsky & ECOG Scores [595]

<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 [66]. Patients with G8 score < 14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [66].

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 vulnerable or frail). The treatment policy is then:

- fit or healthy older men should receive standard treatment;
- vulnerable patients may receive standard treatment after resolution of any geriatric problems;
- frail patients should receive adapted treatment;
- patients who are too sick with terminal illness should receive only palliative treatment [66].

After resolution of reversible impairments, a similar urological approach should be carried out in fit or vulnerable 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.
6.7.1.3 Guidelines for the evaluation of health status in elderly men

<table>
<thead>
<tr>
<th>Recommendations for assessment</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>
<tr>
<td>Treatment options for senior adults according to their health status:</td>
<td></td>
<td></td>
</tr>
<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 vulnerable patients (reversible impairment) after resolution of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>geriatric problems;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Offer adapted treatment to frail 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>

6.7.2 Specific aspects of PCa treatment in older men

6.7.2.1 Localised PCa

6.7.2.1.1 Deferred treatment (active surveillance, watchful waiting)

This topic 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 [597].

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 [580]. 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 (relative risk, 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) [312]. 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 [598, 599].

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 [600]. The drawback of associating ADT with EBRT in senior adults is discussed in Section 6.7. 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 [432].

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 [307, 601].

6.7.2.2 Advanced PCa

6.7.2.2.1 Hormone-naïve metastatic PCa

ADT 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 [66]. Routine bisphosphonates or denosumab to prevent skeletal complications in ADT is not recommended, unless there is a risk of fracture [602].

6.7.2.2.2 Metastatic CRPC

In metastatic CRPC, docetaxel is standard in fit and vulnerable older men [603], with comparable response and tolerance to younger patients [604]. Tolerability has not been specifically studied in frail older men. In elderly
and frail patients, granulocyte colony-stimulating factor prophylaxis should be considered.

Cabazitaxel, abiraterone acetate, enzalutamide, and sipuleucel-T increase survival in chemotherapy-treated and chemotherapy-naive senior adults [605-611].

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

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></td>
</tr>
<tr>
<td>1. Offer standard treatment to fit or healthy older men;</td>
<td>B</td>
</tr>
<tr>
<td>2. Offer standard treatment to vulnerable patients (reversible impairment) after resolution of geriatric problems;</td>
<td></td>
</tr>
<tr>
<td>3. Offer adapted treatment to frail 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>

Recommendation

Localised disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer standard treatment to fit and vulnerable 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 frail or ‘too-sick’ senior adults, offer immediate ADT 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 vulnerable senior adults with intermediate-risk disease.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

Advanced disease (locally advanced / metastatic disease)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<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 vulnerable adults.</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

ADT = androgen-deprivation therapy.

6.8 Side effects of local treatment and health-related quality of life in prostate cancer survivors

6.8.1 Introduction

The majority of PCa patients experience acute and late side effects of the disease and its treatment, which can be short term or long term, change in intensity over time and significantly impact their QoL. Increased life expectancy in PCa makes post-treatment QoL a key issue. Health-related QoL refers to the impact of disease and treatment on well-being, physical, emotional and social functioning, including daily functioning [612]. Health-related QoL is rated by patients, and is important because physicians often underestimate the impact of disease and treatment on patients [613].

Prostate cancer-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel and sexual functioning. General HRQoL refers to well-being, vitality, fatigue, pain, general health status, global QoL, and life satisfaction [614].

Health-related QoL is measured using standardised questionnaires, which provide an objective assessment of general and disease-specific domains [615, 616].

Comparison of the most common contemporary therapies for localised PCa is necessary to inform patients about treatment options and address patient preferences for the various possible outcomes. There is still limited objective data about HRQoL in PCa treatment.

6.8.2 Active surveillance and watchful waiting

Although AS and WW avoids treatment-related side effects, they carry an increased risk of psychological distress, which may significantly affect HRQoL [617].

In general, negative QoL effects remain limited in men with favourable clinical characteristics [618] [277]. Fear of disease progression and general anxiety decreased at 18 months of surveillance with only six of 129 men (5%) discontinuing AS because of anxiety and distress in the PRIAS study [619].

Risk factors for not doing well on AS include: patient perception that the physician is making
most of the decisions, poor physical health, high anxiety, high PSA, lack of a partner, neuroticism, mental impairment, recent diagnosis of PCa, lower number of core samples taken at diagnostic biopsy, and illness uncertainty. These factors are significantly associated with low HRQoL [620, 621] [622]. Interventions to reduce uncertainty and anxiety may enhance HRQoL for men with PCa on AS.

In contrast to AS, men managed with WW in the SPCG-4 trial were not followed closely to induce curative treatment if needed, which could explain the less favourable anxiety and depression scores compared to the PRIAS results [623].

A long-term comparison of WW and RP [623] found that depression, well-being and psychological status did not differ significantly among treatment groups over 8 years. However, men in the RP group reported more physical symptoms related to leakage, erection and libido.

Apart from psychological distress, untreated men may have a higher level of irritative/obstructive urinary symptoms compared to patients treated with RP or RT after 1-3 years [624].

6.8.3 Radical prostatectomy
Radical prostatectomy has a significant negative effect on multiple quality domains, including sexual and urinary function, and physical HRQoL [625-627]. In the PCa Outcomes Study (PCOS), at 2 years 8.7% of men had a lack of urinary control and 41.9% reported sexual dysfunction [628]. Recovery from sexual dysfunction and urinary incontinence occurs over 2-3 years [599, 629], with the latter being at its worst two months after surgery [625].

A recent systematic review found that the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP [326]. A similar study reported mean potency recovery rates at 12 months of 55-81% for patients treated with RALP and 26-63% for patients treated with RRP [325]. The major limitations of the included studies were the frequent retrospective study design and the use of different assessment tools preventing a proper comparison between techniques and series. In a prospective, controlled, non-randomised trial RALP performed modestly better in preserving erectile function compared with open RP, without a statistically significant difference for urinary incontinence or surgical margins [314]. RALP and open RP have comparable functional outcomes and similar HRQoL scores [630].

There are no reliable data to compare HRQoL following RALP and laparoscopic RP. In a controlled cohort study comparing HRQoL after open and laparoscopic RP urinary bother was worse in the laparoscopic RP group at one and three months, but did not differ between the groups thereafter. Bowel and sexual function and bother were similar in the two groups [631].

Age and baseline scores are significant factors impacting functional outcome and HRQoL after RP. Older age has a significant adverse effect on recovery of continence and potency [632]. Younger men reported higher initial sexual and urinary function overall, and experienced greater decreases in sexual function immediately after RP and at 1 year than older men, with similar decrease rates in urinary function and bother. Relative sexual function decreases at 2 years were similar [633]. The same study showed that declines in quality domains are higher in men with above average baseline scores regardless of age.

General HRQoL domains such as pain and energy worsen immediately post-RP, but usually improve by 12 months [629].

New methods for reporting outcomes after RP combine major outcomes, including continence, potency and cancer control [310] and peri-operative complications and positive surgical margins [634]. Pentafecta rates reflect post-operative expectations and satisfaction more accurately and are used in counselling patients with clinically localised PCa. The use of trifecta and pentafecta outcomes in post-operative HRQoL assessment needs further validation.

6.8.4 External-beam radiotherapy and low-dose rate brachytherapy
External-beam radiotherapy and I-125 LDR brachytherapy is associated with acute and late GU or gastrointestinal toxicity with impact on erectile function. In contemporary practice, the NCIC toxicity grading system is increasingly used, but most studies have used the RTOG scales, which are described in Tables 6.8.1 and 6.8.2. Risk factors for acute or late gastrointestinal toxicities after RT include advanced age, pre-existing diabetes mellitus, haemorrhoids, inflammatory bowel disease, a history of prior abdominal surgery, larger rectal volume and the concomitant use of androgen deprivation [469].

Pre-treatment GU complaints, prior TURP and the presence of acute GU toxicity are suggested as contributing to long-term urinary morbidity.
Table 6.8.1: 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. [635]*.

<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>GI</td>
<td>GI</td>
<td>GI</td>
</tr>
<tr>
<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>
<td>Obstruction, fistula, or perforation GI bleeding requiring transfusion; Abdominal pain or tenesmus requiring tube decompression or bowel diversion.</td>
</tr>
<tr>
<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>
<td>Haematuria requiring transfusion Obstruction not resulting from Clots. Ulceration Necrosis</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; GU = genito-urinary.

Table 6.8.2: 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. [635]*

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

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

In a large prospective longitudinal study assessing HRQoL and satisfaction with outcome in PCa survivors the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months [625]. Patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence. At 1-2 years after LDR brachytherapy, incontinence was reported by 4-6% of patients. Eighteen percent of the LDR brachytherapy group and 11% of the EBRT group reported distress from overall urinary symptoms at 1 year [625].

External beam radiotherapy and LDR brachytherapy significantly affect the bowel and rectal HRQoL domains [625], which are almost as important as urinary problems [636, 637]. Symptom onset occurs during or early after treatment, and sometimes persists into follow-up. Rectal urgency, frequency, pain, faecal incontinence, or haematochezia-caused distress related to bowel function was reported in 9% of patients at 1 year after EBRT or LDR brachytherapy [625]. At 2 years after dose-escalated EBRT, ≤ 11% of patients had problems with bowel HRQoL. Bowel HRQoL was related to baseline function, ≤ 25% volume of rectum treated with 70 Gy, and aspirin [638]. Bowel and rectal symptoms were less severe after LDR brachytherapy than EBRT [615].

Overall, the HRQoL at 6 years after LDR brachytherapy did not significantly differ from baseline. Changes in symptoms scores returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. The only clinically relevant changes occurred in sexual activity. At 6 years after treatment, 70% of the patients had diminished sexual activity compared with baseline, 12% had improved sexual activity, and 18% had no change in sexual activity [639].

Contemporary RT techniques, like IMRT with IGRT is associated with lower rates of severe toxicity and a high HRQoL [640]. At 4 years, freedom from grade 2 GI and GU toxicity was 92% and 76%, respectively. Bowel domain remained stable over the 2-year follow-up period and was higher for patients who met ideal rectal constraints [641].

Dietary intervention did not significantly affect gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT [642].

Among general domains fatigue is most commonly reported following EBRT, with the highest level seen at the end of treatment. Four percent of patients reported severe fatigue 5-years post-treatment, adversely affecting HRQoL [643]. Men treated with interstitial LDR brachytherapy had only slight declines in general HRQoL. Physical and functional status declines have been reported in the first few months after implantation, but pre-treatment function was regained by most men after 1 year [639].

Adjuvant ADT may exacerbate the adverse effects of EBRT or LDR on sexuality, vitality [625] and long-term bowel function [644]. 18 months of adjuvant ADT led to earlier testosterone recovery and better QoL compared to 36 months of adjuvant ADT [645].

6.8.5 Complications of high-intensity focused ultrasound
Urinary retention appears to be one of the most common side-effects of HIFU, developing in almost all
patients, with the mean interval of catheterisation via a suprapubic tube varying between 12 and 35 days [503, 646, 647]. Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common, and is sometimes even performed at the time of HIFU. Post-operative impotence occurs in 55-70% of patients.

Elterman et al. [648] have treated 95 patients with clinically organ-confined PCa using the Sonablate 500 device (SonaCare Medical, Charlotte, NC, USA) and have evaluated the type and frequency of treatment-associated complications. With a minimum follow-up of six months, 17% (7/41) of the men had significant incontinence, and 2% developed significant ED. Early and late subvesical obstruction necessitating surgical treatment occurred in 17 (17.9%) and 20 (21.1%) patients, respectively.

Moderate to severe stress urinary incontinence was rare, occurring in fewer than 6.4% of men, and decreased in more recent treatment to 3.1% [649]. Acute urinary retention was seen in 7.6% of men. Even in more recent treatment, the rate of urethral-rectal fistula was 0.7%.

Health-related QoL outcomes following primary HIFU therapy have not been prospectively studied using validated questionnaires. High complication rate after HIFU treatment is presumably associated with a clinically significant reduction in the urinary and sexual function domains and requires further investigation.

6.8.6 Cryotherapy

6.8.6.1 Complications of cryosurgery for primary treatment of PCa

Erectile dysfunction occurs in about 80% of patients and this remains a consistent complication of the CSAP procedure, independent of the generation of the system used [650]. The complication rates described in third-generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% [651-656]. The development of fistula is usually rare, being < 0.2% in modern series. About 5% of all patients require TURP for subvesical obstruction.

Quality of life and sexual function following CSAP were investigated in a clinical phase II trial that recruited 75 men [657]. Quality of life analysis with the prostate-specific FACT-P questionnaire showed that most subscales return to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes were seen when comparing data at 36 months with those at 12 months. With regard to sexual function, 37% of men were able to have intercourse three years after CSAP.

In a prospective, randomised clinical trial, 244 men with newly diagnosed organ-confined PCa were randomised to receive either EBRT or to undergo CSAP [658]. After three year of follow up, sexual function was significantly less impaired in the EBRT group.

6.8.7 Hormonal therapy

There is a lack of data on the effects of HT on QoL, with only a single, large, prospective, RCT comparing orchietomy + flutamide or placebo in M1 patients. Combined therapy resulted in a lower QoL in the first 6 months, with more frequent diarrhoea and worse emotional functioning, compared with castration alone [659]. 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 [660]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [661]. 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 [662].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at 12 months [663]. 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 [664], preserved libido and erectile function [665].

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

6.8.7.1 Side-effects, quality of life and cost of hormonal therapy

The many deleterious side-effects of long-term ADT have been well known for years. As the use of ADT increases, it is increasingly important to consider these side-effects. A systematic review of the side-effects of long-term ADT has recently been published [666].
6.8.7.1.1 Sexual function
Loss of libido and ED are common. The management of acquired ED is mostly non-specific [667].

6.8.7.1.2 Hot flushes
Hot flushes are the most common side-effect of ADT. They appear 3 months after starting ADT, usually persist long-term and have a significant impact on QoL.

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications. Soya 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 [668].

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 [669]. After 6 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 [670], the efficacy of clonidine, vernalipride, gabapentine [671] and acupuncture [672] must be compared in prospective, randomised, controlled trials.

6.8.7.1.3 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.

6.8.7.1.3.1 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) [673]. Hip fractures in men are associated with a significant risk of death [674]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture. The WHO FRAX tool (http://www.shef.ac.uk/FRAX) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) are common and occur during the first year of ADT [675]. Both changes increase the fracture risk.

- **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.

- **Hormonal treatment modalities**
  Bicalutamide monotherapy could be a bone-protective treatment [676,677], 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 [562].

- **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 [678] or yearly [679] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [680]. A quarterly regimen could be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [681].

  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 8 years of follow-up [682]. This benefit has never been observed with more recent bisphosphonates.

- **Denosumab (a fully human monoclonal antibody against receptor activator of NF-kappaB 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 2 years, using a 60 mg subcutaneous regimen every 6 months [683]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, p = 0.006). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient’s weight or
the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every 4 weeks), a delay in bone metastases of 4.2 months has been shown [684] without any impact on OS, but with an increase in side effects. Therefore, this regimen cannot be recommended.

6.8.7.1.3.2 Metabolic effects
Lipid alterations are common and may occur as early as the first 3 months of treatment [675]. 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 [685], 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 [686]:
- 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 [687].

6.8.7.1.3.3 Cardiovascular morbidity
Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [688]. Several studies showed that ADT, after only six months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [689]. The RTOG 92-02 [690] and 94-08 [398] 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 [691]. 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 [692] or presenting with a metabolic syndrome [693].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [694]. 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 [695]. Preventive advice includes non-specific measures: loss of weight, increased exercise, improved nutrition and smoking cessation.

6.8.7.1.3.4 Fatigue
Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure [696, 697], with prolonged efficacy [698] and improved specific survival [699].

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 [666].

6.8.8 Comparison of health-related quality of life between treatment modalities
So far, most comparisons between treatment-related QoL were assessed in non-randomised observational cohorts, with limited follow-up. Only a few trials have directly compared treatment modalities. When comparing general HRQoL for treatments of clinically localised PCa [614, 700] the differences were limited. Data from longitudinal studies show that surgery and RT have a greater impact on role functioning and vitality/energy with surgery being associated with increased dysfunction [701]. Most men recovered function by one year post treatment.

Disease-specific outcomes of PCa, including urinary, bowel and sexual functioning, differ between treatment modalities, with the magnitude of adverse impact of treatment being time-depended. Urinary incontinence
increased sharply after RP, whereas bowel problems and urinary irritation-obstruction occur after EBRT and LDR brachytherapy [615]. Sexual function deteriorates immediately after surgery and then improves, whereas sexual function continued to slowly decline after EBRT and brachytherapy. At one year RP incurred a significantly higher incidence of urinary incontinence (39-49%) and ED (80-91%) compared with RT (6-7% and 41-55%, respectively) [636]. Bowel problems (urgency) affected 30-35% of the EBRT group vs. 6-7% of the RP group [636]. There was no change in urinary function after surgery and little change in bowel function after ERBT after 1 year [615]. Patients with bowel dysfunction at one year after ERBT treatment may expect only modest improvement. Although diarrhea continues to subside, there is little change in tenesmus and rectal urgency, while rectal bleeding becomes more prevalent. Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0-6 months after treatment (84.5%) than patients treated with RP (63.3%) [702]. Urinary bother did not differ significantly (67.7% vs. 67.4%, respectively). Decreased sexual function did not return to pre-treatment levels in either group.

Short-term (up to 2 years) outcomes of open RP, RALP, brachytherapy, and cryotherapy were compared in a non-randomised cohort of patients [703]. At a mean follow up of 24 months LDR brachytherapy and prostate cryoablation were associated with better urinary function and bother scores compared to open RP and RALP. Brachytherapy and cryotherapy had a 3-fold higher rate of return to baseline urinary function compared to open RP and RALP. Sexual function and bother scores were highest after brachytherapy, with a 5-fold higher rate of return to baseline function compared to cryotherapy, open RP and RALP. All 4 treatments were associated with relatively transient and less pronounced impact on bowel function and bother [703].

Longer (3 years) follow-up confirmed time-dependent changes in adverse effects, e.g., increased urinary symptoms after ERBT or increased sexual dysfunction after LDR brachytherapy, which tended to reduce any differences between treatments over time [704]. RP caused greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive symptoms compared with LDR brachytherapy. Treatment differences persisted for up to 3 years [704].

At 5 years, incontinence was reported in 14-16% of RP and 4% of EBRT patients. Bowel urgency and painful haemorrhoids were more common in the EBRT group. Sexual function declined similarly in both groups. Erectile dysfunction was more prevalent in the RP group (79.3 vs. 63.5%) [628].

A randomised comparative trial of RP and LDR brachytherapy was closed after 2 years due to poor accrual [705]. After median follow up of 5.2 years for LDR brachytherapy vs. RP, there were no differences in bowel or hormonal domains. LDR brachytherapy patients scored better for urinary QoL and sexual domains, and patient satisfaction.

At 15-year follow up, there were no significant differences in disease-specific functional outcomes between RP and EBRT, which were seen at 2 and 5 years follow up in the PCOS study [706].

In a population-based study of PCa survivors, up to 18 years post-diagnosis, men treated with RP had clinically worse urinary bother and sexual functioning; those treated with EBRT with/concurrent ADT had the worst bowel symptoms, sexual activity, fatigue, pain and dyspnoea. Despite this, there was no statistically or clinically significant difference in global HRQoL between men treated with RP, EBRT with concurrent ADT or observation, which may be explained by change in perception of symptoms by PCa survivors (‘response shift’), when survival is prioritised above symptoms experienced or physical limitations [707]. In the same study men treated with brachytherapy had the highest global HRQoL and men treated with ADT alone the lowest. However, the somewhat overly positive outcome of brachytherapy should be interpreted with caution, because of selection bias, and under-estimation of irritative voiding symptoms by the EORTC questionnaire.

A study in Norway investigated the relationship between urinary, bowel or sexual dysfunction and global HRQoL in PCa survivors, including untreated patients [624]. Irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global HRQoL, whereas erectile function and use of medication for ED were not [624]. All typical adverse events (moderate/severe IPSS, urinary incontinence, irritative intestinal symptoms, faecal leakage, poor sexual drive and poor erectile function) were significantly associated with low global HRQoL in univariate analyses. Low educational level, comorbidity and moderate or high neuroticism were all significantly associated with low global HRQoL in univariate analyses. No significant associations with global QoL were observed for age, a paired relationship or D’Amico risk group.

Many men treated for clinically localised PCa experience post-treatment problems that may affect their daily lives. Each patient must decide which side-effect profile is most acceptable when making treatment decisions.
**Guidelines on quality of life in PCa management**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform patients with low-risk PCa that the functional outcomes of active surveillance are better than for local active treatment.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Inform patients that functional outcomes after RALP and open prostatectomy are similar.</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Inform Patients that long-term (15 years) QoL outcomes of EBRT and RP are similar.</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

*EBRT = external beam radiation therapy; RALP = robot assisted laparoscopic prostatectomy; RP = radical prostatectomy; QoL = quality of life.*

### 6.9 Summary of guidelines for the primary treatment of prostate cancer

**EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>PSA &lt; 10 ng/mL and GS &lt; 7 and cT1-2a</td>
<td>PSA 10-20 ng/mL or GS 7 or cT2b</td>
<td>PSA &gt; 20 ng/mL or GS &gt; 7 or cT2c</td>
</tr>
</tbody>
</table>

**Primary treatment of prostate cancer**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General comments</td>
<td>Discuss several treatment modalities (active surveillance, surgery and radiotherapy) with patients suitable for such treatments.</td>
<td>A*</td>
<td></td>
</tr>
<tr>
<td>In patients who are surgical candidates for radical prostatectomy, 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.</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer EBRT to all risk groups of non-metastatic PCa.</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer IMRT for definitive treatment of PCa by EBRT.</td>
<td>A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk PCa</strong></td>
<td>Watchful waiting</td>
<td>Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>While on watchful waiting, base the decision to start non-curative treatment on symptoms and disease progression.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Offer active surveillance to patients with the lowest risk of cancer progression: &gt; 10 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>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Base follow-up on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Offer RP to patients with a life expectancy &gt; 10 years.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Offer a nerve-sparing surgery in pre-operatively potent patients with low risk of extracapsular disease (T1c, GS &lt; 7 and PSA &lt; 10 ng/mL, or refer to Partin tables/nomograms).</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not perform LND in low-risk PCa</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In low-risk PCa, the total dose should be 74 to 78 Gy.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume &lt; 50 mL, offer LDR brachytherapy.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only offer cryotherapy and HIFU within a clinical trial setting. The lack of long-term efficacy compared to standard modality has to be discussed with patients.</td>
<td>C</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>Description</td>
<td>Recommendation Level</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
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<td></td>
</tr>
<tr>
<td>Focal treatment</td>
<td>Do not offer focal therapy of PCa as a therapeutic alternative outside clinical trials.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Androgen suppression</td>
<td>Unsuitable.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk PCa</td>
<td><strong>Watchful waiting</strong></td>
<td>Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.</td>
<td>A</td>
</tr>
<tr>
<td><strong>Active surveillance</strong></td>
<td>Not an option.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td><strong>Radical prostatectomy</strong></td>
<td>Offer RP to patients with a life expectancy &gt; 10 years.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Offer a nerve-sparing surgery in pre-operatively potent patients with low risk of extracapsular disease (T1c, GS &lt; 7 and PSA &lt; 10 ng/mL, or refer to Partin tables/nomograms).</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In intermediate-risk, extracapsular disease, use mpMRI as a decision tool to select patients for nerve-sparing procedures.</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perform an eLND if the estimated risk for positive lymph nodes exceeds 5%.</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not perform a limited LND.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<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>
<td></td>
</tr>
<tr>
<td></td>
<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>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not offer adjuvant HT for pN0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>In intermediate-risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (4-6 mo).</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Androgen suppression monotherapy</td>
<td>No place in asymptomatic patients.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>High risk PCa</td>
<td><strong>Watchful waiting</strong></td>
<td>High risk localised: Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>High risk locally advanced: In locally advanced M0 patients unwilling or unable to receive any form of local treatment, offer a deferred treatment policy using ADT as monotherapy to asymptomatic patients with a PSA-DT &gt; 12 months and a PSA &lt; 50 ng/mL and non-poorly differentiated tumour.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td><strong>Active surveillance</strong></td>
<td>Not appropriate.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td><strong>Radical prostatectomy</strong></td>
<td>Do not offer NHT before RP.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perform an eLND in high-risk PCa.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not perform a limited LND.</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk localised: Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy of &gt; 10 years.</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Offer nerve-sparing surgery in pre-operatively potent patients with low risk of extracapsular disease (refer to Partin tables/nomograms).</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In high-risk disease, use multiparametric MRI as a decision-making tool to select patients for nerve-sparing procedures.</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk locally advanced: Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1). Do not consider nerve sparing surgery.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td></td>
<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>
<td></td>
</tr>
</tbody>
</table>
### Radiotherapy

Inform patients with pT3,N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.  

In patients with high-risk localised PCa, use a total dose of 76-78 Gy in combination with long-term ADT (2-3 years is recommended).

In patients with locally advanced cN0 PCa, offer radiotherapy in combination with long-term ADT (2-3 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.

### N1 patients

**cN1**  
In patients with cN+ PCa, offer pelvic external beam irradiation in combination with immediate long-term ADT.

**pN1 after eLND**  
Offer adjuvant ADT for node-positive (pN+).

Offer adjuvant ADT with additional radiotherapy.

Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes showing microscopic involvement, with a PSA < 0.1 ng/mL and absence of extranodal extension.

### Metastatic PCa

**Watchful waiting**  
In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.

**Active surveillance**  
Unsuitable.

**Radical prostatectomy**  
Unsuitable outside clinical trial.

**Radiotherapy to the prostate**  
Unsuitable outside clinical trial.

**Androgen suppression**  
Offer surgical or medical castration (LHRH agonist or antagonist).

Offer castration combined with chemotherapy to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.

Offer castration alone with or without an antiandrogen to patients unfit for, or unwilling to consider castration combined with chemotherapy.

Do not offer castration combined with local treatment/other new hormonal treatments (abiraterone acetate or enzalutamide) outside clinical trials.

In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.

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).

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 7 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. | B |
| In asymptomatic M1 patients, offer intermittent treatment to highly motivated patients, with a major PSA response after the induction period. | 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 6-7 months of treatment. Resume treatment when the PSA level is > 10-20 ng/mL (or back to the original level, if < 20 ng/mL). | C |
| In M1 patients, offer combined treatment with LHRH agonists and NSAA when an intermittent modality is used. | A |

### Castrate resistant status

Ensure that testosterone levels are confirmed as < 50 ng/mL, before diagnosing mCRPC. B

Do not treat patients for non-metastatic CRPC outside of a clinical trial. A

Counsel, manage and treat patients with mCRPC in a multidisciplinary team. A

In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented.

Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent. A

Treat patients with mCRPC with life prolonging agents. Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T). A

Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m² every 3 weeks. A

In patients with mCRPC and progression following docetaxel chemotherapy, offer further life-prolonging treatment options, which include cabazitaxel, abiraterone, enzalutamide and radium-223. A

Offer bone protective agents to patients with skeletal metastases to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis, in particular, must be avoided. A

Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates. A

Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, radionuclides, and adequate use of analgesics. B

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. A

*Upgraded following panel consensus.

ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; HT = hormonal therapy; IPSS = International Prostate Symptom Score; LDR = low-dose-rate; LHRH = luteinising-hormone-releasing hormone; eLND = (extended) lymph node dissection; IMRT = intensity-modulated radiotherapy; LN = lymph node; mCRPC = metastatic castrate-resistant prostate cancer; mpMRI = multiparametric magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSA-DT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.
Guidelines for the treatment of senior adults (> 70 years of age)

**Recommendations for assessment**

<table>
<thead>
<tr>
<th>Recommendation</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 &lt; 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 vulnerable patients (reversible impairment) after resolution of geriatric problems;</td>
<td></td>
</tr>
<tr>
<td>3. Offer adapted treatment to frail 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 management**

<table>
<thead>
<tr>
<th>Localised disease</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer standard treatment to fit and vulnerable 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 frail or ‘too-sick’ senior adults, offer immediate ADT 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 vulnerable senior adults with intermediate-risk disease.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

**Advanced disease (locally advanced / metastatic disease)**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<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 vulnerable adults.</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

**ADT = androgen deprivation therapy; PSA = prostate specific antigen; TRUS = transrectal ultrasound;**

6.10 Treatment of PSA-only recurrence after treatment with curative intent

6.10.1 **Background**

Primary curative procedures such as RP and RT are well-established therapeutic options in the management of localised PCa. Despite technical improvements, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or RT develop PSA-recurrence (see Sections 6.2 and 6.3). While a rising PSA level universally precedes metastatic progression and PCSM, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a PSA rise is not a surrogate for these survival endpoints. 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 has to be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.10.2 **Definitions**

6.10.2.1 **Definition of biochemical failure**

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. However, following RP, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL and rising [708]. A retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa [709] was used to determine the best PSA cut-off point for defining BCR. Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively [709].

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

6.10.3 **Natural history of biochemical failure**

Once a PSA relapse has been diagnosed, it is important to determine 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 doubling time [PSA-DT] and interval to PSA failure).
6.10.3.1 Post-radical prostatectomy biochemical failure

According to Pound et al. [375], not all patients with BCF after RP develop clinical recurrence. The authors evaluated the follow-up data for 1,997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data were confirmed by Boorjian et al. in a study including approximately 2,400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only a few died of PCa (5.8%) [711]. Overall, these studies demonstrated a general trend among men with PSA-only recurrence after RP (i.e. 7-40% of relapsing men): for every 100 men treated with RP, approximately 15-30 will develop BCR and 2-6 of those will die of PCa.

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. Compiling the results of several studies, a subgroup with a high risk of metastases and PCSM was characterised by a PSA-DT < 3 months, SVI (pT3b), specimen Gleason score 8-10, or time to PSA-recurrence < 3 years. Furthermore, a low-risk subgroup was defined as patients with a PSA-recurrence > 3 years following surgery, specimen Gleason score < 7, pathologic organ-confined disease and limited extracapsular extension (pT3a), and PSA-DT > 12 months [712-715]. Patients in the high-risk subgroup universally have an exponentially higher risk of developing metastases and dying of PCa.

Patients in the low-risk subgroup typically respond very well to salvage RT with a high probability of PSA being undetectable [716]. 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 [717]. Trock et al. demonstrated that salvage RT was associated with a significant 3-fold increase in PCa-specific survival relative to those who received no salvage treatment. The increase in PCa-specific survival associated with salvage RT 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 [717].

6.10.3.2 Post-radiotherapy biochemical recurrence

Similar to patients experiencing PSA-recurrence after RP, patients with a PSA-rise following RT can be subdivided into prognostic categories. A high-risk subgroup with elevated risk of metastases and PCSM are those patients with a PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 or clinical stage cT3b-T4. Conversely, patients at low risk of metastases and PCSM are those with a PSA-DT > 15 months, biopsy Gleason score < 7, clinical stage < cT3a and time to biochemical progression > 3 years [714, 718, 719].

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 biochemical progression < 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 factors [719].

6.10.4 Assessment of metastases

6.10.4.1 Bone scan and abdominopelvic computed tomography

The standard workup to detect PCa metastases usually includes a bone scan and abdominopelvic CT. However, because BCF after RP or RT precedes clinical metastases by 7-8 years on average, the diagnostic yield of common imaging techniques is poor in asymptomatic patients [720]. In men with PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [721, 722].

Only 11-14% of patients with BCF after RP have positive CT [721]. In a series of 132 men with BCF after RP, the mean PSA level and PSA velocity associated with positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [723]. Therefore, bone scan and abdominopelvic CT should only be considered in patients with BCF 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 [721, 723].

6.10.4.2 Choline and Acetate positron emission tomography (PET)/computed tomography (CT)

In patients with BCF, choline or acetate PET/CT has reported sensitivities and specificities of 55-96% and 57-100%, respectively [241, 724-726]. Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [727] and may be positive for bone metastases in up to 15% of patients with BCF after RP and negative bone scan [728]. The specificity of choline PET/CT is also higher than bone scan with less false positive and indeterminate findings [249, 729]. Detection of lymph node 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 [241, 724, 726, 730]. In patients
with BCF 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 recent 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 [724].

Despite these limitations, choline PET/CT may change medical management in 18-48% of patients with BCF after primary treatment [731-734]. Positron emission tomography/computed tomography can detect metastases missed by conventional imaging thereby prompting palliative management rather than useless and potentially morbid salvage treatments. It can also trigger aggressive metastasis-directed therapy in oligometastatic patients [735]. Conversely, a PET/CT examination showing only local relapse may lead to salvage therapy in patients initially scheduled for palliative treatment. 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) [734].

Positron emission tomography/computed tomography cannot be recommended in all patients, but should be limited to patients who are fit enough for curative salvage treatment.

After RP, the optimal PSA cut-off level for PET/CT analysis seems to be between 1 and 2 ng/mL [726, 730]. It is unclear whether PSA velocity or PSA-DT thresholds can be used to further select groups of patients in whom PET/CT could be recommended.

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 [726]. 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 [736]. In another study of 140 patients the choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [737].

6.10.4.3 Other radionuclide techniques
A 111In-capromab pendetide scan (ProstaScint™) yielded disappointing results in patients with BCF after RP or RT [720, 721]. Its use is therefore not recommended. 68Ga-PSMA PET is considered still experimental in this setting. 18F-Fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases [729]. However, 18F-Fluoride is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [249].

6.10.4.4 Whole-body and axial magnetic resonance imaging (MRI)
Little is known regarding the accuracy of whole-body or axial MRI in patients with BCF after RP or RT [738]. Therefore, the role of these techniques in detecting occult bone or lymph node metastases in the case of BCF remains to be assessed.

6.10.4.5 Assessment of local recurrences
6.10.4.5.1 Local recurrence after radical prostatectomy
The precise localisation of the local recurrence by imaging techniques is needed only if histological proof of the recurrence is mandatory before salvage treatment and/or if this 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 [720]. As a consequence, salvage RT is usually decided on the basis of the BCF, 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 salvage RT without local imaging.

Nonetheless, 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 84-88% and 89-100%, respectively [739-741]. However, the mean PSA level in these studies was 0.8-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Recently, two studies evaluated mpMRI in patients with PSA level < 0.5 ng/mL. One found a sensitivity of only 13% in men with PSA level < 0.3 ng/mL [742], while the other reported a sensitivity of 86% in patients with PSA level < 0.4 ng/mL [743]. Therefore, it remains to be seen whether MRI is able to correctly detect local recurrences in patients with PSA level < 0.5 ng/mL in order to allow a stereotaxic boost to the recurrence site during salvage RT. Choline or acetate PET/CT can also detect local recurrences, but are less sensitive than MRI [725, 744].
6.10.4.5.2 Local recurrence after radiation therapy

In patients with BCF 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 necessary to obtain histological proof of the local recurrence before treating the patient [720].

Transrectal US is not reliable in depicting local recurrences after RT. In contrast, mpMRI has yielded excellent results [720, 745-748] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with choline and acetate PET/CT, but PET/CT has poorer spatial resolution than MRI [731, 732, 737, 749].

6.10.4.6 Guidelines for imaging in patients with biochemical failure

<table>
<thead>
<tr>
<th>PSA recurrence after RP</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 ≥ 1 ng/mL: choline PET/CT imaging is recommended.</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-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 RT</th>
<th>LE</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Perform prostate mpMRI only in patients who are considered candidates for local salvage therapy, use mpMRI to localise abnormal areas and guide biopsies.</td>
<td>3</td>
<td>B</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>
<td>2b</td>
<td>B</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>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

CT  =  computed  tomography;  mpMRI = multiparametric  magnetic  resonance imaging; PET  =  positron  emission tomography; PSA-DT  =  prostate-specific  antigen doubling time.

6.10.5 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 (CAD, AD);
- Intermittent androgen deprivation (IAD);
- Observation.

Following RT, the same therapeutic options - with the exception of repeat percutaneous RT - may apply in relation to PSA recurrences. In addition, salvage RP, cryotherapy or brachytherapy may be indicated in carefully selected patients.

6.10.5.1 Radiotherapy (Salvage radiotherapy [SRT] - 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 [495, 750-752], providing patients with a ~80% chance of being progression-free 5 years later [496]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or salvage RT alone (n = 160) within 2 years of BCR, showed that salvage RT was associated with a 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 [717]. Despite the indication for salvage RT, a “wait and see” strategy is an option in patients with a long PSA-DT of > 12 months [711]. For an overview see Table 6.10.1.
Table 6.10.1: Selected studies on post-prostatectomy salvage radiotherapy (SRT), sorted by pre-salvage radiotherapy (SRT) PSA level*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>HT %</th>
<th>pre-SRT PSA (ng/mL) median</th>
<th>Median dose (Gy)</th>
<th>bNED / PFS year</th>
<th>5-yr results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegmann, et al. [753]</td>
<td>2011</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. [496]</td>
<td>2009</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 ≤ 0.5 vs. &gt; 0.5</td>
</tr>
<tr>
<td>Goenka, et al. [754]</td>
<td>2011</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. [755]</td>
<td>2010</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. [756]</td>
<td>2010</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. [757]</td>
<td>2006</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. [758]</td>
<td>2005</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. ≥ 1.3</td>
</tr>
<tr>
<td>Pisansky, et al. [759]</td>
<td>2000</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. [760]</td>
<td>2012</td>
<td>441</td>
<td>24</td>
<td>&lt; 1 (58%)</td>
<td>68</td>
<td>63/55% (3)</td>
<td>44/40% HT / no HT</td>
</tr>
<tr>
<td>Stephenson, et al. [495]</td>
<td>2007</td>
<td>1540</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.

The addition of HT to salvage RT (n = 78) was not associated with an additional increase in the CSS compared with salvage RT alone [717]. So far, adding ADT to salvage RT has only shown benefit in terms of biochemical PFS after 5 years in retrospective series [754, 761] and in PFS for “high-risk” tumours [760], however data from prospective randomised trials are lacking. Results are awaited from recently completed randomised controlled phase III studies: the Radiation Therapy Oncology Group RTOG 96-01 comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the post-operative setting and the French GETUG 16 trial, comparing salvage EBRT with- or without 6 months of ADT. To date there is no recommendation for patients with primary pN0- stage at RP for a combination of salvage RT plus additional ADT.

### 6.10.5.1.1 Dose, target volume, toxicity

The optimal salvage RT 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 according to the pathological stage after RP) [750]. Similarly, a USA guideline panel regarded 64-65 Gy as the minimum dose that should be delivered post RP [762]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at 3-5 years [756]. In a systematic review, the pre-salvage RT PSA level and salvage RT 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 [750, 763, 764].

There have been various attempts to define common outlines for “clinical target volumes” of PCa [765-767] and for organs at risk of normal tissue complications [768]. However, depending on the applied techniques and accepted constraints, a satisfactory consensus has not yet been achieved.

In one report on salvage RT with 66.6–70.2 Gy in 1.8 Gy fractions, only 2.7% of the patients had moderate proctitis or cystitis grade II. Four patients (1.3%) had grade III cystitis. Six out of 301 patients (2%) developed urethral stricture which was not solely attributable to salvage RT but also resulted from RP alone [751]. In a retrospective cohort of 285 men receiving 3D-CRT (38%) or IMRT (62%) with 66 Gy in 95% of cases, the high-dose subgroup did not show a significant increase in toxicity [754]. In an analysis involving 30 participating centres, a quality assurance programme assessing target volumes, RT techniques (3D-CRT, IMRT,
VMAT) and RT doses (64 vs. 70 Gy) it was found that 3D-CRT was applied in nearly half of the centres and was not associated with significantly worse rectum and bladder dose-volume histogram parameters, for salvage RT using 70 Gy, when compared with IMRT [769].

However, with dose escalation (72 Gy) or up to a median of 76 Gy, the rate of severe side effects especially for the genito-urinary system clearly increases, even with newer planning and treatment techniques [770, 771]. 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 (5-y: 3D-CRT 15.8% vs. IMRT 16.8%) [770]. After a median salvage IMRT dose of 76 Gy, the 5-year risk of grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [771].

### 6.10.5.1.2 Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy (SRT)

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 salvage RT does not impair PCa control, but clearly helps to reduce overtreatment which is a major issue in ART [772].

Both approaches (ART and SRT) together with the efficacy of neoadjuvant HT are currently being compared in three prospectively randomised clinical trials: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d’Etude des Tumeurs Uro-Génitales (GETUG 17).

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. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of RT when it is used, and provides justification when it is not, this will help the discussion between the physician and the patient.

### 6.10.5.2 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 systematic review using studies published from 2000 onwards [4]. 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 early HT group) [773]. Other studies did not find any differences between early versus delayed, or no, HT. One study found an unfavourable effect of HT [774]. 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 [711], 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 [717]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [775]. 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.

The link between PSA relapse and survival is weak at best, and the management approach has to be individualised [717, 719]. 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 [695, 776]. However, high-risk patients with a long life expectancy may benefit from HT. Therefore, personalised risk stratification is warranted, taking patient-specific (age, comorbidity, patient preferences) and disease-specific (Gleason score, PSA-DT) factors into account in clinical decision-making.

Based on currently available evidence, the benefit of early systemic HT for non-metastatic PCa relapse remains unproven. Accordingly, early HT cannot be systematically recommended in the setting of biochemical or local disease recurrence. 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.

6.10.5.3 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 these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [375].

6.10.6 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 [777-786]. As a general rule, 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.

6.10.6.1 Salvage radical prostatectomy (SRP)
Salvage RP 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.

6.10.6.1.1 Oncological outcomes
In a recent systematic review of the literature, Chade et al. showed that SRP gave 5- and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The 10-year CSS and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS [787].

In most contemporary series, organ-confined disease, negative surgical margins (SM), and the absence of seminal vesicle and/or lymph node metastases were favourable prognostic indicators associated with a better disease-free survival of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [786].
Table 6.10.2: Oncological results of selected SRP case series, including at least 30 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</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, et al. [789]</td>
<td>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, et al. [785]</td>
<td>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, et al. [790]</td>
<td>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.

6.10.6.1.2 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%) [791]. In more recent series, these complications appear to be less common [784, 787]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [787].

Table 6.10.3: Perioperative morbidity in selected SRP case series, including at least 30 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</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. [784]</td>
<td>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. [792]</td>
<td>2005</td>
<td>138</td>
<td>5</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sanderson, et al. [788]</td>
<td>2006</td>
<td>51</td>
<td>2</td>
<td>41</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Gotto, et al. [791]</td>
<td>2010</td>
<td>98</td>
<td>9</td>
<td>41</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Heidenreich, et al. [785]</td>
<td>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; SRP = salvage radical prostatectomy.

6.10.6.2 Summary of salvage radical prostatectomy
In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, a pre-SRT PSA < 10 ng/mL and biopsy Gleason score ≤ 7, no lymph node involvement pre-SRT, and whose initial clinical staging was T1 or T2 [787].

6.10.7 Salvage cryoablation of the prostate
6.10.7.1 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 5-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 [793]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year biochemical recurrence-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 [794].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The 5-year BCR-FS was 61% following SRP, significantly better than the 21% detected after SCAP. The 5-year OS was also significantly higher in the SRP group (95% vs. 85%) [795].
Table 6.10.4: Oncological results of selected SCAP case series, including at least 50 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</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.</td>
<td>1997</td>
<td>150</td>
<td>17</td>
<td>44</td>
<td>-</td>
<td>Nadir + 0.2</td>
</tr>
<tr>
<td>Bahn, et al.</td>
<td>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.</td>
<td>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.</td>
<td>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.</td>
<td>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.</td>
<td>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.

6.10.7.2 Morbidity

According to Cespedes et al. [800], the risks of urinary incontinence and ED at least 12 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 fistula rate was 1.2% and 3.2% of patients required a TURP for removal of sloughed tissue [794]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.10.5) [801].

Table 6.10.5: Perioperative morbidity, erectile function and urinary incontinence in selected SCAP case series, including at least 50 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>Incontinence, %</th>
<th>Obstruction/Retention, %</th>
<th>Rectourethral fistula, %</th>
<th>ED, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters</td>
<td>1997</td>
<td>150</td>
<td>73</td>
<td>67</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>Bahn</td>
<td>2003</td>
<td>59</td>
<td>8</td>
<td>-</td>
<td>3.4</td>
<td>-</td>
</tr>
<tr>
<td>Ismail</td>
<td>2007</td>
<td>100</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Pisters</td>
<td>2008</td>
<td>279</td>
<td>4.4</td>
<td>3.2</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>Ahmad</td>
<td>2013</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.

6.10.7.3 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 10 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.

6.10.8 Salvage brachytherapy for radiotherapy failure

Following local recurrence after previous definitive RT there is no indication for salvage EBRT as the total dose is limited and therefore the chance of cure is low. For carefully selected patients with primary localised PCa and histologically proven local recurrence, high- or low-dose rate (HD/LDR) brachytherapy remain the effective treatment options with an acceptable toxicity profile [803-805]. However, the published series are relatively small; therefore 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 [803]. With a median follow-up of 60 months the 5-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 MSCCC in New York [806]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after 5 years was 69% (median follow-up 36 months), Grade 2 late side effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side effects have been reported [807].

Using LDR-brachytherapy with 103Pd (palladium), long-term outcome was reported in 37 patients with a median follow-up of 86 months [804]. The biochemical control rate after 10 years was 54%. However, the crude rate of ≥ grade 2 toxicity was 46% and ≥ grade 3 toxicity was 11%. These side effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side effects seem to be lower with HDR-brachytherapy [808].
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. Therefore salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.10.9 **Salvage High-intensity focused ultrasound (HIFU)**

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

**Table 6.10.6: Oncological results of selected salvage HIFU case series, including at least 20 patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</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. [810]</td>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelet, et al. [811]</td>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uchida, et al. [812]</td>
<td>2011</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. [813]</td>
<td>2011</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.

6.10.9.2 **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.

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

6.10.10 **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 5-year metastasis-free survival rate was 88% with HT vs. 92% with WW (p = 0.74) [814].

6.10.11 **Salvage lymph node dissection**
Novel imaging modalities improve the early detection of nodal metastases [815]. The surgical management of (recurrent) nodal metastases has been the topic of several retrospective analyses [815, 816, 817]. The majority of treated patients showed biochemical recurrence but clinical recurrence-free and cancer specific 10-year survival over 70% has been reported [818]. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [577]. Addition of RT to the lymphatic template after salvage LND may improve BCR rate [819]. No level 1 evidence is available on the effects of salvage nodal dissection on survival [820].

6.10.11.1 **Guidelines for salvage lymph node dissection**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss salvage lymph node dissection 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.</td>
<td>C</td>
</tr>
</tbody>
</table>

LND = lymph node dissection.
6.10.12  
**Guidelines for imaging and 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>Biochemical recurrence after radical prostatectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer patients with a PSA rise from the undetectable range and favourable prognostic factors ($\leq$ pT3a, time to biochemical recurrence $&gt; 3$ year, PSA-DT $&gt; 12$ months, Gleason score $\leq 7$) 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. The total dose of salvage radiotherapy 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>Biochemical recurrence after radiotherapy</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.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Due to the increased rate of side effects, perform salvage radical prostatectomy 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>Systemic salvage treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not routinely offer 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>

ADT = androgen-deprivation therapy; PSA-DT = prostate-specific antigen doubling time.

6.11  
**Treatment: Castration-resistant PCa (CRPC)**

6.11.1  
**Background**

Our knowledge of the mechanisms involved in the development of castration-resistant PCa (CRPC), remains incomplete [821, 822]. An alteration in normal androgen signalling is thought to be central to the pathogenesis of CRPC [823]. It is mediated through two main, overlapping, mechanisms. These are androgen receptor (AR)-independent and AR-dependent.

6.11.2  
**Definition of progressing PCa after castration**

**Table 6.11.1: Definition of CRPC**

<table>
<thead>
<tr>
<th>Castrate serum testosterone $&lt; 50$ ng/dL or 1.7 nmol/L plus either;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA $&gt; 2$ ng/mL or,</td>
<td></td>
</tr>
<tr>
<td>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) [824].</td>
<td></td>
</tr>
<tr>
<td>Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.</td>
<td></td>
</tr>
</tbody>
</table>

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 2 years [825], 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 doubling time have been associated with time to first bone metastasis, bone metastasis-free and OS [825, 826]. 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 [827] suggested a bone 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 3 months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level.

The rest of this Section focuses on management of men with proven metastatic CRPC (mCRPC).
6.11.3 **Assessing treatment outcome in castration-resistant PCa (CRPC)**

Precise quantification of the effect of treatments on metastatic bone disease is difficult to quantify and rarely used in clinical practice. Improvements in QoL, PFS and PCa-specific survival are all used, but the gold standard remains OS [828].

6.11.3.1 **PSA level as marker of response**

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a surrogate marker. Trials of the vaccines sipuleucel-T (Provenge phase III) [829] and TRICOM (PROSTVAC phase II) [830] have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs [831]. In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effect of drugs on PSA expression should be considered when interpreting PSA response data, which should be viewed together with other clinical data [832-835]. Nevertheless, it has been shown reproducibly that > 30% PSA decline following therapy is associated with a significant survival advantage [836, 837]. An improved PSA response was also associated with prolonged survival in the TAX 327 study, with a median survival of 33 months when the PSA was normalised (< 4 ng/mL) vs.15.8 months for an abnormal PSA [838].

6.11.4 **Androgen deprivation in castration-resistant PCa**

Eventually men with PCa show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in CRPC is debatable [839].

Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [840, 841]. 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 6.11.2: Randomised phase III controlled trials - first-line treatment of mCRPC*

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Selection criteria</th>
<th>Main outcomes</th>
</tr>
</thead>
</table>
| **DOCETAXEL**
| SWOG 99-19 [842] 2004 | docetaxel/EMP, every 3 weeks, 60 mg/m², EMP 3 x 280 mg/day | mitoxantrone, every 3 weeks, 12 mg/m² prednisone 5 mg BID | **OS**: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) **PFS**: 6.3 vs. 3.2 mo. (p < 0.001) |
| TAX 327 [838] [603] 2008 | docetaxel, every 3 weeks, 75 mg/m² prednisone 5 mg BID Or docetaxel, weekly, 30 mg/m² prednisone 5 mg BID | mitoxantrone, every 3 weeks, 12 mg/m², Prednisone 5 mg BID | **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) |
### ABIRATERONE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Entry Criteria</th>
<th>Outcomes</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| COU-AA-302 Ryan [843-845] | Abiraterone + prednisone | Placebo + prednisone | No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms. No visceral metastases. | **OS:** 34.7 vs. 30.3 mo. (HR: 0.81 p = 0.0033). FU: 49.2 mo.  
**rPFS:** 16.5 vs. 8.3 mo. p < 0.0001 | **Main side effects G3-4:** 4% cardiac disorders in the placebo group vs. 8% on abiraterone, increased alanine aminotransferase 6% vs. <.1%, and hypertension 5% vs. 3%.

### ENZALUTAMIDE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Entry Criteria</th>
<th>Outcomes</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| PREVAIL Beer [846] | Enzalutamide | Placebo | No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms. 10% had visceral mets. | **OS:** 32.4 vs. 30.2 mo (p < .001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84)  
**rPFS:** 20.0 mo. vs. 5.4 mo. HR: 0.186 (95% CI: 0.15, 0.23) p < 0.0001 | **Main side effects (G3-4)**: Hypertension (7%), fatigue (2%) and hot flushes (< 1%)

### SIPULEUCEL-T

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Entry Criteria</th>
<th>Outcomes</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Kantoff [830] | Sipuleucel-T [609] | Placebo [609] | Some with previous docetaxel. ECOG 0-1. Asymptomatic or minimally symptomatic. | **OS:** 25.8 vs. 21.7 mo. (p=0.03 HR: 0.78; 95% CI: 0.61-0.98). FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo. (no difference) | **Main side effects outcomes:** 31.7% vs. 35.1%.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Entry Criteria</th>
<th>Outcomes</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Small [829] | Sipuleucel-T [829] | Placebo [71] | ECOG 0-1. No visceral metastases. No bone or cancer pain. No corticosteroids. | **OS:** 25.9 vs. 21.4 mo (p < 0.01). FU: 36 mo.  
**PFS:** 11.7 vs. 10.0 wk. | **Main side effects outcomes:** 31.1% vs. 29.3% grade 3, 24.45% both groups grade 4.

**BID** = twice a day; **ECOG** = Eastern Cooperative Oncology Group; **EMP** = estramustine; **FU** = follow-up; **PFS** = progression-free survival; **rPFS** = radiographic progression free survival; **OS** = overall survival.

6.11.5 **Hormonal drugs targeting the endocrine pathways in the pre-docetaxel space**

6.11.5.1 **Abiraterone**

Abiraterone was evaluated in 1,088 chemo-naïve mCRPC patients in the phase III trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [843]. 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) [845]. Adverse events (AEs) related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1 - 2 (see Table 6.11.2 for more details).

6.11.5.2 Enzalutamide
A randomised phase III trial (PREVAIL) [846] 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 a significant improvement in both co-primary endpoints, in rPFS (HR: 0.186 [CI: 0.15-0.23] p < 0.0001), and OS (HR: 0.706 [CI: 0.6- 0.84] p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension (see Table 6.11.2 for more details).

6.11.6 Non-hormonal therapy
6.11.6.1 Docetaxel regimen
A significant improvement in median survival of 2-2.9 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy [838, 842]. The standard first-line chemotherapy is docetaxel 75 mg/m² 3 weekly doses combined with prednisone 5 mg BID, up to 10 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 [848]. A better risk group definition was presented more recently, 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 3 significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [849]. Age by itself is not a contraindication to docetaxel [604] but attention must be paid to closer monitoring and comorbidities as discussed in Section 6.7.2.2.2.2 [850]. In men with mCRPC who are thought to be Unable to tolerate the standard regime using docetaxel 50mg/m² every 2-weeks seems well tolerated with less Grade 3-4 adverse events and prolonged time to treatment failure although survival data are not available [851].

6.11.6.2 Vaccine
In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [826]. 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.
Figure 6.11.1: Flowchart of the potential therapeutic options after PSA progression following hormonal therapy in metastatic patients.

PS = performance status; mCRPC = metastatic castrate resistant prostate cancer; mets = metastases.

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 first “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 was 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 produced following the St. Gallen Consensus Conference [852] (see flowchart).

6.11.7 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 [852]. Prostate-specific antigen alone is not reliable enough for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA [847]. Instead PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [842]. A majority of experts at a recent consensus meeting suggested regular review and repeat blood profile every 2-3 months with bone
scintigraphy and CT scans at least every 6 months even in the absence of a clinical indication [852]. 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.

6.11.8 Treatment after first-line docetaxel for mCRPC
All patients who receive docetaxel-based chemotherapy for mCRPC will eventually progress. A number of clinical trials investigated the role of further chemotherapy. Intermittent docetaxel re-treatment in patients who had clearly responded to first-line docetaxel showed a PSA response in about 60% with a median time to progression of about 6 months, while treatment-associated toxicity was minimal and similar to that of first-line docetaxel [853, 854]. No survival improvement has been demonstrated with docetaxel rechallenge in responders. All treatments in this setting are presented in Table 6.11.3.

Table 6.11.3: Randomised controlled phase III - second-line trials for mCRPC*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Selection criteria</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABIRATERONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fizazi</td>
<td>2012</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>de Bono</td>
<td>2011</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>RA -223</td>
<td>2013</td>
<td>RA 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). FU: 2 years.</td>
</tr>
<tr>
<td>CABA ZITAXEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahl</td>
<td>2013</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: 2 years.</td>
</tr>
<tr>
<td>deBono</td>
<td>2010</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>
</tbody>
</table>

Main side-effects outcomes: Similar.

Main side-effects outcomes: Adverse events related to mineralocorticoid excess with abiraterone.

Main side-effects outcomes: Similar.

Main side-effects outcomes: 56% vs. 62% grade 3-4.

Main side-effects outcomes: Similar.

Main side-effects outcomes: 82% vs. 58% neutropenia.
**ENZALUTAMIDE**

<table>
<thead>
<tr>
<th>Scher [606]</th>
<th>2012</th>
<th>enzalutamide</th>
<th>placebo</th>
<th>Previous docetaxel.</th>
<th>ECOG 0-2.</th>
<th>OS: 18.4 vs. 13.6 mo. (p &lt; 0.001)</th>
<th>HR: 0.63, 95% CI: 0.53-0.75).</th>
<th>FU: 14.4 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radiologic PFS: 8.3 vs. 2.9 mo.</td>
<td>HR: 0.40, 95% CI: 0.35-0.47 p &lt; 0.0001</td>
<td>Main side-effects outcomes: 45.3% vs. 53.1% grade 3-4.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Only studies reporting survival outcomes as primary endpoints have been included.*

OS = overall survival; PFS = progression-free survival.

6.11.8.1 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 [607]. Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) plus 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 [828]. This drug 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 [856].

6.11.8.2 Abiraterone acetate

Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [605] and the final results have been reported more recently [608]. A total of 1,195 patients with mCRPC were randomised 2:1 to abiraterone acetate plus prednisone or placebo plus prednisone. All patients had progressive disease based on the 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 side effects 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).

6.11.8.3 Enzalutamide

The planned preliminary analysis of the AFFIRM study was published in 2012 [606]. 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 2 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.

6.11.8.4 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. In general subsequent treatments can be expected to have a smaller response [857, 858] with evidence of cross-resistance between enzalutamide and abiraterone [859].
6.11.9 Bone targeted therapies 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 [860]. 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.

6.11.9.1 Common complications due to bone metastases

Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation is an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [861]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [862, 863]. 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 external beam irradiation [864]. Otherwise, EBRT, with or without systemic therapy, is the treatment of choice.

6.11.9.2 Painful bone metastases

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [865], even as a single fraction [866].

6.11.9.2.1 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 RA-223 or placebo, plus standard of care. The primary end-point was OS. RA-223 significantly improved median OS by 3.6 months (HR: 0.70; p < 0.001) [855]. 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 RA-223, this did not differ significantly from that in the placebo arm [855]. Radium-223 was effective and safe no matter if the patients were docetaxel pretreated, or not [867].

6.11.9.2.2 Bisphosphonates

Zoledronic acid has been used in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anticancer treatments but docetaxel was available. 643 patients who had CRPC [868] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. The 8 mg dose was poorly tolerated so reduced to 4 mg but did not show a significant benefit. However, at 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer 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.

The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind [864, 865]. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as long-term intravenous bisphosphonate administration [869]. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.11.9.2.3 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB 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) [684]. 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 [870]. 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 [684].
6.11.10  Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant PCa

**Summary of evidence**

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

**Recommendation**

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>A</td>
<td>Ensure that testosterone levels are confirmed to be &lt; 50 ng/mL, before diagnosing CRPC.</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>Do not treat patients for non-metastatic CRPC outside of a clinical trial.</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>Counsel, manage and treat patients with mCRPC in a multidisciplinary team.</td>
</tr>
<tr>
<td>2a</td>
<td>A</td>
<td>In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented. <strong>Comment:</strong> Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>Treat patients with mCRPC with life prolonging agents. Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).</td>
</tr>
</tbody>
</table>

CRPC = castration-resistant PCa.

6.11.11  Guidelines for cytotoxic treatment in castrate-resistant PCa

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>3</td>
<td>B</td>
<td>In non-metastatic CRPC, offer cytotoxic therapy only in a clinical trial setting.</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>Counsel, manage and treat patients with mCRPC in a multidisciplinary team.</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m² every 3 weeks.</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<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>
</tr>
<tr>
<td></td>
<td></td>
<td>Base second-line treatment decisions of mCRPC on pre-treatment performance status, comorbidities and extent of disease.</td>
</tr>
</tbody>
</table>

mCRPC = metastatic castration-resistant PCa.

6.11.12  Guidelines for supportive care of castrate-resistant PCa

These recommendations are in addition to appropriate systemic therapy.

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1a</td>
<td>B</td>
<td>Offer bone protective agents to patients with skeletal metastases to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.</td>
</tr>
<tr>
<td>1a</td>
<td>B</td>
<td>Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, radionuclides, and adequate use of analgesics.</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<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>
</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 BT, 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. 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 and this 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 [871, 872]. 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 [873]. However, others have argued for a higher cut-off of 0.4 ng/mL for patients at high risk of clinical progression [872].

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 [874]. 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 5 years [875]. 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 [710]. It applies to patients with or without HT.

After HIFU or cryotherapy, there are various definitions for PSA relapse [506]. Most of these are based on a cut-off PSA level of ~1 ng/mL, combined with negative post-treatment biopsy. No endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of BCF.

7.1.3.3 Prostate-specific antigen monitoring after radical prostatectomy
Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP [876]. 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 indicates distant metastases, whereas a later, slowly increasing, level most likely indicates local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [877]. Local treatment failure and distant metastases occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [878].

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 [879], although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. Biochemical failure after RT is currently defined as PSA > 2 ng/mL above the nadir [710]. After RT, PSA-DT is correlated with site of recurrence: patients with local recurrence have a doubling time of 13 months compared to 3 months for those with distant failure [880].

7.1.3.5 Digital rectal examination
Local recurrence after curative treatment is possible without a concomitant rise in PSA level [878]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. PSA 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) [881].

7.1.3.6 Transrectal ultrasound, bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and 11C-choline positron emission tomography computed tomography (PET/CT)
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 6.19.4 for a more detailed discussion).

7.1.3.6.1 Transrectal ultrasonography/magnetic resonance imaging biopsy
Biopsy of the prostate bed and urethrovesical anastomosis 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. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months post-operatively, every 6 months thereafter until 3 years, and then annually. The first clinic visit is mainly to detect 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 PSA level &gt; 0.2 ng/mL is associated with residual or recurrent disease.</td>
<td></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>B</td>
</tr>
<tr>
<td>Palpable nodules and increasing serum PSA are signs of local recurrence.</td>
<td>B</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum PSA measurement supplemented by DRE. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 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>

DRE = digital rectal examination; PSA = prostate-specific antigen.

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 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 upmost 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 (see Section 6.6.2), in locally advanced and metastatic PCa [882], as in salvage ADT for relapse following treatments with curative intent [883].

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 3 months of ADT is independently associated with a shorter progression-free and OS rate [884] and might explain significant fatigue. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [885]. 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 [214].
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 [842], 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 (< 1 nmol/L). 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 [522], known as the ‘acute on-chronic effect’ or ‘breakthrough response’.

The timing of measurements is not clearly defined. A 3 to 6-month testosterone level assessment is suggested to ensure castration is achieved and maintained. If not, switching to another agonist or antagonist, or to an orchietomy 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 7.5). The patient's general
practitioner should probably be more involved.

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 6.8.7.1.3.1). It is suggested that routine bone monitoring should be performed every 2 years during castration [886], or yearly if there are other risk factors [887, 888]. 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 [884, 885]. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

7.2.4 When to follow-up

After the initiation of ADT, it is recommended that patients are followed at 3 - 6 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 3-6 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.

7.2.5 Guidelines for follow-up during hormonal treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
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<tbody>
<tr>
<td>Evaluate patients at 3 - 6 months after the initiation of treatment.</td>
<td>A</td>
</tr>
<tr>
<td>As a minimum, tests should include serum PSA measurement, 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 6 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 3 to 6 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, 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>

CRPC = castrate-resistant PCa; DRE = digital rectal examination; PSA = prostate-specific antigen.
8. REFERENCES


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9. CONFLICT OF INTEREST

All members of the 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 publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.